ISSN 1980-5764

Dementia & Neuropsychologia

Volume 15 • Number 1
March 2021
São Paulo • Brazil

OFFICIAL JOURNAL OF THE SCIENTIFIC DEPARTMENT OF COGNITIVE NEUROLOGY AND AGING OF THE BRAZILIAN ACADEMY OF NEUROLOGY

ORIGINAL ARTICLE

Dementia & Neuropsychologia

Volume 15 • Number 01
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OFFICIAL JOURNAL OF THE SCIENTIFIC DEPARTMENT OF COGNITIVE NEUROLOGY AND AGING OF THE BRAZILIAN ACADEMY OF NEUROLOGY

Indexed in

PubMed (US National Library of Medicine National Institutes of Health)

SciELO (Scientific Electronic Library Online)

Scopus (The Largest Abstract and Citation Database of Peer-reviewed Literature)

SJR (SCImago Journal Rank)

LILACS (Literature on the Health Sciences in Latin America and the Caribbean)

PsycINFO (American Psychological Association)

LATINDEX (Sistema Regional de Información en Línea para Revistas Científicas de América Latina, el Caribe, España y Portugal)

QUALIS/CAPES (Classificação de Periódicos, Anais, Jornais e Revistas)

Full texts available electronically at
www.demneuropsy.com.br
www.scielo.br
www.pubmed.gov

Editorial production
Zeppelini Publishers
Tel: 55 11 2978-6686
www.zeppelini.com.br

ACADEMIA BRASILEIRA DE NEUROLOGIA

Rua Vergueiro, 1353 - Liberdade, São Paulo - SP.
Edifício Top Towers Offices - Torre Sul - 04101-000
Telefone: (11) 5083-3876

Dementia & Neuropsychologia (ISSN1980-5764), the official scientific journal of the Cognitive Neurology and Aging Department of the Brazilian Academy of Neurology, is published by the Brazilian Academy of Neurology,a non-profit Brazilian association.
Regularly published on March, June, September, and December since 2007.

Dementia & Neuropsychologia / Brazilian Academy of Neurology / Associação Neurologia Cognitiva e do Comportamento. -- v. 1, n. 1 (2007). -- São Paulo: Cognitive Neurology and Aging Department of the Brazilian Academy of Neurology and of the Brazilian Association of Geriatric Neuropsychiatry, 2007-

v.: il.

Published in English, 4 times per year.
ISSN 1980-5764

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Original Article

https://doi.org/10.1590/1980-57642021dn15-010001

Clinical characteristics of older patients with COVID-19: a systematic review of case reports

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ABSTRACT. In the context of the current COVID-19 pandemic, higher morbidity and mortality have been reported in older adults. This age group presents physiological changes and its own clinical conditions such as frailty, dementia, among others. **Objective:** To describe the characteristics of COVID-19 patients, both over and under 80 years old, by conducting a systematic review of the literature describing case reports, and to summarize and critically assess these characteristics. **Methods:** Systematic review. The study was registered on the Registry of Health Research Projects (PRISA) of the Peruvian National Institute of Health (code EI00000631). Five electronic databases (Scopus, PubMed, PubMed Central, LILACS, and SCIELO) were systematically searched during the period between December 31, 2019 and April 16, 2020. The search focused on case reports, case studies, and case series of older people with COVID-19 infection aged over or under 80 years. When selecting the cases, priority was given to clinical and epidemiological profile, laboratory and imaging patterns, and comprehensive geriatric evaluation. **Results:** 1,149 articles were identified; after applying the filters, a total of 15 publications of case reports and complete records of 27 older adults were obtained. The most frequent age group was between 60 to 69 years old. There is little literature regarding case reports of older adults aged over 80 years. The most frequent parameters were hypertension, fever, cough, respiratory distress, ground-glass opacification in chest radiography and tomography. Furthermore, decrease in PaO_2/FiO_2 ratio and lymphocytes, and increase in C-reactive protein and Interleukin 6 were observed. **Conclusions:** This systematic review found little available information of patients under 80 years old, and far less for those over 80 years old, and an absence of comprehensive geriatric assessment.

Keywords: coronavirus infections, SARS-CoV-2, aged, case reports, systematic review.

CARACTERÍSTICAS CLÍNICAS DE PACIENTES IDOSOS COM COVID-19: UMA REVISÃO SISTEMÁTICA DE RELATOS DE CASOS

RESUMO. No contexto da atual pandemia de covid-19, maior morbidade e mortalidade têm sido relatadas em idosos. Sabe-se que essa faixa etária apresenta alterações fisiológicas e condições clínicas próprias, como fragilidade, demência, entre outras. **Objetivo:** Descrever as características de pacientes com covid-19, maiores e menores de 80 anos, por meio de uma revisão sistemática da literatura que descreve relatos de casos, e resumir e avaliar criticamente essas características. **Método:** Revisão sistemática. O estudo foi registrado no Registro de Projetos de Pesquisa em Saúde (PRISA) do Instituto Nacional de Saúde do Peru (código EI00000631). Local: cinco bases de dados eletrônicas (Scopus, PubMed, PubMed Central, LILACS e SCIELO) foram sistematicamente pesquisadas entre 31 de dezembro de 2019 e 16 de abril de 2020. A busca se concentrou em relatos de caso, estudos de caso e séries de casos mais antigos pessoas com infecção por SARS-CoV-2 com mais e menos de 80 anos. Na seleção dos casos, a prioridade foi dada ao perfil clínico e epidemiológico, padrões laboratoriais e de imagem, e avaliação geriátrica abrangente. **Resultados:** Foram identificados 1.149 artigos.

This study was conducted at the Universidad de San Martín de Porres, School of Medicine, Research Centre of traditional Medicine & Pharmacology, and Research Centre of Aging, Lima, Peru.

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Disclosure: The authors report no conflicts of interest.

Funding: This research was supported by the Traditional Medicine and Pharmacology Research Center and Aging Research Center, Universidad de San Martín de Porres.

Received on July 26, 2020. Accepted in final form on October 15, 2020.

Após a aplicação dos filtros, obteve-se um total de 15 publicações de relatos de caso e registros completos de 27 idosos. A faixa etária mais frequente foi de 60 a 69 anos. Há pouca literatura sobre relatos de casos de adultos com mais de 80 anos. Os parâmetros mais frequentes foram hipertensão, febre, tosse, dificuldade respiratória, vidro fosco na radiografia e tomografia de tórax. Também foram observados diminuição da PaO2 / FiO2 e linfócitos, e aumento da proteína C reativa e Interleucina 6. **Conclusões:** Esta revisão sistemática encontrou poucas informações disponíveis sobre pacientes com menos de 80 anos, em quantidade ainda menor para aqueles com mais de 80 anos, além de uma ausência de avaliação geriátrica abrangente.

Palavras-chave: infecção por SARS-CoV-2, covid-19, idosos, relatos de casos, revisão sistemática.

INTRODUCTION

On December 31, 2019, a cluster of new pneumonia cases (fever, dry cough, and dyspnea) was reported in the city of Wuhan, China. The outbreak of a new coronavirus (CoV), called Coronavirus Disease 2019 (COVID-19), was thus caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The infection progressively spread throughout the world.[1] The World Health Organization (WHO) declared COVID-19 a global pandemic on March 11, 2020, by which date over 5,406,282 cases and 343,562 deaths[2] had been confirmed.

In Latin America, the first COVID-19 case was reported in Brazil on February 26, 2020,[3] whereas in Peru the first case was reported on March 6, 2020.[4] As of the date of this study, Peru has approximately 129,751 confirmed cases and 3,788 deaths.[5] COVID-19 may affect people of any age; however, with a fatality rate above 8%, people over the age of 70 years with or without comorbidities seem to be more susceptible.[6] All countries report that the highest mortality rate for severe disease is verified for those aged over 80 years.[7]

One of the factors of greater virulence and severity of COVID-19 in older people are the physiological changes that occur at this age. Immunosenescence is characterized by a decreased function of innate and acquired immunity that may be conducive to an imbalance and, hence, to a chronic proinflammatory state, which make patients susceptible to infections and noncommunicable chronic diseases.[8]

In addition, older people present other clinical conditions, such as frailty, sarcopenia, disability, cognitive decline, anxiety, depression, and others, which exacerbate and are conducive to a negative progression of the disease.[9] For this reason, researching and classifying these conditions are accepted as the best strategy to define the need for care and to predict the prognosis.[10,11] On the other hand, healthcare systems are not adapted to treat older adults.[12]

Although an individual is considered old from the age of 60 years, various classifications based on age groups have been proposed. However, taking this into consideration, the cutoff at the age of 80 years becomes relevant and is consistent with progressive physiological changes and clinical conditions.[13]

In contrast, in the general population, the current diagnosis of COVID-19 is based on epidemiology history, clinical pattern observation, auxiliary exams, such as chest X-ray and Computed Tomography, and is confirmed by molecular and/or serological tests.[14-17]

According to the National Institute of Statistics and Information, older adults in Peru represented 10.14% of the total population in 2017.[18] The current COVID-19 pandemic is more lethal in older people; in Peru, reports show that 2,609 of the 3,788 deaths were of older adults.[5] It is necessary to gather information that allows to differentiate older people suffering from COVID-19.

The purpose of this article is to describe the clinical characteristics of COVID-19 patients, aged both over and under 80 years, by conducting a systematic review.

METHODS

This is an observational, cross-sectional, and systematic review study.

The ethical aspects of the study observed at all times included beneficence, non-maleficence, confidentiality, and justice principles. The study was registered on the Registry of Health Research Projects (PRISA) of the Peruvian National Institute of Health (*Instituto Nacional de Salud* – INS) with code EI00000631.

The systematic review focused on all studies on clinical case reports that presented detailed clinical information of older people with confirmed diagnosis of COVID-19 infection, particularly centered on these four fundamental items:

- Clinical and epidemiological profile.
- Laboratory Tests Pattern.
- Comprehensive Geriatric Assessment (CGA).
- Aged 80 years and over/under 80 years.
- The information used in this study was collected on a step-by-step approach as follows:
- Publication period: studies carried out from December 31, 2019 to April 16, 2020 were considered.

- Study characteristics: case reports, case studies, and case series were used.
- Databases: the databases Scopus, PubMed (Medline), PubMed Central, LILACS (Latin American & Caribbean Health Sciences Literature), and SCIELO (Scientific Electronic Library Online) were consulted.
- Process to identify data acquisition: different Boolean expressions (AND and OR) were used with the descriptive Medical Subject Headings: "COVID-19", "SARS-CoV-2," "2019n-CoV," "new coronavirus," "novel coronavirus," "2019-novel coronavirus," "COVID-19 pandemic," "COVID-19 virus disease," "Wuhan coronavirus," "2019-nCoV disease," "2019-nCoV infection," "coronavirus disease-19," "COVID-19 virus infection," "aged," "aged, 80 and over," "frail elderly," "oldest old," "octogenarian," "nonagenarian," "centenarian," "elderly." The complete search strategy is presented in Annex 1. Next, the titles were reviewed, and duplicate articles were eliminated. Then, the four fundamental items were examined.

Inclusion criteria:
- English, Spanish or Portuguese languages.
- Older adults (aged over 60 years).
- Patients with confirmed diagnosis of COVID-19.
- Complete clinical information.

Exclusion criteria:
- Original articles.
- Review.
- Editorial.
- Short communications.
- Letters.
- Special announcements.
- Any form opposite to the inclusion criteria.

Process for the selection of clinical case reports: seven independent reviewers selected the clinical case reports, in the following order:
- Review of titles and abstract.
- Contrasting of selected studies, and resolution of divergences through discussion and consensus.
- Extensive reading of the clinical case reports.
- Confirmation of clinical case reports after contrasting with the inclusion criteria.

Extraction of objective information and data management: information was independently extracted by seven reviewers; an *ad hoc* data collection form was used. The forms were compared and resolutions were reached through discussion and consensus.

Data presentation: descriptive tables were prepared considering the four fundamental items of the study. Absolute and relative frequencies, mean and standard deviation, median and interquartile range are presented, as appropriate. The *Statistical Package for the Social Sciences* (SPSS) software, version 25, was used.

RESULTS

Table 1 shows the used keywords and the strategies implemented for the systematic search in the selected databases.

The systematic review of the databases yielded a total of 1,149 results. After applying the filters, a total of 15 publications dealing with clinical case reports were obtained, and the review process is shown in Figure 1.

A total of 15 studies that met the inclusion criteria were selected; complete records of 27 older adults were obtained from these clinical case report articles. Table 2 shows epidemiological data, estimated contact times, medical treatment, medical history, signs, and symptoms. Three phases are recorded: outpatient management, hospitalization management, and management in the Intensive Care Unit (ICU). The following frequencies were observed: age group between 60 to 69 years (74.1%), men (51.9%), and residents from Wuhan (63%). The most frequent comorbidity was hypertension (37%); 14% of older people had at least one comorbidity and 6%, more than two comorbidities. The most frequent signs and symptoms were fever, cough, and respiratory distress, which were present in more than 50% of patients.

Table 3 shows the results of the imaging tests. In hospitalized patients, the most common finding on radiography was ground-glass opacification (58.3%), lung involvement of bilateral distribution (100%), distribution of peripheral lesions (66.7%), basal opacities (75%), and pleural effusion (58.3%). In contrast, the main findings on tomography were bilateral lung involvement (83.3%) and peripheral location of the lesions (61.1%), considering that the ground-glass opacification pattern (88.9%) prevailed.

Table 4 shows the patients' results of laboratory tests during their stay in hospital and ICU. In hospitalization, a decrease in PaO_2/FiO_2 ratio (mean of 157.75), lymphocytes (mean of 0.72), and platelets (mean of 137.46) were observed. Conversely, there was an increase in lactate dehydrogenase (mean of 502), C-reactive protein (mean of 58.26), urea (mean of 9.44), and Interleukin 6 (IL-6) (mean of 232.53). Regarding ICU patients, there were more acute effects on PaO_2/FiO_2 ratio, leukocytes, lymphocytes, and C-reactive protein.

Table 1. Keywords and implemented strategies.

Systematic review items
*Keywords**
COVID-19, SARS-CoV-2, Wuhan coronavirus, 2019-nCoV, novel coronavirus, new coronavirus, 2019-novel coronavirus, COVID-19 pandemic, COVID-19 virus infection, coronavirus-19 disease, 2019-nCoV infection, 2019-nCoV disease, COVID-19 virus disease, Aged 80 and over, Oldest-Old, Nonagenarian, Octogenarian, Centenarian, Nonagenarians, Octogenarians, Centenarians, Frail Elderly, Aged, Elderly. Anciano de 80 o más Años, Ancianos de 80 Años y más Anciano, Anciano Frágil, Centenarios, Nonagenarios, Octogenarios, Adulto Mayor, Ancianos, Persona Mayor, Persona de Edad, Personas Mayores, Salud de la Persona Anciana, Salud de la Persona Mayor, Salud de la Tercera Edad, Tercera edad, y Longevos.
SCOPUS search strategy
(TITLE-ABS-KEY ("COVID-19") OR TITLE-ABS-KEY ("SARS-CoV-2") OR TITLE-ABS-KEY ("Wuhan coronavirus") OR TITLE-ABS-KEY ("2019-nCoV") OR TITLE-ABS-KEY ("novel coronavirus") OR TITLE-ABS-KEY ("new coronavirus") OR TITLE-ABS-KEY ("2019-novel coronavirus") OR TITLE-ABS-KEY ("COVID-19 pandemic") OR TITLE-ABS-KEY ("COVID-19 virus infection") OR TITLE-ABS-KEY ("coronavirus disease-19") OR TITLE-ABS-KEY ("2019-nCoV infection") OR TITLE-ABS-KEY ("2019-nCoV disease") OR TITLE-ABS-KEY ("COVID-19 virus disease")) AND (TITLE-ABS-KEY ("Aged, 80 and over") OR TITLE-ABS-KEY ("Oldest Old") OR TITLE-ABS-KEY ("Nonagenarian") OR TITLE-ABS-KEY ("Octogenarian") OR TITLE-ABS-KEY ("Centenarian") OR TITLE-ABS-KEY ("Nonagenarians") OR TITLE-ABS-KEY ("Octogenarians") OR TITLE-ABS-KEY ("Centenarians") OR TITLE-ABS-KEY ("Frail Elderly") OR TITLE-ABS-KEY ("Aged") OR TITLE-ABS-KEY ("Elderly"))
PubMed Central search strategy
((((((("Aged, 80 and over"[MeSH Terms] OR ("aged"[MeSH Terms] OR "Frail Elderly"[MeSH Terms])) OR (((((((("Aged, 80 and over"[Abstract]) OR Aged[Abstract]) OR "Frail Elderly"[Abstract]) OR "Oldest Old"[Abstract]) OR Nonagenarians[Abstract]) OR Nonagenarian[Abstract]) OR Octogenarians[Abstract]) OR Octogenarian[Abstract]) OR Centenarians[Abstract]) OR Centenarian[Abstract]) OR Elderly[Abstract])) OR (((((((("Aged, 80 and over"[Title]) OR Aged[Title]) OR "Frail Elderly"[Title]) OR "Oldest Old"[Title]) OR Nonagenarians[Title]) OR Nonagenarian[Title]) OR Octogenarians[Title]) OR Octogenarian[Title]) OR Centenarians[Title]) OR Centenarian[Title]) OR Elderly[Title])))))) AND (((COVID-19[Supplementary Concept]) OR ((((((((((((2019-nCoV[Abstract]) OR COVID-19[Abstract]) OR SARS-CoV-2[Abstract]) OR "new coronavirus"[Abstract]) OR "novel coronavirus"[Abstract]) OR "2019-novel coronavirus"[Abstract]) OR "COVID-19 pandemic"[Abstract]) OR "COVID-19 virus infection"[Abstract]) OR "coronavirus disease-19"[Abstract]) OR "2019-nCoV infection"[Abstract]) OR "2019-nCoV disease"[Abstract]) OR "Wuhan coronavirus"[Abstract]) OR "COVID-19 virus disease"[Abstract])) OR ((((((((((((2019-nCoV[Title]) OR COVID-19[Title]) OR SARS-CoV-2[Title]) OR "new coronavirus"[Title]) OR "novel coronavirus"[Title]) OR "2019-novel coronavirus"[Title]) OR "COVID-19 pandemic"[Title]) OR "COVID-19 virus disease"[Title]) OR "Wuhan coronavirus"[Title]) OR "2019-nCoV disease"[Title]) OR "2019-nCoV infection"[Title]) OR "coronavirus disease-19"[Title]) OR "COVID-19 virus infection"[Title]))
PubMed (Medline) search strategy
((((((((((((((((2019-nCoV[Other Term]) OR COVID-19[Other Term]) OR SARS-CoV-2[Other Term]) OR "new coronavirus"[Other Term]) OR "novel coronavirus"[Other Term]) OR "2019-novel coronavirus"[Other Term]) OR "COVID-19 pandemic"[Other Term]) OR "COVID-19 virus disease"[Other Term]) OR "Wuhan coronavirus"[Other Term]) OR "2019-nCoV disease"[Other Term]) OR "2019-nCoV infection"[Other Term]) OR "coronavirus disease-19"[Other Term]) OR "COVID-19 virus infection"[Other Term])) OR COVID-19[Supplementary Concept]) OR ((((((((((((2019-nCoV[Title/Abstract]) OR COVID-19[Title/Abstract]) OR SARS-CoV-2[Title/Abstract]) OR "new coronavirus"[Title/Abstract]) OR "novel coronavirus"[Title/Abstract]) OR "2019-novel coronavirus"[Title/Abstract]) OR "COVID-19 pandemic"[Title/Abstract]) OR "Wuhan coronavirus"[Title/Abstract]) OR "COVID-19 virus disease"[Title/Abstract]) OR "2019-nCoV disease"[Title/Abstract]) OR "2019-nCoV infection"[Title/Abstract]) OR "coronavirus disease-19"[Title/Abstract]) OR "COVID-19 virus infection"[Title/Abstract])))) AND ((((((((((((((("Aged, 80 and over"[Title/Abstract] OR Aged[Title/Abstract]) OR "Frail Elderly"[Title/Abstract]) OR "Oldest Old"[Title/Abstract]) OR Nonagenarians[Title/Abstract]) OR Nonagenarian[Title/Abstract]) OR Octogenarians[Title/Abstract]) OR Octogenarian[Title/Abstract]) OR Centenarians[Title/Abstract]) OR Centenarian[Title/Abstract]) OR Elderly[Title/Abstract]) OR (("Aged, 80 and over"[MeSH Terms] OR "aged"[MeSH Terms]) OR "Frail Elderly"[MeSH Terms])) OR ((((((((("Aged, 80 and over"[Other Term] OR Aged[Other Term]) OR "Frail Elderly"[Other Term]) OR "Oldest Old"[Other Term]) OR Nonagenarians[Other Term]) OR Nonagenarian[Other Term]) OR Octogenarians[Other Term]) OR Octogenarian[Other Term]) OR Centenarians[Other Term]) OR Centenarian[Other Term]) OR Elderly[Other Term])))

Continue...

Table 1. Continuation.

Systematic review items
SCIELO search strategy
(((ab:(2019-nCoV)) OR (ab:(COVID-19)) OR (ab:(SARS-CoV-2)) OR (ab:("Wuhan coronavirus")) OR (ti:(2019-nCoV)) OR (ti:(COVID-19)) OR (ti:(SARS-CoV-2)) OR (ti:("Wuhan coronavirus")))) AND (((ab:("Anciano de 80 o más Años")) OR (ab:(Anciano)) OR (ab:("Anciano Frágil")) OR (ab:("Ancianos de 80 Años o más")) OR (ab:("Ancianos de 80 Años y más")) OR (ab:("Ancianos de 80 o más Años")) OR (ab:(Centenarios)) OR (ab:(Nonagenarios)) OR (ab:(Octogenarios)) OR (ab:("Adulto Mayor")) OR (ab:(Ancianos)) OR (ab:("Persona Mayor")) OR (ab:("Persona de Edad")) OR (ab:("Personas Mayores")) OR (ab:("Personas de Edad")) OR (ab:("Salud de la Persona Anciana")) OR (ab:("Salud de la Persona Mayor")) OR (ab:("Salud de la Tercera Edad")) OR (ab:("Tercera edad")) OR (ab:(Longevos)) OR (ti:("Anciano de 80 o más Años")) OR (ti:(Anciano)) OR (ti:("Anciano Frágil")) OR (ti:("Ancianos de 80 Años o más")) OR (ti:("Ancianos de 80 Años y más")) OR (ti:("Ancianos de 80 o más Años")) OR (ti:(Centenarios)) OR (ti:(Nonagenarios)) OR (ti:(Octogenarios)) OR (ti:("Adulto Mayor")) OR (ti:(Ancianos)) OR (ti:("Persona Mayor")) OR (ti:("Persona de Edad")) OR (ti:("Personas Mayores")) OR (ti:("Personas de Edad")) OR (ti:("Salud de la Persona Anciana")) OR (ti:("Salud de la Persona Mayor")) OR (ti:("Salud de la Tercera Edad")) OR (ti:("Tercera edad")) OR (ti:(Longevos))))
LILACS search strategy *(af:((tw:(2019-nCoV)) OR (tw:(COVID-19)) OR (tw:(SARS-CoV-2)) OR (tw:("new coronavirus")) OR (tw:("novel coronavirus")) OR (tw:("2019-novel coronavirus")) OR (tw:(""COVID-19 pandemic"")) OR (tw:(""COVID-19 virus infection"")) OR (tw:(""coronavirus disease-19"")) OR (tw:(""2019-nCoV infection"")) OR (tw:(""2019-nCoV disease"")) OR (tw:(""Wuhan coronavirus"")) OR (tw:(""COVID-19 virus disease""))))) AND (af:((af:((tw:(aged)) OR (tw:("Anciano de 80 o más Años")) OR (tw:(Anciano)) OR (tw:("Anciano Frágil")) OR (tw:("Ancianos de 80 Años o más")) OR (tw:("Ancianos de 80 Años y más")) OR (tw:("Ancianos de 80 o más Años")) OR (tw:("Centenarios")) OR (tw:("Nonagenarios")) OR (tw:("Octogenarios")) OR (tw:("Viejísimos")) OR (tw:(""Adulto Mayor"")) OR (tw:(""Ancianos"")) OR (tw:(""Persona Mayor"")) OR (tw:(""Persona de Edad"")) OR (tw:(""Personas Mayores"")) OR (tw:(""Personas de Edad"")) OR (tw:(""Salud de la Persona Anciana"")) OR (tw:(""Salud de la Persona Mayor"")) OR (tw:("Aged, 80 and over")) OR (tw:(Aged)) OR (tw:("Health of the Elderly")) OR (tw:("Frail Elderly")) OR (tw:("Oldest Old")) OR (tw:(Nonagenarians)) OR (tw:(Nonagenarian)) OR (tw:(Octogenarians)) OR (tw:(Octogenarian)) OR (tw:(Centenarians)) OR (tw:(Centenarian)) OR (tw:(Elderly)) OR (tw:(""Tercera edad"")) OR (tw:(Longevos)) OR (tw:("Anciano de 60 o más Años")) OR (tw:("Aged, 60 and over")))) OR (af:((mh:("Anciano de 80 o más Años")) OR (mh:(Anciano)) OR (mh:("Anciano Frágil"))))))*

*Excerpted from Medical Subject Headings of the National Library of Medicine of the United States of America, and Health Sciences Descriptors from BIREME – Latin American and Caribbean Center for Information in Health Sciences. OR and AND are Booleans. SCOPUS: Elsevier's abstract and citation database. PUBMED CENTRAL (PMC) is a free full-text archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health, National Library of Medicine (NIH/NLM). PUBMED (MEDLINE) is a database of references and abstracts on life sciences and biomedical topics of the U.S. National Library of Medicine (NLM). SCIELO: Scientific Electronic Library Online is a bibliographic database supported by the São Paulo Research Foundation (FAPESP) and the Brazilian National Council for Scientific and Technological Development (CNPq). Latin American and the Caribbean Health Sciences Literature (LILACS) is an online bibliographic database in medicine and health sciences, maintained by the Latin American and Caribbean Center on Health Sciences Information.

Table 5 shows the medications used during hospitalization and ICU. During hospitalization, the most frequent treatment observed consisted in antivirals (51.9%), of which Interferon was the most used (57.1%). Antibiotics and antivirals were used in the ICU in a similar frequency, and the most widely used antiviral was the Lopinavir-Ritonavir combination (75%).

DISCUSSION

Epidemiological characteristics

During the COVID-19 pandemic, older people have disproportionately been severely affected by the disease, and indeed have required hospitalization and accounted for high death rates, particularly those aged over 80 years.[19] Considering this new virus, it is undoubtedly necessary to collect new data and develop evidence-based strategies concerning prevention and management of people affected by the virus.[20] This research only found 27 reported cases of older adults with COVID -19 that met the inclusion criteria; their median age was approximately 65 years and only one case was of an individual aged over 80 years.[21] Despite this group being the most affected by this pandemic, there are no significant studies on epidemiology or clinical manifestations of COVID-19 in older adults.

Likewise, the relatively low median age reported by this investigation would explain the verified evolution: only one death, 3.7% of the total. Wu et al.,[22] in a cohort of patients, found that aging over 65 years alone is an independent risk factor for developing acute respiratory distress syndrome (ARDS) and for death probably due to less rigorous immune response. These results have been corroborated by various publications worldwide.[23,24]

On the other hand, some research in older people with COVID-19 have indicated that the contributing factors for poor health outcomes include the physiological changes of aging,[25] but mainly the multiple comorbidities related to age,[26] such as heart and lung diseases, diabetes, dementia, and polypharmacy. However, a preprint has found that, in older adults from Mexico, comorbidities or inequalities in accessing healthcare systems (difficulty in accessing a healthcare service or not having health insurance) are predictors of severity for COVID-19, regardless age.[27] Hence, it should be noted that some literature has reported that a significant

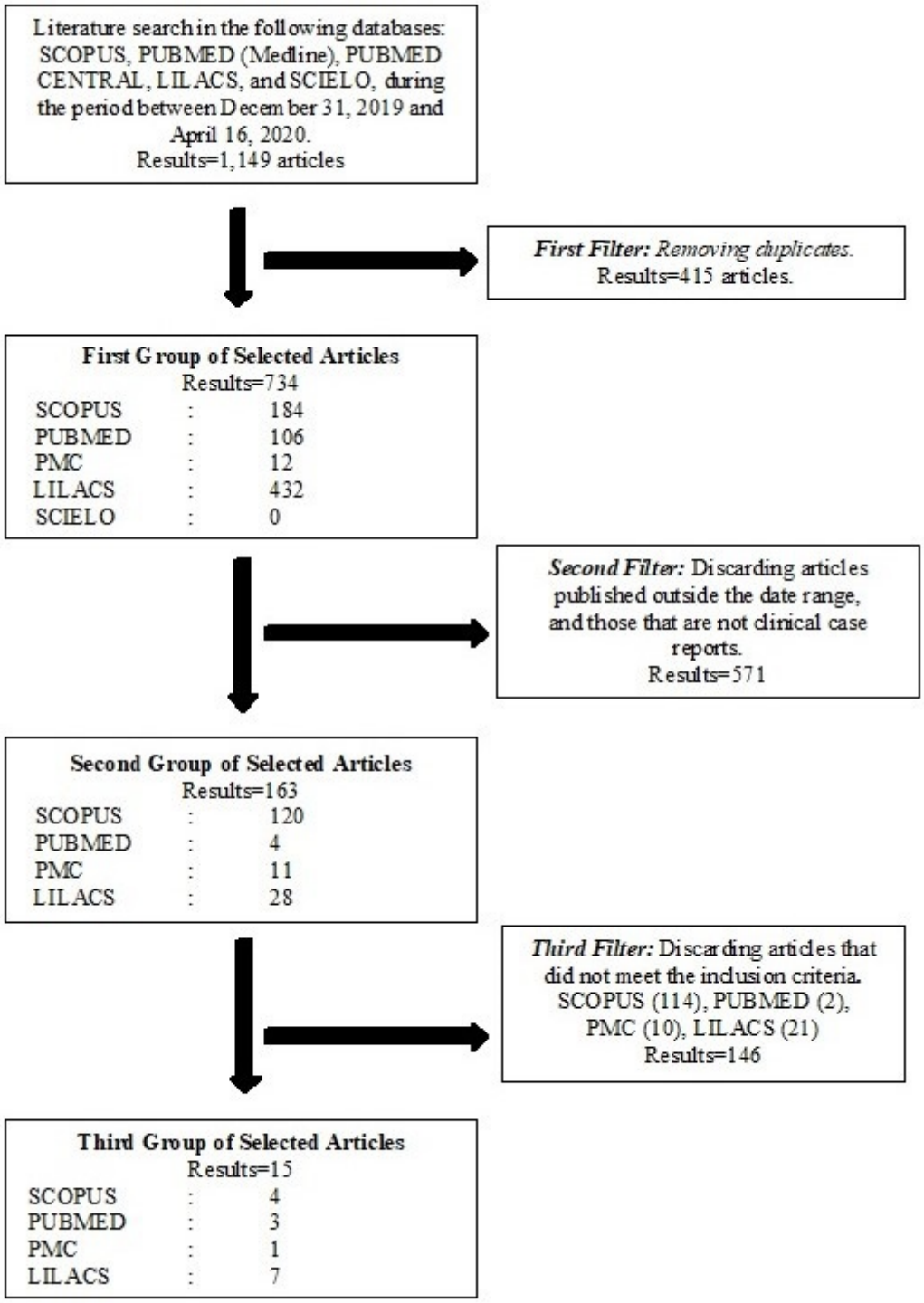

Figure 1. Eligibility screening for systematic review.

Table 2. Clinical characteristics of older patients with COVID-19 infection.

Features		Total cases	Outpatient management cases	Hospitalization management cases[¢]	ICU management cases*
Number		27	3	26	13
Age, median (IQR**)		65 (63–70)	65 (63–66)	65 (63–67.8)	66 (63–69)
Age (%/n)					
60–69		74.1/20	100/3	76.9/20	76.9/10
70–79		22.2/6	0	19.2/5	15.4/2
≥80		3.7/1	0	3.8/1	7.7/1
Sex (%/n)					
Women		48.1/13	33.33/1	50/13	53.8/7
Men		51.9/14	66.7/2	50/13	46.2/6
Possible city of infection (%/n)					
Wuhan-Hubei		63/17	66.7/2	65.4/17	61.5/8
Other than Wuhan		29.6/8	33.3/1	30.8/8	30.8/4
No data available		7.4/2	0	3.8/1	7.7/1
Critical times					
Contact and onset of symptoms	mean±SD	6.97±3.23	-	7.43±2.57	6.56±3.84
	n	15		7	8
Onset of symptoms and medical evaluation	mean±SD	3.50 (1.25–7.75)[€]	-	3 (1–4.75)[€]	5.83±4.63
	n	24		12	12
Onset of symptoms and hospital admission	mean±SD	6.00 (3.00–8.00)[€]	-	6.09±5.17	7.08±3.94
	n	23		11	12
Onset of symptoms and appearance of dyspnea	mean±SD	7±5.29	-	4±6.08	7.75±5.08
	n	15		12	3
Medical history (%/n)					
Arterial hypertension		37./9	-	-	38.5/5
Coronary heart disease		3.7/1			0
Heart failure		3.7/1			0
Diabetes mellitus		14.8/4	-	-	15.4/2
Chronic bronchitis		3.7/1	-	-	7.7/1
Oncological disease[β]		11.1/3	-	-	7.7/1
Chronic kidney disease		7.4/2	-	-	7.7/1
Non-nephrotic proteinuria		3.7/1	-	-	0
Others[$]		14.8/4			57.1/4
At least one comorbidity		51.8/14	-	-	53.8/7
Two or more comorbidities		22.2/6	33.3/1	19.2/5	7.7/1

Continue...

Table 2. Continuation.

Features	Total cases	Outpatient management cases	Hospitalization management cases[Ç]	ICU management cases*
Symptoms and Signs (%/n)				
Fever (%/n)¶	88.9/24	-	92.3/24	85.7/6
Maximum temperature mean±SD (n)	38 (37.7–39) [€]	-	38.39±0.6 (9)	36.4±1.20 (2)
Maximum temperature (%/n)				
≤37.5	18.2/2	0	0	100/2
37.51–38.3	36.4/4	0	44.4/4	0
≥38.3	45.5/5	100/3	55.6/5	0
Cough (%/n)	70.4/19	-	79.2/19	-
Dry cough	31.6/6	-	-	-
Not specified	68.4/13	-	-	-
Dyspnea[ϴ]	59.3/16	-	57.7/15	100/13
Myalgia	25.9/7	-	26.9/7	30.8/4
Chills	22.2/6	-	23.1/6	30.8/4
Fatigue	22.6/6	-	23.1/6	0
Dizziness	7.4/2	-	7.7/2	7.7/1
Sore throat	7.4/2	-	8.7/2	0
Diarrhea	7.4/2	-	7.7/2	15.4/2
Rhinorrhea	3.7/1	-	4.3/1	0
Other symptoms	22.2/6	-	19.2/5	7.7/1
Syncope	3.7/1	-	3.8/1	0
Headache	3.7/1	-	3.8/1	0
Thoracic oppression	3.7/1	-	3.8/1	0
Nausea or vomiting	7.4/2	-	3.8/1	7.7/1
Back pain	3.7/1	-	3.8/1	0
Symptoms leading patients to seek medical care				
Fever	44.4/12	-	-	46.15/6
Cough	14.8/4	-	-	7.69/1
Dyspnea	7.4/2	-	-	15.38/2
Fatigue	3.7/1	-	-	0
Diarrhea	3.7/1	-	-	7.69/1
Syncope	3.7/1	-	-	1
Dizziness	3.7/1	-	-	7.69/1
Myalgia	3.7/1	-	-	7.69/1
Thoracic oppression	3.7/1	-	-	0

Ç: in three cases, patients were initially discharged and followed by outpatient management. However, they were subsequently admitted to the hospital. After medical evaluation, 23 other cases were admitted to the hospital. β: three patients had a history of oncological disease: multiple myeloma, thyroid cancer, and gastric cancer. *: Of the 27 cases, one patient was directly admitted to ICU, whereas 12 patients were initially admitted to the hospital and then transferred to ICU (n=3). SD: Standard deviation. IQR: interquartile range. €: do not present normal distribution according to the statistical test of Shapiro-Wilk ($p<0.05$), being expressed as median (IQR). ¶: six patients (n=6) who presented fever and chills. ϴ: respiratory distress symptoms were assessed in the first medical evaluation and throughout the disease process.

Table 3. Chest radiography and tomography features in older patients with COVID-19 infection.

Characteristics	Upon admission (n=27)	During hospitalization (n=27)	During ICU stay (n=13)
Chest X-ray performed (%/n)	37/10	44.4/12	57.1/4
Chest X-ray parenchymal radiopacity (%/n)			
Consolidation	40/4	16.7/2	75/3
Ground-glass opacification	10/1	58.3/7	25/1
No radiopacity	30/3	0	0
Affected lung (%/n)			
Right lung	10/1	0	25/1
Left lung	10/1	0	0
Bilateral	40/4	100/12	75/3
Injury distribution (%/n)			
Peripheral	20/2	66.7/8	0
Perihilar	10/1	8.3/1	0
Both	10/1	0	25/1
Injury localization (%/n)			
Basal opacities	30/3	75/9	50/2
Apical opacities	0	0	0
Other locations	10/1	0	25/1
Other findings (%/n)			
Pleural effusion	0	58.3/7	25/1
Nodular lesion	0	0	50/2
Chest CT scan performed (%/n)	37/10	66.7/18	57.1/4
Affected lung (%/n)			
Right lung	20/2	11.1/2	0
Left lung	10/1	0	0
Bilateral	50/5	83.3/15	75/3
Injury localization (%/n)			
Central injuries	10/1	5.6/1	ND
Peripheral lesions	20/2	61.1/11	ND
Both	20/2	5.6/1	ND
Main parenchymal pattern			
Ground-glass Opacification	70/7	88.9/16	75/3
Consolidation	10/1	5.6/1	0
Reticular	0	0	0
Mixed	0	0	25/1
Other findings (%/n)			
Nodular lesion	10/1	16.7/3	50/2
Thickened interlobular	20/2	22.2/4	50/2
Nonspecific injury margin	ND	11.1/2	ND
Crazy-paving pattern	30/3	16.7/3	50/2
Cystic lesion	ND	ND	25/1
Pleural thickening	ND	16.7/3	50/2
Pleural effusion	ND	44.4/8	25/1
Lymphadenopathy	30/3	16.7/3	50/2

ICU: intensive care unit; ND: no data.

proportion of older people living in nursing homes failed to be hospitalized and died, drawing attention to their limited access to healthcare services such as an adequate management with a comprehensive geriatric approach, including palliative care.[19,28-30]

Moreover, health profiles, stress response, and functional ability of older adults significantly vary. While some of them have low intrinsic capacity — i.e., they are care-dependent —, others have high functional capacities and actively participate in and contribute to their communities.[31] Geriatric medicine has shown that efficient health interventions in older adults should be determined by the conditions of frailty, functional ability, and care dependence of older adults.[32-35] In addition, reporting and generating information on some specific variables, such as polypharmacy, living in long-term care facilities, multiple comorbidities, and physical dependence, would enrich the literature on COVID-19 and older people available to date.[20,36] However, in this investigation, no case report referred to the evaluation of functionality, frailty condition, functional, cognitive and emotional state, or to polypharmacy or regular residence in long-term institutions. All of these aspects are considered important for the prognosis of older people.

Regarding the epidemiological characteristics of older adults with COVID-19, this study, like reports from other countries,[5,20,31-38] found that men aged 60 to 69 years were the most affected and that more than half of older people with COVID-19 had some comorbidity, and this proportion is much higher when compared with young patients with underlying conditions.[39] For Liu et al.,[38] these findings would indicate weaker immune functions in male older adults, thus increasing the risk of infection by SARS-CoV-2.

Table 4. Laboratory parameters of older patients with COVID-19 infection.

	Normal values	During hospitalization (n=26)	During ICU stay (n=7)
Laboratory values mean±SD (n)			
PaO_2/FiO_2 ratio	>400	157.75±68.26	81±7.07 (2)
Hemoglobin (g/dl)	13–17.5	13 (5)	-
Leukocytes count (*10^9/L)	3.5–9.5	4.61 (4.13–6.73)/17€	17.54±5.87 (3)
Lymphocytes count (*10^9/L)	1.10–3.20	0.72±0.28 (17)	0.42±0.08 (3)
Neutrophils count (*10^9/L)	1.8–6.3	3.92±1.46	-
Platelets count (*10^9/L)	150-450	137.46±37.87	-
CD4 (cells/µL)	34–52	39.32±10.61	-
CD8 (cells/µL)	21–39	17.28±5.80	-
Myoglobin (ng/mL)	0–110	40.10 (32.7–111.9)/7€	-
Troponin (ngmL)	0–0.1	0.012 (0.012–0.014)/(8) €	-
Creatine phosphokinase -MB (ng/ml)	0–2.37	0.90 (0.23–42.00)/11€	-
Lactate dehydrogenase (UI/L)	114.0–240.0	502±310.90 (14)	-
Glutamic-oxaloacetic transaminase (GOT/AST) (UI/L)	5-40	33.6 (24.6–49.00)/13€	-
Glutamic pyruvic transaminase (GPT/ALT) (UI/L)	5-40	26.5 (16.50–39.65)/13€	-
Albumin (g/L)	40.0–55.0	38.28±2.99 (11)	-
C-reactive protein (mg/L)	<10	58.26±34.42 (16)	208±93.24 (3)
Creatinine (µmol/L)	58–110	81.90 (53.55–98.50)/13€	-
Urea (mmol/L)	0.5-2.7	9.44±4.93 (12)	-
Interleukin 6 (pg/mL)	<1.5	232.53±209.97 (3)	-
D-dimer (mg/L)	<0.5	0.45 (0.30–0.60)/4€	-
Procalcitonin (ng/mL)	0–0.5	0.09 (0.04–0.20)/8€	-

€: non-Gaussian distribution according to the Shapiro-Wilk statistical test ($p<0.05$), in such a way that they are expressed as median and interquartile range (IQR/n); NV: normal values.

Clinical manifestations

Furthermore, a large percentage of older adult patients with COVID-19 included in this review had fever when admitted to the hospital, a fact that has also been reported by other investigations[40,41] in middle-aged groups. Likewise, Zhou et al.[42] report an average of 11 days lapsing from the onset of symptoms to admission in patients aged 46 to 67 years and an average of seven days from the onset of the first symptom to the appearance of dyspnea. In contrast, this study found that, in this population, an average of six days lapsed from the onset of the first symptom to hospitalization, and an average of seven days until the onset of dyspnea.

An important result of this investigation suggests that dyspnea is not a frequent symptom at hospital admission in adults and older patients with COVID-19, but is rather developed later. This is consistent with the severity of the disease. Previous studies have shown that the duration from symptom onset to dyspnea was 7–8 days in patients with COVID-19,[41,42] one day after hospital admission. Those studies have also shown that only 18.7% of patients have dyspnea at the time of admission,[19,40-43] but it was usually more frequent in patients admitted to the ICU, who required mechanical ventilation, or who died.[43,44] Although these investigations focused their study on the adult population, these

Table 5. Medication pattern among older patients with COVID-19 infection at the Intensive Care Unit and at the hospital.

Treatments (%/n)	During hospitalization (n=27)	Destination after hospitalization			During ICU stay (n=13)	Destination after ICU stay		
		Medical discharge	ICU	Not specified		Medical discharge	Death	Stay in ICU
Antibiotics	14.8/4	25/1	50/2	25/1	30.77/4	50/2	25/1	25/1
Antivirals	51.9/14	14.3/2	64.3/9	21.4/3	30.77/4	50/2	25/1	25/1
Lopinavir-Ritonavir	37.5/5	20/1	60/3	20/1	75/3	66.7/2	0	33.3/1
Oseltamivir	28.6/4	0	100/4	0	0	0	0	0
Ribavirin	50/7	0	85.7/6	14.3/1	0	0	0	0
Others	85.7/12	16.7/2	58.3/7	25/3	15.4/2	0	0	0
Interferon	57.1/8	0	75/6	25/2	0	0	0	0
Umifenovir	21.4/3	66.7/2	33.3/1	0	7.7/1	0	0	100/1
Abidor	7.14/1	0	0	100/1	0	0	0	0
Remdesivir	-	-	-	-	7.7/1	0	100/1	0
Antimalarial treatment								
Hydroxychloroquine	100/2	0	100/2	0	15.4/2	100/2	0	0
Immunological treatment	14.8/4	50/2	25/1	25/1	23.1/3	66.7/2	0	33.3/1
Gamma globulin	75/3	33.33/1	33.33/1	33.33/1	7.7/1	0	0	100/1
Tocilizumab	25/1	100/1	0	0	-			
Convalescent plasma	-	-	-	-	15.4/2	100/2	0	0
Other treatments								
Chinese Traditional Medicine	11.1/3	33.33/1	33.33/1	33.33/1	7.7/1	0	0	100/1
Abidor+"Chinese Traditional Medicine"+Methylprednisolone	33.3/1	0	0	100/1	0	0	0	0
Lopinavir/Ritonavir/ Umifenovir+Shufeng Jiedu (SFJDC)	66.67/2	50/1	50/1	0	100/1	0	0	100/1
Methylprednisolone	23.1/3	33.33/1	0	33.7/1	15.4/2	100/2	0	0

ICU: intensive care unit.

results are similar to those found in the present review, considering the low median age of older people already discussed. In contrast, the absence of dyspnea at the time of the medical consultation can be explained by Gattinoni et al.,[45] who indicate that patients infected with SARS-CoV-2 would initially have severe hypoxemia due to vasoplegia, which, on account of low lung compliance, can increase ventilation and compensate it. This phenomenon is called silent hypoxemia.

Radiological findings

Regarding the imaging findings, it was evident that the most predominant radiological finding at the time of admission, during hospitalization, and in the ICU was the ground-glass opacification pattern, a result similar to that found in other studies.[46-51] However, this investigation only found a few cases with sequential radiological examinations. In this regard, it is worth considering the timing of the X-ray or CT, since there is evidence that the patterns may vary specifically depending on the timing of the natural history of the disease.[47] Thus, it is suggested that, in future radiological studies, the day of the imaging examination should be considered regarding the patients' onset of symptoms. Likewise, it was found that the locations of the lesions were mostly peripheral, which is in accordance with what has been reported in younger ages.[47-50] Conversely, Salehi et al.,[48] found atypical initial imaging presentation of consolidative opacities superimposed on ground glass mainly in older populations. In this review, a basal consolidation pattern was more frequent observed in plain chest X-rays, whereas, the ground-glass pattern is more likely to be observed in CT scan. Therefore, the imaging findings in older people do not differ from that found in younger age groups, and the CT scan, due to its high sensitivity for the diagnosis of COVID-19,[51] could potentially be used as a detection technique in epidemic areas. Nevertheless, it is necessary to carry out more studies and consider a larger sample to determine this hypothesis.

Laboratory features

Moreover, alterations in laboratory tests were similar to those presented in other articles for middle-aged groups.[52,53] Concerning altered values, the PaO_2/FiO_2 ratio was less than 150 in most of the patients, demonstrating that the infection causes a severe level of hypoxemia.[53] In the white series, leukocytosis in patients admitted to the ICU was found. In contrast, lymphopenia worsens during the ICU stay, with decrease in the CD8 lymphocyte group. These findings corroborate another study in which decreases in leukocytosis, CD8 lymphocytes, and Natural Killer cells occur, possibly associated with overexpression of the Natural-Killer receptor group 2-A (NKG2A), which is induced by SARS-CoV-2 causing functional fatigue of the lymphocytes from the initial phase of the disease.[54,55] The evaluation of troponins was normal, despite 37% of the patients having some cardiovascular history. A meta-analysis found that troponins were elevated in patients with severe COVID-19.[56] Finally, the presence of increased urea values is associated with higher hospital mortality in COVID-19 patients due to reported kidney involvement.[57]

It is worth emphasizing that, according to laboratory evidence, the inflammatory process has been present in older people with COVID-19 since hospitalization. According to Zhao et al.,[58] in a study that included 82.4% older people, the increase in C-reactive protein, interleukin 6, and procalcitonin was observed in more than 60% of cases. Likewise, another study indicated that increased lactate dehydrogenase and C-reactive protein are strongly associated with the presence of severe COVID-19 disease.[59] Both results are supported by Chen et al.,[43] who indicate that low values of these markers are associated with patients who recovered from the disease. On the other hand, excessive increase in IL-6 after acute lung damage leads to multiple organ failure (MOF) and to a cytokine storm.[45] Additionally, increase in C-reactive protein may be partly attributed to the effects of IL-6.[60] Although the production of procalcitonin in viral infections is inhibited by interferon (INF-y), procalcitonin is elevated in severe patients. This could reflect the presence of an over-aggregated bacterial infection, which would cause increase in the concentrations of interleukin 1 beta (IL1-b), tumor necrosis factor alpha (TNF-a), and IL-6.[61]

Used therapies

Regarding treatment, antivirals were the most frequently used drugs in older adults, but their efficacy for the treatment of COVID-19 is unclear. This review found that 51.9% of hospitalized older patients with COVID-19 received some antiviral; however, 64% of them ended up in the ICU. One of the most widely used antivirals was Lopinavir-Ritonavir. Nevertheless, the only clinical trial of this drug observed that hospitalized adult patients with severe COVID-19 did not show any benefits over standard care.[62] The second most widely used antiviral during hospitalization in the reviewed cases was Interferon. Recently, a clinical trial carried out by Hung et al.,[63] evaluated the triple therapy of Interferon beta-1b, Ribavirin plus Lopinavir-Ritonavir, finding that this combination has better performance than the treatment with Lopinavir-Ritonavir alone in alleviating symptoms and shortening duration of virus clearance and hospital stay in patients with mild to moderate COVID-19 infection. However, this study did not have a placebo group and the triple therapy was only

administered to those patients with an illness duration of seven days or less. On the other hand, Remdesivir, an experimental antiviral (GS-5734), has been subject to only one clinical trial to date; such study found that adult patients with a median age of 65 years, admitted to the hospital for severe COVID-19, and given the drug had no clinical benefits.[64] Nevertheless, the complete results of a clinical trial funded by the US National Institute of Allergy and Infectious Diseases are still being evaluated and, according to its preliminary report, such drug would have shortened the recovery time of hospitalized adults with COVID-19 (average age of 59 years).[65] Other antivirals, such as Oseltamivir, have limited activity against SARS-CoV-2, while Favipiravir and Umifenovir, the internationally available influenza antivirals, have different viral targets and require further investigation.[66]

Likewise, aminoquinolines was not frequently used for the treatment of older people (two out of the 27 cases); however, the latest studies on aminoquinolines are controversial. Initially, Gautret et al.,[67] found that Hydroxychloroquine treatment was significantly associated with reduced viral load in patients with COVID-19 and its effect was enhanced by Azithromycin. However, this study did not include the criterion of clinical severity of participants, the mean age was around 51.2 years, no randomization was used, and sample size was limited. Then, Tang et al.,[68] found that Hydroxychloroquine treatment did not result in a significantly higher likelihood of negative conversion than standard care alone of hospitalized adult patients (mean age of 46 years) with mild to moderate COVID-19 infection. Other observational studies found that treatment with Hydroxychloroquine, Azithromycin, or both was not significantly associated with differences in hospital mortality,[69] risk of intubation, or death,[70] and it did not appear to have any effect on reducing admissions to intensive care or death.[71] Furthermore, in patients aged 60 years and older, Hydroxychloroquine for the treatment of COVID-19 has a high risk of prolongation of the corrected QT (QTc) interval, and concurrent treatment with Azithromycin is associated with greater changes in electrocardiogram.[72] To date, the clinical trial from Mehra et al.,[73] conducted with 96,032 adult patients (mean age of approximately 53.8 years), the largest sample to date, failed to determine a benefit of Hydroxychloroquine or Chloroquine, when used alone or with a macrolide, in the hospital results of COVID -19; those who did not survive had a mean age of 60 years and had some comorbidity. Thus, taking into account the current evidence, the administration of aminoquinolines in older people should be done with caution and be strictly monitored, considering adverse effects and polypharmacy due to the large number of interactions with other drugs. Even in countries where Hydroxychloroquine has been indicated to treat COVID-19, such use should be reconsidered or the monitoring and care should be strengthened.

As for immunological treatments in older adults with COVID-19, scientific evidence is insufficient to support their use; however, new clinical evidence could shed light on such treatments. To date, there are no published results of clinical trials on convalescent plasma treatment,[74] except one clinical trial (NCT04345991) that will finish its study in June 2021[75] and nine others that will be completed in the following months. However, no specification has been given on whether they will assess older people and whether the results of this group will be separately presented. Similarly, there are no clinical trials to support Tocilizumab treatment. However, the relevant intervention of IL-6 in cytokine storm allows some authors to theorize that Tocilizumab may become an effective medicine for patients with severe COVID-19.[46]

An important outcome of the present study was the scarce information found in the literature regarding case reports of COVID-19 infection in adults aged over 80 years.

In addition, the authors found no evidence of case reports of COVID-19 infection in older patients that considered specific conditions, such as frailty, dementia, emotional status, level of functionality, polypharmacy, and others, and how to manage them.

The age group was between 60 to 69 years, and the main clinical, laboratory, radiological, and therapy-related findings were as follows: a) more than one comorbidity; b) fever, which was the most frequently reported manifestation at hospital admission; c) dyspnea, which was the most frequently reported manifestation at hospitalization; d) imaging of ground-glass opacification, which was the main outcome at hospital admission and hospitalization; e) increased level of lactate dehydrogenase, C-reactive protein, interleukin 6, and procalcitonin were the most frequently observed features; and f) antivirals, Hydroxychloroquine, antibiotics, corticoids, monoclonal antibodies, and herbal drugs were used as treatment options.

Authors' contributions. ASG, JPG, LSC, AMV, ELC, and EMM: conceptualization, data curation, project administration and funding acquisition. LSC, AMV, ELC, EMM, IAV, JSR, DPP, EYC MCHA, MGF, AMR, CZR, PAM, ZBV, NPG, DQLT, AAM, LGM, MRM, and MGO: investigation, methodology, resources, software, and validation. ASG, JPG, LSC, AMV, ELC, and EMM: visualization, and writing. ASG, and JPG: The final writing version.

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Dement Neuropsychol 2021 March;15(1):16-27

Original Article

https://doi.org/10.1590/1980-57642021dn15-010002

Language in corticobasal syndrome: a systematic review

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ABSTRACT. Language is commonly impacted in corticobasal syndrome (CBS). However, the profile and type of language assessment in CBS are poorly studied. **Objective:** To identify language impairments in CBS. **Methods:** A search was performed in the Medline/PubMed database, according to the PRISMA criteria, using the keywords "corticobasal syndrome" OR "corticobasal degeneration" AND "language". Articles on CBS covering language assessment that were written in English were included, with no constraints on the publication date. **Results:** A total of 259 articles were found and 35 were analyzed, consisting of 531 participants. Twenty-eight studies showed heterogeneous language deficits and seven mentioned nonfluent primary progressive aphasia. The most used tests were the Western Aphasia Battery (8 studies) and the Boston Naming Test (8 studies). **Conclusion:** It was not possible to identify a unique linguistic profile in CBS.

Keywords: corticobasal syndrome, language, neurocognitive disorders, language tests.

LINGUAGEM NA SÍNDROME CORTICOBASAL: UMA REVISÃO SISTEMÁTICA

RESUMO. A linguagem encontra-se comumente alterada na síndrome corticobasal (SCB). No entanto, o perfil e a forma de avaliação da linguagem na SCB são pouco estudados. **Objetivo:** identificar as alterações de linguagem na SCB. **Método:** Realizou-se uma busca na base de dados Medline/PubMed, com as palavras-chave "síndrome corticobasal" OU "degeneração corticobasal" E "linguagem". Artigos sobre SCB envolvendo avaliação de linguagem, escritos em inglês, foram incluídos, sem restrição de data de publicação. **Resultados:** Foram encontrados 259 artigos, e 35 estudos foram analisados, abrangendo 531 sujeitos. Um total de 28 estudos mostraram déficits heterogêneos de linguagem, e sete mencionaram afasia progressiva primária não-fluente. Os testes mais utilizados foram Western Aphasia Battery (8 estudos) e o Teste de Nomeação de Boston (8 estudos). **Conclusão:** Não foi possível identificar um perfil linguístico único em pacientes com SCB.

Palavras-chave: síndrome corticobasal, linguagem, transtornos neurocognitivos, testes de linguagem.

INTRODUCTION

Corticobasal syndrome (CBS) is a progressive, neurodegenerative disease classified amongst atypical parkinsonian syndromes. The syndrome was first described in 1967 by Rebeiz, Kolodny, and Richardson, who presented three cases of patients with initial significant motor impairments followed by final stage cognitive impairments.[1] The initial description focused on motor deficits and showed that cognitive impairments only occurred in the final stage, but it is now known that both can occur in equal proportion in CBS and may manifest as the first symptom.[2-6]

The terms "corticobasal syndrome" and "corticobasal degeneration" (CBD) represent distinct entities. The former denotes the clinical phenotype, whereas CBD is a pathological entity affecting cortical and subcortical regions, whose diagnosis can

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Disclosure: The authors report no conflicts of interest.

Funding: none.

Received on June 03, 2020. Accepted in final form on December 02, 2020

only be confirmed by *postmortem* anatomopathological analysis.[5] An estimated 50% of patients with clinical symptoms of CBS are diagnosed with CBD at *postmortem*. In the remaining patients, tauopathies or amyloid pathology are generally found, such as Alzheimer's disease (AD). CBD is often found in patients clinically diagnosed with other syndromes.[5,7-9]

In CBS, classically, motor symptoms occur asymmetrically and include akinetic-rigid parkinsonism, dystonia, and myoclonic movements. Cognitive symptoms include apraxia, aphasia, cortical sensory deficits, and the alien hand phenomenon.[5,10,11] This syndrome is generally challenging to diagnose owing to its clinical, pathological, radiological, and neuropsychological heterogeneity.[5]

Few studies have thoroughly investigated the profile of speech and language impairments in CBS. Some studies show a pattern similar to the nonfluent variant of primary progressive aphasia (nf-PPA), i.e., deficits at a morphosyntactic level, reduced fluency and apraxia of speech.[3,12-14] However, other studies focusing on language assessment reveal a mixed pattern encompassing characteristics of more than one type of primary progressive aphasia (PPA).[15,16]

This heterogeneity found in the literature on speech and language in CBS may be explained by multiple factors: disease stage at the time of assessment, different underlying pathologies[6] or lack of consensus on linguistic aspects to be assessed in these patients. Gorno-Tempini et al.[17] recommended that language assessment in PPA cover the following domains: naming, word and sentence comprehension, word and sentence repetition, syntactic processing, semantic memory, reading, and motor aspects of speech.

The present review aimed to identify the language impairments in CBS patients.

METHODS

The writing of this manuscript is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (www.prisma-statement.org), according to the following recommendations: introduction containing the description of the rationale and objectives of the review; methods containing the eligibility criteria, the information sources, the process for selecting studies, the data collection process, the definition of all variables for which data were sought, the methods used for assessing risk of bias of the studies, and how the results were analyzed; and discussion containing the summary of evidence, the limitations and the conclusions of the review.

The outcome of interest of this review is the profile of language in patients with CBS. Articles on CBS covering speech and language assessment were included, with no constraints on the publication date. Exclusion criteria were: 1) studies on CBD associated with syndromes other than CBS; 2) intervention studies in CBS; 3) studies written in languages other than Portuguese or English; 4) studies that could not be accessed via our University and were not open access.

The literature search was conducted using the electronic database Medline/PubMed, and it was based on manuscripts published up to February 2020. The keywords used were the following: "corticobasal syndrome" AND "language", "corticobasal degeneration" AND "language". The search was guided by the Population, Intervention, Comparison and Outcome (PICO) strategy. The population refers to the CBS patients, the intervention refers to the language assessment, the comparison is related to intragroup or between group comparisons, and the outcomes are the results from the language assessment.

All titles and abstracts were independently screened by two authors (IJA and MLS), according to the eligibility criteria previously established. The articles that were not excluded in this screening stage were fully read. A disagreement between the authors was resolved by consensus.

One author (IJA) extracted data from included studies and a second author (MLS) checked the information. Data were transferred to a data extraction sheet (using Microsoft Excel®) and included: 1) first author's name and year of publication; 2) sample size; 3) clinical and demographic data (gender, age, disease duration); 4) main speech and language results; and 5) speech and language tests used in the evaluation or speech and language abilities evaluated (when tests not mentioned). We classified the studies into three categories based on language evaluation:

- Comprehensive assessment: evaluation included all language domains recommended for testing PPA patients.[17]
- Restricted assessment: evaluation included some of the language domains recommended for testing PPA patients.[17]
- No tests or language skills mentioned: the tests or language skills evaluated were not reported.

Two authors (IJA and MLS) independently assessed the methodological quality and the risk of bias of the manuscripts included in this review through the JBI Critical Appraisal tool for cross-sectional studies.[18] This tool has eight questions regarding the criteria for inclusion of the sample, the clarity of the description of the sample and the setting, the validity and reliability of the outcomes' measurement, the appropriateness of statistical analysis and four questions that refer

exclusively to clinical trial studies. Each question must be answered as "yes", "no", "unclear" or "not applicable". All the questions regarding clinical trials were marked as "not applicable". Each question that was marked as "yes" received 1 point. The question that refers to the outcome measurement was answered exclusively on the basis of the language evaluation described in each study. For most studies included, language was only one of the clinical characteristics assessed.

Discrepancies between the two authors were discussed until consensus was reached. All manuscripts were then classified into one of three groups, according to the score obtained on the JBI Critical Appraisal tool: "low quality", if the study had less than 50% of the maximum score; "moderate quality", for studies with 50 to 80% of the maximum score; and "high quality", for studies with at least 80% of the maximum score.

Finally, confidence in the overall findings of the present review was assessed through the Confidence in the Evidence from Reviews of Qualitative Research (GRADE CERQual).[19] This instrument is based on four components: 1) methodological limitations of the primary studies, 2) relevance of those studies to the review question, 3) coherence of results among primary studies, and 4) adequacy of data, i.e., the degree to which data support the review finding. From the analysis of these four components, the review may be classified as high confidence ("it is highly likely that the review finding is a reasonable representation of the phenomenon of interest"), moderate confidence ("it is likely that the review finding is a reasonable representation of the phenomenon of interest"), low confidence ("it is possible that the review finding is a reasonable representation of the phenomenon of interest"), and very low confidence ("it is not clear whether the review finding is a reasonable representation of the phenomenon of interest).[19]

The first component, methodological limitations, was judged using the JBI Critical Appraisal tool. Relevance, coherence and adequacy of data were judged exclusively on the basis of the language evaluations of primary studies.

Two authors (IJA and MLS) independently scored each component of the CERQual tool and its final classification. Discrepancies were discussed until consensus was reached.

RESULTS

The search on the Medline/PubMed database led to the retrieval of 259 articles, of which 79 were duplicate articles, giving a total of 180. After a screening of titles and abstracts, another 128 articles were excluded (literature reviews, letters to editor, articles in Japanese, studies on unrelated topics and inaccessible articles). A total of 52 articles were read in full, of which 17 were subsequently excluded (studies on CBD associated with syndromes other than CBS and studies on unrelated topics). We included 35 manuscripts in the present review (Figure 1).

Due to the heterogeneity of the population and outcomes of the studies included, it was not possible to perform a meta-analysis.

The demographic and clinical data of the studies are given in Table 1. The sample size was very heterogeneous, ranging from 1 to 55 CBS patients, with a median value of 11 and a mean of 15.2. CBS patient age ranged from 47 to 76 years, with a median of 66.2 and mean of 65.31 years. The mean number of female patients in the studies was slightly higher than that of male patients (12.14 and 8.9, respectively). Disease duration at the time of assessment ranged from 3 months to 8.08 years, with a median of 3.32 and mean of 3.46 years.

The profile of language impairments is given in Table 2. Seven studies (20%) cited nf-PPA as the predominant language deficit profile in patients with CBS.[4;12-14,20-22] Twelve studies (34.28%) investigated specific aspects of language.[23-34] In two (5.71%) studies, the language impairments were not described in detail.[26-35] The remaining studies mentioned a variety of different symptoms, including agraphia[15,23,31,36-39] speech apraxia,[2,23,36,37,39,40] dysarthria,[36,41] a mixed type of PPA,[16] logopenic variant of PPA (L-PPA),[15,21] anomic aphasia,[3,4,42] transcortical motor aphasia[42] and Broca's aphasia.[42]

The tests used for assessment and classification of type of evaluation are also given in Table 2. The most

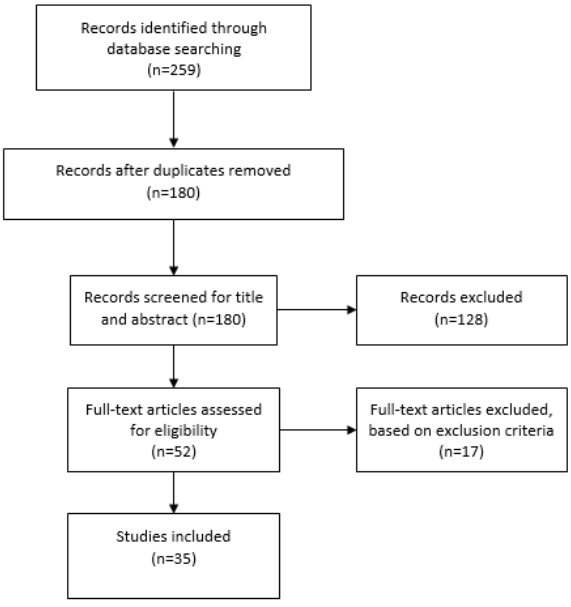

Figure 1. Literature search flow diagram.

Table 1. Sociodemographic and clinical characteristics of studies selected.

Authors, year of publication	Sample size	Gender (male/female)	Age (years)	Disease duration (years)
Kertesz et al., 2000[2]	35	movement disorder=5/10 cognitive disorder=14/6	movement disorder=61.9 cognitive disorder=63.6	movement disorder=5.4 cognitive disorder=7.1
Frattali et al., 2000[42]	15	8/7	67.7	4.5
Graham et al., 2003[50]	10	7/3	67.6	3.35
Frattali et al., 2003[26]	prospective study=34 retrospective study=9	prospective study=18/16 retrospective study=4/5	prospective study=67.91 retrospective study=71.3	prospective study=3.8 retrospective study=2.78
Gorno-Tempini et al., 2004[20]	1	0/1	not applicable	not applicable
McMonagle et al., 2006[3]	55	motor onset=10/9 cognitive onset=16/20	n/a	motor onset=2.7 cognitive onset=3.6
McMillan et al., 2006[32]	16	n/a	66.3	n/a
Cotelli et al., 2006[29]	10	n/a	63.8	n/a
Cotelli et al., 2007[30]	11	n/a	64.6	n/a
Donovan et al., 2007[23]	1	0/1	60	4
Koenig et al., 2007[28]	experiment 1=8 experiment 2=9	experiment 1=3/5 experiment 2=5/4	experiment 1=64.5 experiment 2=70.1	n/a
Silveri and Ciccarelli, 2007[31]	5	2/3	63.8	1.6
Halpern et al., 2007[27]	16	9/7	67.07	3.9
Kim et al., 2008[45]	1	1/0	55	n/a
Shelley et al., 2009[12]	12	6/6	75.5	8.08
Gross et al., 2010[24]	20	9/11	67.4	3.9
Valverde et al., 2011[35]	1	0/1	74	0,25
Borroni et al., 2011[47]	30	21/9	63.5	2.5
Troiani et al., 2011[33]	11	n/a	65.5	n/a
Passov et al., 2011[36]	1	0/1	49	2
Dopper et al., 2011[41]	1	1/0	61	2
Caso et al., 2012[21]	2	0/2	case 1=64 case 2=70	case 1=2 case 2=4
Assal et al., 2012[37]	1	0/1	64	n/a
Mathew et al., 2012[4]	40	22/18	70	initial assessment=3 follow-up=4.9
Sakurai et al., 2013[38]	1	0/1	65	n/a
Burrell et al., 2013[15]	14	7/7	66.1	2.9
Turaga et al., 2013[51]	17	11/6	66.35	4.06
Marshall et al., 2015[40]	1	0/1	47	1
Abe et al., 2016[13]	26	9/17	76	2.3
Di Stefano et al., 2016[16]	45	23/22	69.2	3.2
Ash et al., 2016[34]	33	15/18	65.3	4.2
Kim et al., 2016[22]	1	0/1	58	4
Magdalinou et al., 2018[25]	4	n/a	n/a	n/a
Mazzon et al., 2018[39]	1	1/0	74	1
Dodich et al., 2019[14]	33	15/18	70.4	3.06

n/a: not available.

Table 2. Profile of speech-language impairments, tests used for assessment, type of evaluation employed, and quality of studies included.

Authors, year of publication	Main speech/language results	Speech and language tests or abilities tested	Classification of the language evaluation	Quality of studies
Kertesz et al., 2000[2]	Initially, only word finding difficulties; verbal apraxia in 3/35 patients	WAB	Comprehensive assessment	High
Frattali et al., 2000[42]	Anomic, Broca's and transcortical motor aphasia	WAB (1st section)	Restricted assessment	Moderate
Graham et al., 2003[50]	Specific linguistic deficit involving phonologic processing	Letter fluency (FAS), semantic fluency, picture naming, word-picture matching, PPT, Single-word reading (The surface list), nonword reading, oral spelling, phoneme blending and phoneme segmentation	Restricted assessment	Moderate
Frattali et al., 2003[26]	Aphasia, without details	WAB (1st section)	Restricted assessment	Moderate
Gorno-Tempini et al., 2004[20]	nf-PPA	Motor speech evaluation, BDAE (verbal agility component, repetition), WAB (spontaneous speech section, written picture description, repetition, auditory word recognition, sequential command), BNT, PPT, CYCLE-R, PALPA (Regularity and Reading, Lexical Morphology and Grammatical Class, Homophone Decision), Gathercole and Baddeley's Non-Word Repetition task	Comprehensive assessment	High
McMonagle; Blair; Kertesz, 2006[3]	Majority classification of anomic aphasia (55%) in both groups (cognitive and motor onset), but more motor onset patients were normal and more cognitive onset patients had severe aphasias	WAB (1st section)	Restricted assessment	Moderate
McMillan et al., 2006[32]	Non-aphasic patients with CBD are significantly impaired in their comprehension of quantifiers	Sentence comprehension task	Restricted assessment	Moderate
Cotelli et al., 2006[29]	Action naming is impaired in FTD, PSP and CBS in comparison to object naming	Token Test, phonemic and semantic verbal fluency, action and object naming, Battery for Analysis of the Aphasic Deficits (action–object comprehension tasks)	Restricted assessment	Moderate
Cotelli et al., 2007[30]	CBS patients present with syntactic knowledge deficits	AAT (repetition, naming, writing and comprehension), BADA (sentence comprehension tasks)	Comprehensive assessment	Moderate
Donovan et al., 2007[23]	Aphasia, speech apraxia, alexia, agraphia, social language usage deficits	Pragmatic Protocol, Revised Token Test, WAB, BNT, Battery of Adult Reading Function, Woodcock Reading Mastery Tests, Comprehensive Test of Phonological Processing	Comprehensive assessment	High
Koenig et al., 2007[28]	CBS patients were impaired in similarity-based categorization process	Semantic decision task	Restricted assessment	Moderate
Silveri and Ciccarelli, 2007[31]	Hypofluent speech, agrammatism, anomia, word-finding difficulties, agraphia	Confrontation naming task of objects and verbs, semantic and phonemic fluency	Restricted assessment	Moderate

Continue...

Table 2. Continuation.

Authors, year of publication	Main speech/language results	Speech and language tests or abilities tested	Classification of the language evaluation	Quality of studies
Halpern et al., 2007[27]	CBS patients were less accurate and slower at judging smaller Arabic numeral dot array compared to FTD patients and controls	PPT	Restricted assessment	Moderate
Kim et al., 2008[45]	Language functions relatively preserved	BNT	Restricted assessment	Low
Shelley et al., 2009[12]	nf-PPA	n/a	No tests or language skills are mentioned	Low
Gross et al., 2010[24]	CBS patients have a higher-level deficit integrating described events into a coherent narrative	BNT, PPT	Restricted assessment	Moderate
Valverde et al., 2011[35]	Aphasic, without details	n/a	No tests or language skills are mentioned	Moderate
Borroni et al., 2011[47]	The AD-like group showed greater impairment of memory performances, language and psychomotor speed while the nAD-like group had more severe extrapyramidal syndrome	Semantic and phonemic verbal fluency, Token Test,	Restricted assessment	Moderate
Troiani et al., 2011[33]	CBS patients were significantly impaired in their judgments of quantified statements	Philadelphia Brief Assessment of Cognition (used to exclude aphasic patients), BNT, phonemic verbal fluency (FAS), Oral Sentence Comprehension Test, short sentence comprehension task	Restricted assessment	Moderate
Passov et al., 2011[36]	Mild apraxia of speech, mild hypokinetic dysarthria, apraxic agraphia	"Formal speech pathology evaluation"; picture description task; confrontation naming task; comprehension of simple and complex commands; writing; spelling; motor speech disorders	Comprehensive assessment	High
Dopper et al., 2011[41]	nonfluent speech with perseverations, word-finding difficulties and comprehension deficits, hypokinetic dysarthria	n/a	No tests or language skills are mentioned	Moderate
Caso et al., 2012[21]	nf-PPA, L-PPA	AAT, Token Test, phonemic and semantic verbal fluency	Comprehensive assessment	High
Assal et al., 2012[37]	crossed-PAOS followed by peripheral agraphia	Bachy 90-item battery (confrontation naming), MTL (auditory and written language comprehension, and writing), written descriptions of the Bank Robbery Picture, and the Cookie Theft Picture, and oral spelling with the French version of the WAIS III	Comprehensive assessment	Moderate
Mathew et al., 2012[4]	nf-PPA (60%) and anomic aphasia (40%)	n/a	No tests or language skills are mentioned	Moderate
Sakurai et al., 2013[38]	Progressive apraxic agraphia with micrographia, and acalculia	WAB, reading and writing test with 100 single-character kanji and kana transcription	Comprehensive assessment	Moderate

Continue...

Table 2. Continuation.

Authors, year of publication	Main speech/language results	Speech and language tests or abilities tested	Classification of the language evaluation	Quality of studies
Burrell et al., 2013[15]	Impaired single word repetition (61.5%), dysgraphia (58.3%), phonological errors in spontaneous speech (46.2%), impaired sentence repetition (38.5%), and word-finding difficulty (30.8%). Agrammatism and anomia were only occasionally identified. There was a trend for greater impairment of sentence repetition in PiB-positive cases	Motor speech disorder, phonological errors, agrammatism, word-finding difficulty, anomia, word and sentence repetition	Restricted assessment	Moderate
Turaga et al., 2013[51]	phonemic verbal fluency impairment	ACE-R (phonemic verbal fluency, semantic verbal fluency, naming)	Restricted assessment	Moderate
Marshall et al., 2015[40]	PAOS	n/a	No tests or language skills are mentioned	Moderate
Abe et al., 2016[13]	nf-PPA (34,61%)	Standard Language Test of Aphasia	Comprehensive assessment	High
Di Stefano et al., 2016[16]	Mixed progressive aphasia, including disorders of L-PPA (anomia, sentence repetition impairment) and S-PPA (deficits in single-word comprehension)	BDAE, picture naming test, single-word comprehension task, semantic and phonemic verbal fluency, sentence repetition test, assessment of motor speech disorders and agrammatism	Comprehensive assessment	High
Ash et al., 2016[34]	CBS were significantly impaired in the production of quantifiers	BNT, semantic verbal fluency, semi-structured speech sample (description of the Cookie Theft picture from the BDAE)	Restricted assessment	Moderate
Kim et al., 2016[22]	nf-PPA	WAB, BNT, semantic and phonemic verbal fluency	Comprehensive assessment	High
Magdalinou et al., 2018[25]	Impaired verbal fluency and sentence generation	BNT, Graded Naming Test, Verb Naming Task, PALPA (sentence comprehension), Sentence Production Program for Aphasia (expressive grammar), phonemic and semantic verbal fluency, National Adult Reading Test, sentence completion tasks	Restricted assessment	Moderate
Mazzon et al., 2018[39]	Apraxia of speech, characterized by slow overall speech rate, mild dysphonia, abnormal prosody, distorted and inconsistent speech sound substitutions, segmentation of syllables in words productions, mild dysgraphia with letter substitutions and omissions	Motor Speech Evaluation, AAT, Cookie Thief Test	Comprehensive assessment	High
Dodich et al., 2019[14]	nf-PPA, other language disorders	Connected speech production (speech apraxia and articulation difficulties, anomia, circumlocutions, agrammatism), CAGI battery (naming and word-picture matching), phonemic and semantic controlled associations, AAT (repetition), Token Test, BADA (sentence comprehension) phonemic (P-F-L) and semantic (animals-fruits-cars) verbal fluency	Comprehensive assessment	High

AAT: Aachen Aphasia Test; ACE-R: Addenbrooke's Cognitive Examination – revised; AD: Alzheimer's disease; BADA: Batteria per l'Analisi dei Deficit Afasici; BDAE: Boston Diagnostic Aphasia Examination; BNT: Boston Naming Test; CBD: corticobasal degeneration; CBS: Corticobasal syndrome; CYCLE-R: Curtiss-Yamada Comprehensive Language Evaluation-Receptive; FTD: frontotemporal degeneration; L-PPA: logopenic variant of primary progressive aphasia; MTL: Montreal-Toulouse Language Assessment Battery; n/a: not available; nAD: non-Alzheimer's disease; nf-PPA: Nonfluent variant of primary progressive aphasia; PALPA: Psycholinguistic Assessments of Language Processing in Aphasia; PAOS: Progressive apraxia of speech; PP: Pragmatic Protocol; PPA: primary progressive aphasia; PPT: Pyramids and Palm Trees; WAB: Western Aphasia Battery.

frequently used tests in the studies were the Western Aphasia Battery (WAB)[2,3,20,22,23,26,38,42,43] and the Boston Naming Test (BNT),[20,22-25,33,34,44,45] both mentioned by eight studies (22.85%). The Token Test[46] was used in five studies (14.28%)[14,21,23,29,47] and the Aachen Aphasia Test (AAT[48])[14,21,30,39] and Pyramids and Palm Trees (PPT)[20,24,27,49,50] featured in four articles (11.42%).

Regarding the type of evaluation employed in the studies, 13 (37.14%) used a comprehension speech/language assessment,[2,13,14,16,20-23,30,36-39] 17 (48.57%) used a restricted assessment,[3,15,24,29,31-34,42,45,47,50,51] while five (14.28%) failed to mention the tests or language skills evaluated.[4,12,35,40,41]

The assessment of methodological quality of the manuscripts is shown in Table 2. Ten studies (28.57%) were classified as "high quality",[2,13,14,16,20-23,36,39] 23 (65.71%) as "moderate quality",[3,4,15,24-35,37,38,40-42,47,50,51] and two (5.71%) as "low quality".[12,45]

GRADE CERQual analysis was carried out for three separate review findings: comprehensive language impairments, impairment in isolated language processing, and absence of language impairment. The overall CERQual assessment of confidence in the results was considered low for the first two review findings and very low for the last one (Table 3).

DISCUSSION

The purpose of the present literature review was to identify a possible language impairment profile in patients with CBS.

First, regarding the demographic and clinical characteristics of the sample, the mean age of patients was 65.31 years. The slight predominance of more women in studies is in line with the literature,[7] though some studies found no evidence of gender differences.[9,52,53] The sample size was relatively small, with a median value of 11 subjects. This may be explained by the rarity of the syndrome.

Regarding the language profile in CBS, many studies cited the nf-PPA phenotype as a common feature. This profile was found in 20% of the articles.[4,12-14,20-22] Although not a high rate, this phenotype appears to be the most common. Other studies cited a broad range of profiles, which are discussed below.

Frattali and colleagues[42] sought to characterize language profiles in 15 CBS patients. They were classified as having anomic aphasia, Broca's aphasia, or transcortical motor aphasia.

Another study with a similar objective, conducted by Graham,[50] detected language deficits mainly in phonological awareness, spelling and verbal fluency tests,

Table 3. Confidence in the Evidence from Reviews of Qualitative Research assessment of review findings.

Review findings	Studies contributing to the review finding	Methodological limitation	Relevance	Coherence	Adequacy of data	Overall CERQual assessment of confidence
Comprehensive language impairments (presence of aphasia)	2; 3; 4; 12; 13; 14; 15; 16; 20; 21; 22; 23; 35; 41; 42; 47; 50	minor methodological limitation (8 studies with moderate methodological quality and 1 study with low methodological quality)	moderate concerns about relevance (only 8 studies carried out a comprehensive language assessment)	moderate concerns about coherence (inconsistent data across studies regarding language outcomes)	substantial concerns about adequacy of data (6 studies are case reports or case series and 4 have up to 15 participants)	Low confidence
Impairments in isolated language processing	24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 36; 37; 38; 39; 40; 51	moderate methodological limitation (15 studies with moderate methodological quality)	moderate concerns about relevance (only 5 studies carried out a comprehensive language assessment)	moderate concerns about coherence (inconsistent data across studies regarding language outcomes)	substantial concerns about adequacy of data (7 studies are case reports or case series)	Low confidence
Absence of language impairments	45	substantial concerns (low methodological quality)	substantial concerns about relevance (restricted language assessment)	not applicable	substantial concerns about adequacy of data (case report)	Very low confidence

CERQual: Confidence in the Evidence from Reviews of Qualitative Research.

suggesting language impairments related to phonological processing.

Three studies that explored the relationship between clinical aspects and the underlying pathology found different language profiles. Borroni and colleagues[47] assessed 30 patients with CBS, divided into two groups according to results on cerebral spinal fluid (CSF) examination (suggestive of AD and not suggestive of AD). The probable AD group showed more significant impairment on tests of episodic memory and language comprehension, whereas the other group showed more severe extrapyramidal abnormalities. However, language assessment was restricted to a sentence comprehension test (Token Test) and verbal fluency tests.

Burrell and colleagues[15] assessed 14 CBS patients, divided into two groups according to the probable underlying pathology based on amyloid positron emission tomography (PET). The authors found language impairments in the following decreasing order of frequency: word repetition, dysgraphia, sound substitution in spontaneous speech, sentence repetition, and word-finding difficulties. The group with probable AD had a more marked problem on sentence repetition, a characteristic of L-PPA, whose underlying pathology is typically AD. The authors correlated difficulty in sentence repetition with a higher likelihood of AD being the underlying pathology.

In the study by Di Stefano and colleagues,[16] 45 CBS patients were assessed with a comprehensive language battery. Language impairment was the most prevalent cognitive deficit in the sample. Language deficits were found in the following tasks: phonemic and semantic verbal fluency, sentence repetition, and word comprehension. Patients with CSF biomarkers indicating probable AD as underlying pathology showed a positive correlation with Gerstmann syndrome, and the group without AD presented more severe language deficits, especially in picture naming and word comprehension. The authors suggested a mixed aphasia phenotype, including characteristics of L-PPA and the semantic variant of PPA (S-PPA).

The language heterogeneity in CBS was also illustrated in some case reports. Sakurai et al.[38] reported the case of a patient with CBS and apraxic agraphia and micrographia, without other language impairments, detected using a comprehensive language assessment.

Mazzon and colleagues[39] reported the case of a 74-year-old man, who evolved with language impairments, compatible with nf-PPA and apraxic agraphia.

Another case of apraxic agraphia was reported by Passov and colleagues.[36] In this case, apraxic agraphia was the onset symptom. The patient evolved with motor and speech disturbances (hypokinetic dysarthria and speech apraxia).

Assal and colleagues[37] reported the case of a patient with progressive apraxia of speech who evolved with peripheral agraphia and, subsequently, with characteristic CBS symptoms. Imaging scans disclosed hypometabolism and atrophy in the right hemisphere, confirming a case of crossed-apraxia of speech.

In summary, although the nf-PPA phenotype seems to be the most common language profile in CBS, it is possible to find characteristics of L-PPA as well as S-PPA. Other language characteristics, such as writing impairments, difficulty in comprehension and expression of quantifiers (words preceding nouns that convey quantity information), syntactic processing impairment, and deficits in narrative skills may also be present in CBS patients. A review of language in CBS also reported a wide array of language profiles.[6]

Regarding the tests used in the assessment of language impairments in CBS, WAB was the most utilized comprehensive language test in the studies reviewed.[2,3,20,22-3,26,38,42] WAB assesses the following linguistic abilities: speech content, fluency, auditory comprehension, repetition, naming, reading, and writing. It also includes the assessment of non-linguistic skills in its second part: apraxia, calculation, and constructional and visuospatial abilities. Three composite scores can be obtained from WAB: Aphasia Quotient (AQ), Language Quotient (LQ), and Cortical Quotient (CQ). AQ is derived from spontaneous speech, auditory verbal comprehension, repetition, and naming and word-finding tests. It is a widely used measure of aphasia severity. LQ includes, in addition to the abilities covered in AQ, reading and writing, and CQ is derived from the whole test.

A study[54] investigated the use of the revised version of WAB (WAB-R)[55] for detecting PPA subtypes. A total of 169 patients were included, with different PPA subtypes and progressive apraxia of speech (PAOS). On group comparisons, the AQ proved satisfactory for distinguishing PPA subtypes from PAOS. At the individual level, however, sensitivity for detecting aphasia proved low, as 20% of the PPA participants had AQ in the normal range. The authors concluded that, for PPA, WAB-R should be used together with other tests, including an assessment for motor speech disorders.

Another widely used test for language evaluation on CBS was the BNT, mentioned in eight studies.[20,22-25,33,34,45] BNT is a visual confrontation naming test that assesses lexical access and the semantic system.

In one[45] of the eight studies that used BNT, this test was used alone to evaluate language abilities. In other studies, BNT was used as part of a larger battery of language tests.

The Token Test, which was utilized in five studies,[14,21,23,29,47] also assesses a specific language ability,

i.e., verbal comprehension, including simple and complex sentences. Again, except for one study,[47] the others used the Token Test as part of a larger language battery.[14,21,23,29]

AAT, like WAB, is a comprehensive language assessment battery, initially developed in German. AAT includes the assessment of spontaneous language, verbal comprehension, repetition (words and phrases of increasing length), reading and writing, and naming abilities. The four studies that included this test were conducted in Italian universities, and used the Italian version.[14,21,30,39]

PPT is a semantic access test. It consists of pictures of objects presented in triads, in which the one on the top must be matched to one of two others (the distractor or the target picture), on the basis of some type of association, which varies across the triads. The distractor and the target pictures are always semantic coordinates. PPT comprises 52 triads. This test has the advantage of not requiring a verbal response, which is very useful to assess semantic knowledge in patients with severe aphasia or motor speech disorders.

PPT was part of a larger language battery in three of the four studies that utilized it.[20,24,50] In the survey conducted by Halpern et al.,[27] the language assessment, however, was based exclusively on the PPT score. Nevertheless, this study aimed to assess the semantic knowledge of numbers.

Regarding the type of evaluation used in the assessment of language impairments in CBS, results showed that just over a third of the studies included in this review performed a comprehensive assessment,[2,13,14,16,20-3,30,36-39] in strict compliance with recommended guidelines for assessing PPA.[17]

Of the studies performing a restricted assessment, some sought to analyze specific aspects of language. Frattali and colleagues[26] investigated the occurrence of yes/no reversal phenomenon in CBS; in other words, when a patient verbalizes or gestures "no" when meaning "yes", or vice versa. This error was found in almost half of the sample and was attributed to deficits in inhibitory control and mental flexibility.

Three studies by the same group[32-34] investigated comprehension and expression of quantifiers, showing that CBS patients had significantly worse performance in comprehension and expression of quantifiers compared to controls. In all of those three studies, patients were non-aphasic as inclusion criteria, and they were tested on only a few linguistic abilities.

Three other studies focused on verb and syntactic processing in CBS.[29-31] CBS patients had more significant impairment in processing verbs than nouns and in syntactic knowledge.

One study[28] investigated semantic memory processing in AD patients, comparing them with CBS patients. The task consisted of similarity-based and rule-based processes for teaching names of non-existent, but biologically plausible animals. CBS patients were impaired in both learning strategies, with disadvantages in the similarity-based processing, as they tended to focus on a single element of the picture.

The narrative skills of CBS patients were investigated by Gross et al.,[24] using a story-telling task based on a book of images. CBS patients displayed impaired discursive abilities, with deficits in organization and coherence, having difficulties integrating elements described into a coherent narrative. The formal aspects of language were not specified in the study.

Another study[25] was based on the notion that patients with CBS, PSP and Parkinson's disease (PD) have reduced verbal output and decreased ability to produce new information, in the absence of other language deficits, a condition referred to as "dynamic aphasia". The authors used tasks that involved generating new information in different situations with an increasing level of difficulty. All patients were impaired in producing sentences from a context and describing pictures.

Halpern et al.[27] compared the number knowledge of CBS patients with those with frontotemporal degeneration (FTD). Patients had to state whether a given Arabic numeral matched the number of black circles displayed on a screen. The stimuli were divided into "low numbers" (2–4) and "high numbers" (5–9). Patients with CBS had worse performance compared to the FTD group, particularly for low numbers, showing impairment in semantic knowledge of numeric values. The patients were described as non-aphasics.

Finally, this diversity of linguistic profiles in CBS is partly due to its clinical-pathological heterogeneity.[6] Some recent articles aimed to identify clinical characteristics indicative of the underlying pathology of CBS, including language characteristics. These articles may call attention to the importance of a comprehensive language assessment, since, in some of these studies, correlations were found between specific language deficits and the biomarker for AD, showing that the linguistic profile may be useful in the identification of the underlying pathology.

However, this review shows that there are still few studies that comprise a complete assessment of language. Moreover, part of the studies included in this review were case reports or studies with a small sample. A higher number of studies with comprehensive language

assessment are necessary to clarify the language profile of CBS patients.

The assessment of the methodological quality of the studies showed that less than a third were classified as "high quality".[2,13-14,16,20-23,36,39] Among the studies classified as "moderate quality",[3,4,15,24-35,37,38,40-42,47,50,51] the majority lost points on the item regarding outcome evaluation, which, here, refers to the language evaluation. This is in line with the classification of the type of evaluation discussed above.

The overall CERQual assessment of confidence in the outcomes of this review was considered low for the findings concerning comprehensive language impairments (presence of aphasia) and impairments in isolated language processing, and very low for the findings concerning absence of language impairments. This is mainly due to the adequacy of data. Fourteen studies were case reports or case series, and some included less than 15 patients. There were also concerns about relevance, as few studies carried out a comprehensive language assessment, and coherence, as the results regarding language were inconsistent across studies. Some studies had methodological limitations.

The main limitation of this review refers to the search, which was performed in only one database. A more exhaustive search would possibly result in more studies with comprehensive language assessment, that could help in delineating the language profile of CBS patients. One possible future direction for a primary study is a more detailed analysis of the motor speech disorders and their form of assessment in CBS. It is well documented that patients with CBS may present with dysarthria and/or apraxia of speech.

The results of the present review showed that the language impairments found in patients with CBS were heterogeneous. Concerning the language assessment, the most used tests for evaluation were WAB and BNT. Finally, most publications were based on restricted language assessments and had moderate methodological quality. Therefore, the data available in the relevant literature are insufficient to identify a single language profile in CBS patients.

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Dement Neuropsychol 2021 March;15(1):28-40

Original Article

https://doi.org/10.1590/1980-57642021dn15-020003

Computerized cognitive stimulation for people with dementia or with mild cognitive impairment:
a bibliometric review

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ABSTRACT. Many studies have found that non-pharmacological interventions, such as cognitive stimulation (CS), can benefit people with dementia (PWD) or with mild cognitive impairment (MCI). The use of the computerized cognitive stimulation (CCS) had proven to be an ally to those who want to detect and mitigate this disease. **Objective:** The purpose of this paper was to analyze the scientific production in CCS in PWD or with MCI in journals indexed in Clarivate Analytics' Web of Science and Elsevier's Scopus since 2000. **Methods:** Data collected from Web of Science and Scopus during 2000–2019. **Results:** The data show that dementia research is exponentially developing following the evolution of widespread use of computer science. As such, this article was of enormous importance doing a bibliometric analysis of what has been done in the area since the beginning of this century. The search terms identified 61 papers related to the use of computers applied to CS in PWD or MCI, and the International Journal of Geriatric Psychiatry and Journal of Alzheimer's Disease had the largest number of publications. The most cited article was the Faucounau et colleagues. Major research' countries are United Kingdom, Spain and United States. **Conclusions:** The findings in these papers were analysed to find recommendations for future work in this area. The CCS has been increasingly used as an intervention tool for PWD or MCI, and there still seems to be a possibility for evolution in good quality publications.

Keywords: bibliometrics, cognition, computers, data analysis, dementia.

ESTIMULAÇÃO COGNITIVA COMPUTADORIZADA PARA PESSOAS COM DEMÊNCIA OU DECLÍNIO COGNITIVO LIGEIRO: UMA REVISÃO BIBLIOMÉTRICA

RESUMO. Muitos estudos têm demonstrado que as intervenções não farmacológicas, como a estimulação cognitiva (EC), podem beneficiar pessoas com demência (PCD) ou com declínio cognitivo ligeiro (DCL). O uso da estimulação cognitiva computadorizada (ECC) tem mostrado ser um meio para detetar e mitigar essa doença. **Objetivo:** O objetivo do presente artigo foi analisar a produção científica em ECC em PCD ou com DCL publicada em revistas indexadas na Web of Science da Clarivate Analytics e na Scopus da Elsevier desde 2000. **Métodos:** Os dados foram coletados na Web of Science e Scopus relativamente aos anos 2000–2019. **Resultados:** Os dados mostram que a pesquisa em demência está se desenvolvendo exponencialmente, acompanhando a evolução do uso generalizado da ciência da computação. Dessa forma, o estudo foi de enorme importância para uma análise bibliométrica do que tem sido feito na área desde o início deste século. Os termos de pesquisa identificaram 61 artigos relacionados ao uso de computadores aplicados à EC em PCD ou DCL, e ambos os periódicos *International Journal of Geriatric Psychiatry* e *Journal of Alzheimer's Disease* tiveram o maior número de publicações. O artigo mais citado foi o de Faucounau et al. Os principais países de pesquisa foram Reino Unido, Espanha e Estados Unidos. **Conclusões:** Os resultados desses artigos foram analisados de forma a possibilitar encontrar recomendações para trabalhos futuros nessa área. A ECC tem sido cada vez mais utilizada como ferramenta nas intervenções para PCD e DCL, e ainda parece haver possibilidade de evolução em publicações de boa qualidade.

Palavras-chave: bibliometria, estimulação cognitiva, computadores, análise de dados, demência.

This study was conducted at the Universidade Portucalense Infante D. Henrique, Porto, Portugal, and Hospital Magalhães Lemos, Porto, Portugal.

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Disclosure: The authors report no conflicts of interest.

Funding: none.

Received on June 30, 2020. Accepted in final form on October 02, 2020.

INTRODUCTION

Dementia is a disorder characterized by deterioration of cognitive and functional abilities and several neuropsychiatry and behavioral symptoms.[1,2] The most common dementia is Alzheimer's disease (AD), which is a degenerative disease, what means that it becomes worse with time.[1] The risk of dementia rises with increasing age, and this disease has a huge economic impact. Mild cognitive impairment (MCI) is characterized by an objective cognitive decline in one or more cognitive domains without any significant impairment in daily life activities.[3] In fact, the MCI is the expected stage between the cognitive decline result of the normal aging and the more serious decline of dementia, and may increase the risk of dementia later developing caused by AD or other neurological conditions. Given the unprecedented personal, societal, and healthcare costs, it is not surprising that global efforts to develop and implement dementia risk reduction strategies are occurring.[4,5]

People with dementia (PWD) experience multiple symptoms that change over a period of years, and these symptoms reflect the degree of damage to nerve cells, wherein the pace at which symptoms of dementia advance from mild to moderate to severe differs from person to person.[1] Though there is no cure for AD, there are some treatments available to ease symptoms and slow the disease progression.

Non-pharmacological interventions in combination with pharmacotherapies have been considered the best approach in the management of PWD[6-8] and many studies have found that non-pharmacological interventions, such as cognitive stimulation (CS), can benefit PWD.[7,9-11] There has been an interest in a variety of technological interventions that can treat symptoms of cognitive, behavioral and psychological impairment. CS is a non-pharmacological intervention to treat people with mild to moderate dementia.[12] According to Piasek et al.,[13] in the absence of a cure for dementia, there is a real need to develop user-centered technologies to enhance the well-being and quality of life of PWD.

The use of the computer, in its different types, has proven to be an ally to those who want to detect and mitigate this disease. Computerized cognitive training programs may be used as a practical and valuable tool in clinic to improve cognitive status.[14,15] García-Casal et al.[16] found that the computer-based cognitive interventions had moderate effects in cognition. However, they led to superior results compared to non-computer-based interventions in cognition.

Dementia and non-pharmacological interventions research, such as computerized cognitive stimulation (CCS), is exponentially developing following the evolution of widespread use of computer. As such, this article intended to be of enormous importance doing a bibliometric analysis about what has been done in the area since the beginning of this century. The motivation for this research was based on our desire to know and clarify the impact of non-pharmacological interventions using a computer and its advantages over the use of traditional methods of CS and to know what has been published in this area. This review is different from all other existing reviews, as it managed to cover a wide range of articles, with key information to understand the impact of the use of technologies in the areas of non-pharmacological interventions. The purpose of this paper was to analyze the scientific production in CCS and PWD or people with MCI in journals indexed in Clarivate Analytics' Web of Science and Elsevier's Scopus.

This document is divided into several sections. First, the research questions are described, followed by the methodology and the results. Then, a summary of the most cited articles is made, as well as an analysis of all documents in the database, ending with a discussion of the results obtained and the conclusions, including a suggested future work.

THE RESEARCH QUESTIONS

The question, along with the purpose of the review, the intended deliverables and the intended audience, determines how the data are identified, collected and presented.[17] There are several questions that we want to answer in this paper:

- Q1: When were the articles published?
- Q2: Where were the articles published?
- Q3: What is the focus of the articles? Has it evolved over the years?
- Q4: Who publishes on the subject? Where do researchers who are interested in PWD work? What country do they live in?
- Q5: What are the most cited articles?

METHODS

The term "bibliometrics" was first used in 1969 by Alan Pritchard, hoping that it would be used explicitly in all studies which seek to quantify the processes of written communication and would quickly gain acceptance in the field of information science.[18] Moed mentioned the potential of this type of study that reveals the enormous potential of quantitative, bibliometric analyses of the scholarly literature for a deeper understanding of scholarly activity and performance, and highlights their policy relevance.[19] In scientific research, it is important to get a comprehensive perspective of research already

being conducted concerning a relevant subject matter[20] and a bibliometric analysis profile on the research trajectory and dynamics of the research activities across the globe.[21] This is a bibliometric study that systematically analyses the literature using two at Elsevier's Scopus (Scopus) and Clarivate Analytics' Web of Science (WoS) databases. This paper conducts a bibliometric analysis of international papers that we expect to provide a useful reference for future research.

The research strategy was designed by the authors according to the literature review previously prepared. In this case, the terms that are identified as relevant to the present study were defined, the time frame (from 2000 to 2019), and the type of publication identified as relevant to the research.

The Scopus search strategy was:

- TITLE-ABS-KEY ("cognitive stimulation" AND comput* AND "dementia").
- DocType: Article OR Review OR Conference Paper.
- PUBYEAR: >1999 AND <2020.

The WoS search strategy was:

- TS=("cognitive stimulation" AND comput* AND "dementia").
- Document Type = (ARTICLE OR MEETING OR REVIEW).
- PY=(2000–2019).

The eligible papers were required to: (a) include participants with a diagnosis of dementia or MCI using a validated cognitive screening measure; (b) examine the effects of CCS; (c) include case series, control group, randomized or non randomized design.

RESULTS

A set of 48 published papers were collected from WoS and 35 from Scopus. The search returned a total of 61 articles and reviews after discounting the duplicate results. Thus, this bibliometric study analyzed the literature using 17 articles from Scopus,[13,22-27] 27 from WoS,[12,16,28-34] and 17 articles indexed in both databases.[35-44] In the articles studied, the trials included most were unregistered, parallel-group or single-site randomised controlled trials. The first article was published in 2005 (Figure 1). The average number of articles is 4 per year. The year with the greatest number of articles is 2018.[10] We can observe in Figure 1 that both curves of publications have an increasing trend until 2018 in both datasets, due to the progress of scientific literature in this field of research. We noted that in the last year there has been a decrease in published papers.

There are 50 sources of publications: only two journals have three publications (*International Journal of Geriatric Psychiatry* and *Journal of Alzheimer's Disease*) and seven others have two publications (one of these is ACM International Conference Proceeding Series) (Table 1). Most of these journals are from the first quartile, three are from United Kingdom and three from United States.

Most articles are written by three authors (21%), 15% are written by five authors and 10% by two authors.

There are 320 authors. Only three of these 320 wrote three articles. The authors with three articles were Hiroko Hayama Dodge from the University of Michigan, (Ann Arbor, United States), Hermine Lenoir from the Université Paris Descartes (Paris, France) and Victoria Meza-Kubo from the Universidad Autónoma de Baja California (Ensenada, Mexico).

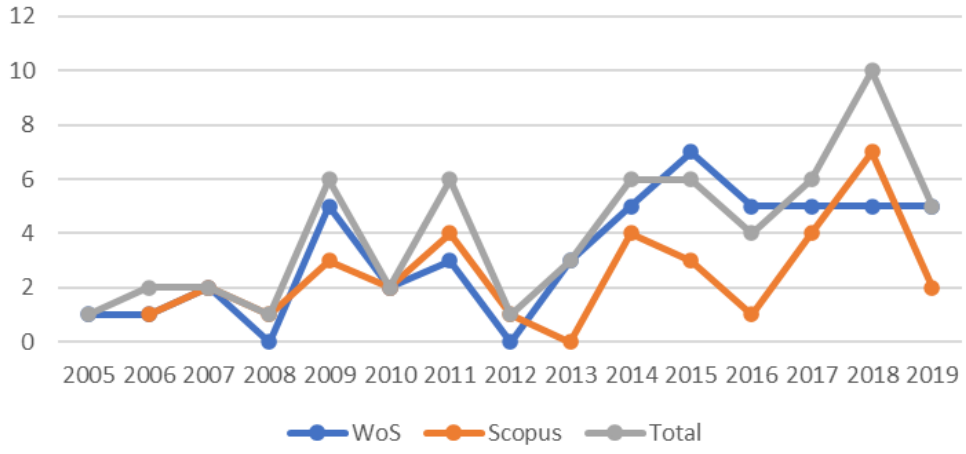

Figure 1. Evolution of published papers.

We found 425 keywords. The 20 most common keyword are "Dementia", "aged", "Cognitive stimulation", "Article", "Mild cognitive impairment", "human", "quality of life", "Cognition", "controlled study", "Alzheimer disease", "caregiver", "cognitive defect", "cognitive therapy", "Neurodegenerative diseases", "adult", "aging", "Alzheimer's disease", "Cognitive stimulation therapy", "Cognitive stimulations" and "technology".

In Figure 2, we can see the network visualization of the keywords, using VOSviewer - Visualizing scientific landscapes. We found three clusters:

- (C1) Alzheimer's disease, cognition, quality of life, technology and treatment.
- (C2) Cognitive impairment, cognitive stimulation, cognitive training and computer.
- (C3) Cognitive function, internet and mild cognitive impairment.

Table 2 shows the most frequent keywords for different periods: until 2009, 2009–2014 and 2014–2019.

The authors are from 20 different countries. The countries with the largest number of articles are: United Kingdom (15%), Spain (12%) and United States (10%).

The network of co-authorship countries has high density and a small number of clusters suggesting being centered on some countries. There are only two clusters with more than two countries:

- (C1) France, Greece, Ireland, Italy, New Zealand and South Korea.
- (C2) Canada, Netherlands, and United Kingdom.

The development of the co-authorship country research collaboration in CCS and PWD is presented in the Figure 3 distributed by degree of centrality, using VOSviewer. It is a centered network around United Kingdom, Spain and United States, France and Italy, which have the highest number of links with other countries, co-authoring several articles and the biggest importance in the development of the field.

We find that there are 93 organizations: 12 of these organizations have more than 2 articles. The most productive organizations by the number of the articles in CCS and PWD for the all period (1999–2020) includes the Consiglio Nazionale delle Ricerche, Aristotle University of Thessaloniki, Ewha Womans University, Hospital Provincial de Zamora, OHSU School of Medicine, Oregon Health and Science University, Portland VA Medical

Table 1. Journals/conference information's.

Journal/Conference	#	Country	SJR 2018	IF 2018	WoS Subject (category)	Quartil	H Index
International Journal of Geriatric Psychiatry	3	United Kingdom	1.41	3.141	Medicine (Geriatrics and Gerontology; Psychiatry and Mental Health)	Q1	116
Journal of Alzheimer's Disease	3	Netherlands		3.517	Neurosciences (Neuroscience & Behavior; Neurosciences & Behavior)		
ACM International Conference Proceeding Series	2	United States	0.17				98
Aging and Mental Health	2	United Kingdom	1.23	2.956	Medicine (Geriatrics and Gerontology; Psychiatry and Mental Health) Nursing (Gerontology; Psychiatric Mental Health)	Q1	74
Alzheimer's and Dementia: Translational Research and Clinical Interventions	2	United States	1.5		Medicine (Neurology (clinical); Psychiatry and Mental Health)	Q1	13
Clinical Interventions in Aging	2	New Zealand	1	2.585	Medicine (Geriatrics and Gerontology) Medicine (miscellaneous)	Q2; Q1	59
Cochrane Database of Systematic Reviews	2	United States	1.61	7,755	Medicine (Medicine (miscellaneous); Pharmacology (medical))	Q1	244
Journal of the American Geriatrics Society	2	United Kingdom	2.13	4.113	Medicine Geriatrics and Gerontology	Q1	208
Lecture Notes of the Institute for Computer Sciences, Social-Informatics and Telecommunications Engineering	2	Germany	0.15		Computer Science (Computer Networks and Communications)	Q4	36

SJR: Scientific Journal Rankings; IF: impact factor.

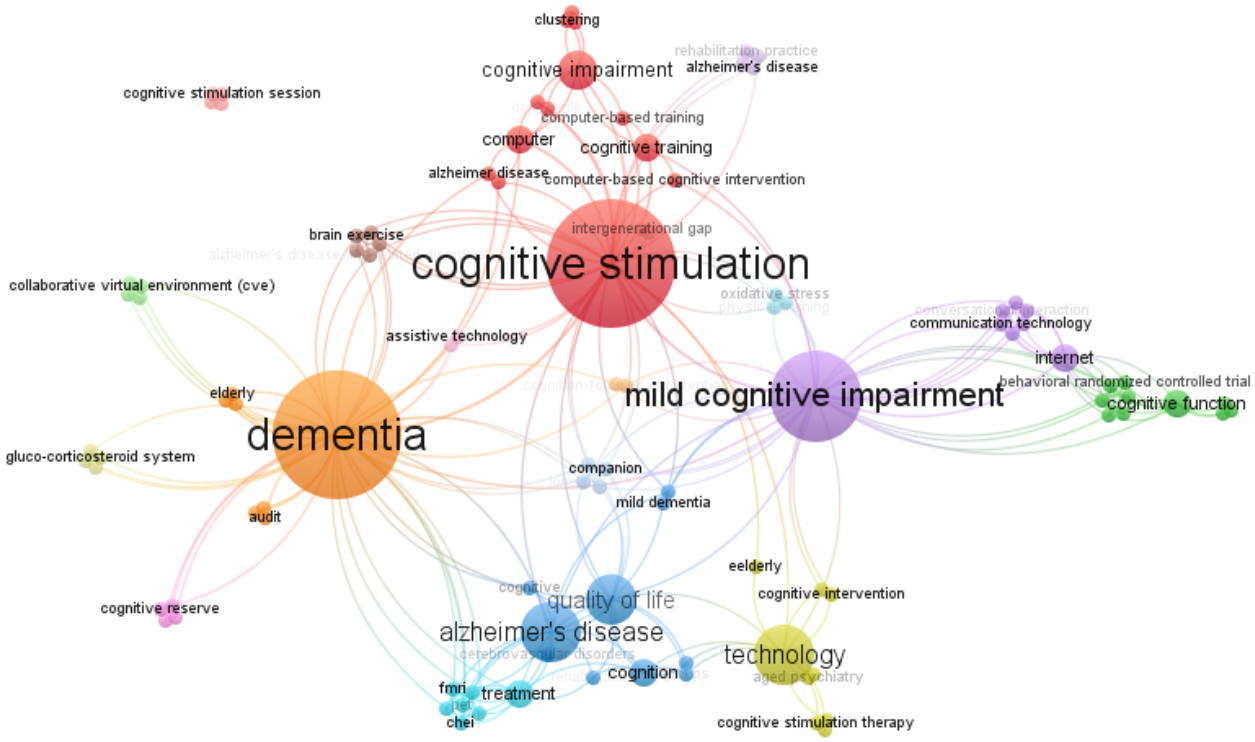

Figure 2. Network visualization, keywords.

Center, Universidad Autónoma de Baja California, Universidad de Salamanca, University of Hull, University of Melbourne and University of Michigan - Ann Arbor.

Because we didn´t use the language exclusion criteria, we can now see that English is used in 89% of the articles. The other languages are Spanish (6%), French (3%) and Korean (3%).

The affiliation of the most cited documents' author is AP-HP Assistance Publique – Hopitaux de Paris (Paris, France), followed by Université Paris Descartes (Paris, France). The next table (Table 3) list the most cited author affiliation.

According to Chen,[45] the most cited papers give historical perspective on scientific progress and reveal recognition of scientific advancement. As usual in the literature, older papers receive more citations than recent one, given the time length of knowledge diffusion. Curiously, the majority of top cited articles belong to a more recent period, and the most cited paper was published in 2010.

The most cited article, with 50 citations, was the Faucounau et al.[36] with the title "Cognitive intervention programmes on patients affected by mild cognitive impairment: a promising intervention tool for MCI?". In this article, they found that though both traditional and computer-based cognitive intervention programs seem to be effective, the computer-based ones present more advantages, namely, the teams that work with patients with cognitive impairment could individualize the program tailored to the patient's neuropsychological pattern and needs; the computer-based cognitive intervention programs allow the user to make an immediate objective comparison with data collected earlier and also help in setting up a systematic training plan by providing instant value-free feedback and enable this tool offer a possibility of a widescale dissemination. In a paper with 44 citations, Viola et al.[38] reported that they implemented a multidisciplinary rehabilitation program on cognition, quality of life, and neuropsychiatry symptoms in patients with mild AD. The group sessions were provided by a multiprofessional team and included computer-assisted cognitive stimulation, memory training, expressive activities, physiotherapy, and physical training. They found that this multimodal rehabilitation program was associated with cognitive stability and significant improvements in the quality of life for Alzheimer's patients. Recently, in 2017, in a paper with 33 citations, García-Casal et al.[16] considered that computer-based cognitive interventions have moderate effects in cognition in PWD. However, they led to superior results compared to non-computer-based interventions in cognition. Another paper (with 27 citations), developed

by Eckroth-Bucher and Siberski,[35] found that blending computer-based with traditional cognitive stimulation activities showed promise in preserving cognitive function in older people. In 2014, in a paper, currently, with 33 citations, González-Palau et al.[40] presented the results of a study using the newly integrated platform (The Long Lasting Memories program) which combined cognitive exercises with physical activity within the context of advanced technologies. This study indicated this program was a promising solution for older adults with and without cognitive impairment, maintaining their well-being with few professional and technical requirements. Breton et al.[22] reported a tool focuses on therapeutic aspects of both cognitive and physical stimulation of the older people, that is, it improves the memory by performing mental activities and physical exercise at the same time. Preliminary tests have shown an increase in the users' motivation while using the tool forgetting that it focuses on the CS. Using another approach to the use of CCS and PWD, Dodge et al.[24] examined the feasibility of a randomized controlled trial to assess conversation-based cognitive stimulation through personal computers, webcams, and a user-friendly interactive Internet interface and they found that daily conversations by way of user-friendly Internet communication programs demonstrated high adherence. They concluded that the increasing daily social contacts through communication technologies

Table 2. Most frequent keywords for different periods.

<2009	2010–2014	2015–2019
Human	Dementia	Dementia
Alzheimer Disease	Aged	Human
Article	Human	Aged
Dementia	Cognitive Stimulation	Cognition
Donepezil	Female	Cognitive Stimulation
Humans	Humans	Cognitive Stimulations
Male	Male	Female
Single Photon Emission Computer Tomography	Mild Cognitive Impairment	Male
Adult	Alzheimer's Disease	Mild Cognitive Impairment
Aged	Neurodegenerative Diseases	Article
Aged, 80 And Over	Quality Of Life	Cognitive Therapy
Alzheimer's Disease	Aged, 80 And Over	Controlled Study
Cognition	Aging	Humans
Cognitive Defect	Article	Neurodegenerative Diseases
Cognitive Therapy	Cognition Disorders	Very Elderly
Female	Controlled Study	Aged, 80 And Over
Galantamine	Treatment Outcome	Cognitive Defect
Major Clinical Study	Alzheimer Disease	Computer Assisted Therapy
Neuroimaging	Cognition	Human Computer Interaction
Nuclear Magnetic Resonance Imaging	Cognitive Defect	Major Clinical Study
Positron Emission Tomography	Cognitive Impairment	Quality Of Life
Priority Journal	Cognitive Therapy	Caregiver
Risk Factors	Cognitive Training	Cognitive Stimulation Therapy
	Computer Science	Mild Cognitive Impairments
	Health Care	Patient Treatment
	Internet	Pilot Study
	Physical Activity	Priority Journal
	Review	Psychology
	Technology	Technology
	Ubiquitous Computing	
	Very Elderly	

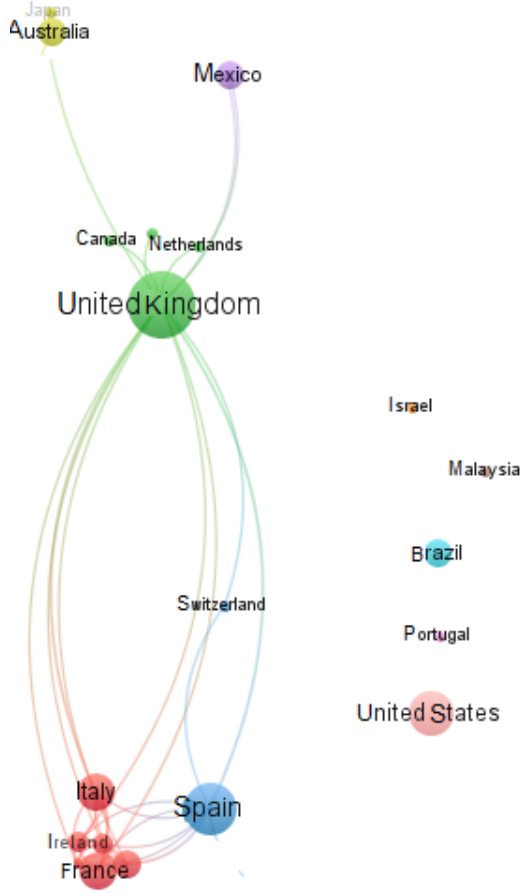

Figure 3. Network visualization, countries.

Table 3. Most cited documents' author affiliation.

	Author	Affiliation
1	Faucounau[36]	AP-HP Assistance Publique - Hopitaux de Paris, Paris, France
	Wu[36]	Université Paris Descartes, Paris, France
	Boulay[36]	Université Paris Descartes, Paris, France
	Rotrou[36]	Université Paris Descartes, Paris, France
	Rigaud[36]	Université Paris Descartes, Paris, France
2	Viola[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Nunes[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Yassuda[38]	School of Arts, Sciences and Humanities, Universidade de São Paulo, SP, Brazil
	Aprahamian[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Santos[38]	Hospital da Faculdade de Medicina da Universidade de São Paulo, SP, Brazil
	Santos[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Brum[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Borges[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Oliveira[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Chaves[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Ciasca[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Ferreira[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	de Paula[38]	Department and Institute of Psychiatry, Universidade de Sao Paulo, SP, Brazil
	Takeda[38]	Department and Institute of Psychiatry, Universidade de São Paulo, SP, Brazil
	Mirandez[38]	Department and Institute of Psychiatry, Universidade de São Paulo, SP, Brazil
	Watari[38]	Department and Institute of Psychiatry, Universidade de São Paulo, SP, Brazil
	Falcão[38]	School of Arts, Sciences and Humanities, Universidade de São Paulo, SP, Brazil
	Cachioni[38]	School of Arts, Sciences and Humanities, Universidade de São Paulo, SP, Brazil
	Forlenza[38]	Department and Institute of Psychiatry, Universidade de SP, SP, Brazil
3	García-Casal[16]	Universidad de Salamanca, Salamanca, Spain
	Loizeau[16]	Center for Gerontology, University of Zurich, Zurich, Switzerland
	Csipke[16]	University College London, Institute of Mental Health, London, UK
	Franco-Martín[16]	Hospital Universitario Río Hortega, Valladolid, Spain
	Perea-Bartolomé[16]	Universidad de Salamanca, Salamanca, Spain
	Orrell[16]	University of Nottingham, Nottingham, United Kingdom
4	González-Palau[40]	Fundación Intras, Valladolid, Spain
	Franco[40]	Hospital Zamora, Zamora, Spain
	Bamidis[40]	Greek Aerospace Medical Association and Space Research, Greece
	Losada[40]	Fundación Intras, Valladolid, Spain
	Parra[40]	Fundación Intras, Valladolid, Spain
	Papageorgiou[40]	University of Athens Medical School, Athens, Greece
	Vivas[40]	The University of Sheffield International Faculty, Sheffield, Greece
5	Venneri[57]	University of Hull, Hull, United Kingdom
6	Eckroth-Bucher[35]	Bloomsburg University, Bloomsburg, United States
	Siberski[35]	College Misericordia, Dallas, United States
7	Breton[22]	Universidad de Deusto, Bilbao, Spain
	Zapirain[22]	Universidad de Deusto, Bilbao, Spain
	Zorrilla[22]	Universidad de Deusto, Bilbao, Spain
8	Dodge[24]	University of Michigan, Ann Arbor, Ann Arbor, United States
	Zhu[24]	University of Michigan, Ann Arbor, Ann Arbor, United States
	Mattek[24]	Oregon Health and Science University, Portland, United States
	Bowman[24]	Oregon Health and Science University, Portland, United States
	Ybarra[24]	University of Michigan, Ann Arbor, Ann Arbor, United States
	Wild[24]	Oregon Health and Science University, Portland, United States
	Loewenstein[24]	University of Florida, Gainesville, United States
	Kaye[24]	Oregon Health and Science University, Portland, United States
9	Westphal[37]	University of Melbourne, Parkville, Australia
	Dingjan[37]	University of Melbourne, Parkville, Australia
	Attoe[37]	University of Melbourne, Parkville, Australia

could offer cost-effective home-based prevention methods. In Table 3, we can also see the reference to the paper by Westphal et al.[37] with 14 citations. They identified and reviewed the latest research in the use of low and high technology in the areas of mood disorders, psychosis, normal ageing, mild cognitive impairment and dementia, and they found that research in the use of low and high technology in late-life mental disorders continued to evolve in its scope and innovation. These authors also considered that to make progress in accessibility and acceptability of technology, involvement of stakeholders and users in the design and application, as well as the examination of cost-effectiveness and robust methodologically designed studies, is necessary.

The Table 4 lists the affiliations of the authors of the most cited articles. Some of the most productive institutions involved in CCS and PWD are Department and Institute of Psychiatry, Universidade de São Paulo, São Paulo, Brazil and Université Paris Descartes, Paris, France.

In the Table 5, we list the information of the ten most cited papers: author, year, title, source, keywords and number of citations (Citats).

The country affiliation with the most cited authors is the United States (25%), followed by Spain (21%), Greece (13%), United Kingdom (13%), Brazil (12%), France (8%), Switzerland (4%) and Australia (4%).

We found five keyword clusters (as we can see in Figure 3):

- (C1) Communication technology, conversational interactivity, internet, mild cognitive impairment, Oregon Centre for Aging, prevention study, randomized controlled clinic, and social engagement.
- (C2) Cognitive impairment, cognitive stimulation, cognitive training, computer-based cognitive inter and computer-based training.
- (C3) Alzheimer's disease, cognition, quality of life, rehabilitation and treatment.
- (C4) Dementia, elderly, Kinect and windows.
- (C5) Alzheimer's disease, cognitive rehabilitation and therapy.

DISCUSSION

The purpose of this paper was to analyze the scientific production in CCS and PWD in journals indexed in Clarivate Analytics' Web of Science and Elsevier's Scopus since 2000. This work was the first bibliometric review study and very useful about the exploration of the literature CCS and PWD or people with MCI from WoS and Scopus databases, and has outlined the evolutionary trajectory of the collective knowledge over the past 21 years and highlighted the areas of active pursuit.

Let us answer the research questions. The bibliometric questions considered are:

Q1: When were the articles published?

The average number of articles is 4 per year. The year with the greatest number of articles is 2018 (10). The curves of publications have an increasing trend until 2018 in both datasets, explaining the progress of scientific literature in this field of research. In 2019, there has been a decrease in published papers.

Q2: Where were the articles published?

There are 50 sources of publications: only two journals have three publications (International Journal of Geriatric Psychiatry and Journal of Alzheimer´s Disease) and seven others have two publications (one of these is

Table 4. Affiliation author, most cited articles.

Affiliation	n
Department and Institute of Psychiatry, Universidade de São Paulo, São Paulo, Brazil	15
Universite Paris Descartes, Paris, France	4
Fundación Intras, Valladolid, Spain	3
Oregon Health and Science University, Portland, United States	3
School of Arts, Sciences and Humanities, Universidade de São Paulo, São Paulo, Brazil	3
Universidad de Deusto, Bilbao, Spain	3
University of Melbourne, Parkville, Australia	3
University of Michigan, Ann Arbor, Ann Arbor, United States	3
Universidad de Salamanca, Salamanca, Spain	2
AP-HP Assistance Publique - Hopitaux de Paris, Paris, France	1
Bloomsburg University, Bloomsburg, United States	1
Center for Gerontology, University of Zurich, Zurich, Switzerland	1
Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, S. Paulo, Brazil	1
College Misericordia, Dallas, United States	1
Greek Aerospace Medical Association and Space Research, Thessaloniki, Greece	1
Hospital Universitario Río Hortega, Valladolid, Spain	1
Hospital Zamora, Zamora, Spain	1
Oregon Health and Science University, Portland, United States	1
The University of Sheffield International Faculty, Sheffield, Greece	1
University College London, Institute of Mental Health, London, United Kingdom	1
University of Athens Medical School, Athens, Greece	1
University of Florida, Gainesville, United States	1
University of Nottingham, Nottingham, United Kingdom	1
University of Hull, Hull, United Kingdom	1

ACM International Conference Proceeding Series), most of these are from the first quartile. With more than two publications: three journals are from United Kingdom and three from United States.

Q3: What is the focus of the articles? Has it evolved over the years?

We found 425 keywords. The 20 most common keyword are "Dementia", "aged", "Cognitive stimulation", "Article", "Mild cognitive impairment", "human", "quality of life", "Cognition", "controlled study", "Alzheimer disease", "caregiver", "cognitive defect", "cognitive therapy", "Neurodegenerative diseases", "adult", "aging", "Alzheimer's disease", "Cognitive stimulation therapy", "Cognitive stimulations" and "technology". We found three clusters:

- (C1) Alzheimer's disease, cognition, quality of life, technology, and treatment.
- (C2) Cognitive impairment, cognitive stimulation, cognitive training, and computer.
- (C3) Cognitive function, internet, and mild cognitive impairment.

The most frequent keywords until 2009 were "Human", "Alzheimer Disease", "Article", "Dementia", "Donepezil" and "Humans"; from 2010–2014, were

Table 5. Most cited papers.

Author	Year	Title	Source	Keywords	Citats
Faucounau et al.[36]	2010	Cognitive intervention programmes on patients affected by mild cognitive impairment: A promising intervention tool for MCI?	Journal of Nutrition, Health and Aging. 2010;14(1):31-5	Cognitive stimulation; Cognitive training; Computer-based cognitive intervention; Mild cognitive impairment	50
Viola et al[38]	2011	Effects of a multidisciplinar cognitive rehabilitation program for patients with mild Alzheimer's disease	Clinics. 2011;66(8):1395-400	Alzheimer's disease; Cognition; Quality of life; Rehabilitation; Treatment	44
García-Casal et al.[16]	2017	Computer-based cognitive interventions for people living with dementia: a systematic literature review and meta-analysis	Aging and Mental Health. 2017;21(5):454-67	Alzheimer disease; Cognitive rehabilitation; cognitive stimulation; computer; dementia	33
González-Palau et al.[40]	2014	The effects of a computer-based cognitive and physical training program in a healthy and mildly cognitive impaired aging sample	Aging and Mental Health. 2013;18(7):838-46	Alzheimer's disease; cognitive stimulation; mild cognitive impairment; mild dementia; physical activity	33
Venneri[57]	2007	Imaging treatment effects in Alzheimer's disease	Magnetic Resonance Imaging. 2007;25(6):953-68		31
Eckroth-Bucher and Siberski[35]	2009	Preserving cognition through an integrated cognitive stimulation and training program	American Journal of Alzheimer's Disease and other Dementias. 2009;24(3):234-45	Cognitive impairment; Cognitive stimulation; Cognitive training; Computer-based training	27
Breton et al.[22]	2012	KiMentia: Kinect based tool to help cognitive stimulation for individuals with dementia	2012 IEEE Proceedings of the 14th International Conference on e-Health Networking, Applications and Services (Healthcom). IEEE; 2012. p. 325-8	Dementia; elderly; Kinect; Windows	21
Dodge et al.[24]	2015	Web-enabled conversational interactions as a method to improve cognitive functions: Results of a 6-week randomized controlled trial	Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2015;1(1):1-12	Communication technology; Conversational interaction; Internet; Mild cognitive impairment; Oregon Center for Aging and Technology (ORCATECH); Prevention study; Randomized controlled clinical trial; Social engagement	21
Westphal et al.[37]	2010	What can low and high technologies do for late-life mental disorders?	Current Opinion in Psychiatry. 2010;23(6):510-5	Aged psychiatry; technology; therapy	14

"Dementia", "Aged", "Human", "Cognitive Stimulation", "Female" and "Humans"; from 2015–2019, were "Dementia", "Human", "Aged", "Cognition", "Cognitive Stimulation" and "Cognitive Stimulations".

Q4: Who publishes on the subject? Where do researchers who are interested in PWD work? What country do they live in?

There are 320 authors. Only three of these 320 wrote three articles: Dodge, Hiroko Hayama (University of Michigan, Ann Arbor, United States), Lenoir, Hermine (Université Paris Descartes, Paris, France) and Meza-Kubo, Victoria (Universidad Autónoma de Baja California, Ensenada, Mexico). There are authors from 20 countries. The countries with the largest number of articles are: United Kingdom (15%), Spain (12%) and United States (10%).

The large projected increase in the number of people with dementia makes finding a treatment to slow or stop dementia as soon as possible essential. The investigations try to find solutions regarding how to deal with dementia in countries with many PWD. As the number of AD cases rises rapidly in an aging global population, the need to understand this puzzling disease is growing and the number of researches is growing in countries like the United Kingdom, Spain and United States.

According to Alzheimer Europe,[46] examining the population data of the United Kingdom, there is an increase in population for the period 2018 and 2025, with a significant increase in the numbers of people aged over 65, and, in particular, the over 85 age range, which more than doubles between this period. It should be noted that PWD will represent 2.67% of the overall population in 2050 compared to 1.56% in 2018. Villarejo-Galende et al.[47] performed a literature review of the published evidence and they found that in Spain most population studies of patients older than 65 report prevalence rates ranging from 4 to 9%. Prevalence of dementia and AD is higher in women for nearly every age group. AD is the most common cause of dementia (50–70% of all cases). According to the Alzheimer Association,[1] millions of Americans have Alzheimer's or other dementias and, as the size and proportion of the U.S. population age 65 and older continue to increase, the number of Americans with Alzheimer's or other dementias will grow. The Alzheimer Association[1] considers that this number will escalate rapidly in coming years, as the population of Americans age. Thus, 65 and older is projected to grow from 55 million in 2019 to 88 million by 2050.

Q5: What are the most cited articles?

The most cited papers give historical perspective on scientific progress and reveal recognition of scientific advancement. For this classification, we use the numbers presented in the Scopus database. We found that the positions coincided with the WoS database. We observed that the most cited paper was the Faucounau et al.,[36] who found that, though both traditional and computer-based cognitive intervention programs seem to be effective, the computer-based ones have more advantages. This paper is in line with the review published studies on CCS and PWD published by Djabelkhir et al.[15] who considered that computerized cognitive training programs may be used as a practical and valuable tool in clinic to improve cognitive status. However, the most cited paper contrasted with another paper by Gates et al.[48] that evaluated the effects of at least 12 weeks of computerized cognitive training on maintaining or improving cognitive function and preventing dementia in people with MCI. They concluded that currently available evidence did not allow them to determine whether or not computerized cognitive training will prevent clinical dementia or improve or maintain cognitive function in those who already have evidence of cognitive impairment. In an systematic review article, Irazoki et al.[49] studies of computerized cognitive interventions for PWD and cognitive impairment were included if they clearly described objectives, users and functioning. On the overall, the programs were aimed at people with different clinical conditions, able to create specific treatments and personalized training, optimized for portable devices, and user-friendly. These authors found that the selected programs differed from each other in terms of objectives, usage mode and characteristics, even if they were used for the same purposes, and they concluded that more information about the features and context of use was needed, as well as more clinical studies, to be able to compare among computerized cognitive programs. This review work was of great importance because the information obtained in the review may be relevant to distinguish programs and select the one that best suits each user.

Some of the most productive institutions involved in CCS and PWD are Department and Institute of Psychiatry, Universidade de São Paulo, São Paulo, Brazil and Université Paris Descartes, Paris, France. The country with the most cited authors is the United States, followed by Spain. The biggest keyword cluster from the most cited articles is communication technology, conversational interactivity, internet, mild cognitive impairment, Oregon Centre for Aging, prevention study, randomized controlled clinic and social engagement.

The progressive increase in the number of scientific papers in CCS and PWD until 2018 likely to combine the effects of a number of factors: the aging of the

population,[50,51] the risk of dementia grows exponentially with age,[1,2,52] an increase in the global prevalence of dementia;[46,53,54] an increase in awareness of dementia as a serious public health problem;[55,56] non-pharmacological interventions in combination with pharmacotherapies have been considered as the best approach in management of PWD,[56] and the computer use in its different types has proven to be an ally to those who want to detect and mitigate this disease.[15]

We consider that determining the effectiveness of non-pharmacologic therapies can be difficult because of the large number of existing therapies (including CCS and PWD), the diversity of therapeutic aims, the diverse dementia stages, the diverse types of dementia and the lack of a standard method for carrying out any non-pharmacological therapy.

The search terms identified 61 papers related to the use of computers applied to cognitive stimulation and PWD or people with MCI. We found that there was an increasing trend in the paper publication in CCS and PWD until 2018 in WoS and Scopus, explaining the progress of scientific literature in this field of research. In the last year, we noted that there has been a decrease in published papers. The International Journal of Geriatric Psychiatry and Journal of Alzheimer's Disease had the largest number of publications in CCS and PWD between 1999 and 2000. Major research' countries are United Kingdom, Spain and United States, and Aristotle University of Thessaloniki (Greece) is the affiliation author with most cited articles. The most productive organizations in the number of the articles in CCS and PWD for the all period (1999–2020) were the Consiglio Nazionale delle Ricerche. Dodge, Lenoir and Meza-Kubo published the largest number of papers. The most cited paper was Faucounau et al.[36] In this paper, the authors clearly emphasized the advantages of using the computer-based cognitive intervention, which have more advantages compared to traditional cognitive intervention: intervention tailored to the patient's neuropsychological pattern and needs; to make an immediate objective comparison with data collected earlier, and thus help in setting up a systematic training.

The 20 most common keyword were "Dementia", "aged", "Cognitive stimulation", "Article", "Mild cognitive impairment", "human", "quality of life", "Cognition", "controlled study", "Alzheimer disease", "caregiver", "cognitive defect", "cognitive therapy", "Neurodegenerative diseases", "adult", "aging", "Alzheimer's disease", "Cognitive stimulation therapy", "Cognitive stimulations" and "technology'. The limitations of this study are related with the inclusion of studies in English only, introducing language bias.

The findings in these papers were analyzed to find recommendations for future work in this area. We concluded that the CCS has been increasingly used as an intervention tool for PWD and MCI and there still seems to be a possibility for evolution in good quality publications. Further research is needed on CCS for PWD using a standard method for carrying out non-pharmacological intervention.

Authors' contributions. SRS and MS: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing — original draft, writing — review & editing.

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Dement Neuropsychol 2021 March;15(1):41-50

Original Article

https://doi.org/10.1590/1980-57642021dn15-010004

Active lifestyle enhances protein expression profile in subjects with Lewy body pathology

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ABSTRACT. Clinical trials of the effects of physical activity have reported improvements in symptoms and quality of life in patients with Parkinson's disease (PD). Additionally, morphological brain changes after exercising were reported in PD animal models. However, these lifestyle-related changes were not evaluated in postmortem brain tissue. **Objective:** We aimed to evaluate, by immunohistochemistry, astrocytes, tyrosine hydroxylase (TH) and structural proteins expression (neurofilaments and microtubules — MAP2) changes in postmortem brain samples of individuals with Lewy body pathology. **Methods:** Braak PD stage≥III samples, classified by neuropathology analysis, from The Biobank for Aging Studies were classified into active (n=12) and non-active (n=12) groups, according to physical activity lifestyle, and paired by age, sex and Braak staging. Substantia nigra and basal ganglia were evaluated. **Results:** Groups were not different in terms of age or gender and had similar PD neuropathological burden (p=1.00). We observed higher TH expression in the active group in the substantia nigra and the basal ganglia (p=0.04). Astrocytes was greater in the non-active subjects in the midbrain (p=0.03) and basal ganglia (p=0.0004). MAP2 levels were higher for non-active participants in the basal ganglia (p=0.003) and similar between groups in the substantia nigra (p=0.46). Neurofilament levels for non-active participants were higher in the substantia nigra (p=0.006) but not in the basal ganglia (p=0.24). **Conclusion:** Active lifestyle seems to promote positive effects on brain by maintaining dopamine synthesis and structural protein expression in the nigrostriatal system and decrease astrogliosis in subjects with the same PD neuropathology burden.

Keywords: Life style, aging, Lewy bodies, postmortem examination, Parkinson disease, dopamine, astrocytes.

O ESTILO DE VIDA ATIVO MELHORA O PERFIL DE EXPRESSÃO DE PROTEÍNAS EM INDIVÍDUOS COM A PATOLOGIA DE CORPOS DE LEWY

RESUMO. Estudos dos efeitos da atividade física relataram melhora nos sintomas e na qualidade de vida de pacientes com doença de Parkinson (DP). Além disso, alterações morfológicas do cérebro após o exercício físico foram relatadas em modelos animais da DP. No entanto, essas mudanças relacionadas ao estilo de vida não foram avaliadas em tecido cerebral *post-mortem*. **Objetivo:** Avaliar a expressão de astrócitos, tirosina hidroxilase (TH) e a expressão de proteínas estruturais (neurofilamentos e microtúbulos — MAP2) por imuno-histoquímica, em amostras cerebrais *post-mortem* de indivíduos com corpos de Lewy. **Métodos:** Amostras com estágio de Braak para DP≥III, classificação neuropatológica, fornecidas pelo biobanco de estudos do envelhecimento foram classificadas em grupos ativos (n=12) e não ativos (n=12), de acordo com o estilo de vida (atividade física), e pareados por idade, sexo e estadiamento de Braak. Analisou-se a substância negra e gânglios da base. **Resultados:** Idade, sexo e classificação para DP foram semelhantes (p=1,00). Observou-se maior expressão de TH no grupo ativo (p=0,04). Amostras de não ativos revelaram maior expressão de astrócitos no mesencéfalo (p=0,03) e nos gânglios da base (p=0,0004); MAP2 nos gânglios da base (p=0,003); os níveis de neurofilamentos foram maiores na substância negra (p=0,006). **Conclusão:** O estilo de vida ativo parece promover efeitos positivos no cérebro, mantendo a síntese de dopamina e a expressão estrutural de proteínas no sistema nigrostriatal e com diminuição da ativação de astrócitos em indivíduos com a mesma classificação neuropatológica para a DP.

Palavras-chave: estilo de vida, envelhecimento, corpos de Lewy, autópsia, doença de Parkinson, dopamina, astrócitos.

This study was conducted at the Laboratory of Cellular Neurobiology, Department of Physiology and Biophysics, Instituto de Ciencias Biomedicas, Universidade de São Paulo, São Paulo, SP, Brazil. Brain tissue was obtained from the Brain Bank of the Brazilian Aging Brain Study Group, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

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Disclosure: The authors report no conflicts of interest.

Funding: This study was supported by The São Paulo Research Foundation (FAPESP, Brazil - #13/25049-2 and #12/50329-6). CCR – Post-doctoral fellowship from The São Paulo Research Foundation (FAPESP), Brazil – Grant number: 2013/25049-2. KHB – Scientific Initiation Scholarship from The São Paulo Research Foundation (FAPESP), Brazil – Grant number: 2016/16166-3. LTG – supported by National Institutes of Health (NIH), USA – Grant number: K24AG053435. LRB – supported by The São Paulo Research Foundation (FAPESP) and National Council for Scientific and Technological Development (CNPq), Brazil.

Received on August 10, 2020. Accepted in final form on November 03, 2020.

INTRODUCTION

Although Parkinson disease (PD) is the most common form of α-synucleinophaties with movement disorder, and second most common neurodegenerative disorder worldwide, doubts about PD are still unclear.[1] PD neuropathology classification is based on the detection of altered α-synuclein, responsible for the formation of Lewy bodies in the tissue and neuroanatomic distribution of this alteration in the brain, as proposed by the Braak staging criteria for PD,[2] classifying it as a Lewy body pathology (LBP).[1] Several studies have shown a variety of possible mechanisms for PD, including increased oxygen free radicals, mitochondrial dysfunction, protein degradation and aggregation dysfunction, and neuroinflammation,[3] which is responsible for promoting the death of dopaminergic cells. The levels of tyrosine hydroxylase (TH) are severely reduced in the substantia nigra (SN) of PD patients.[4] TH is decreased after dopaminergic cell death, thus it is considered a good index of dopaminergic function in postmortem studies.[4]

PD is increasingly thought to be associated with glial pathology. Astrocytes, the most present class of glial cells in the mammalian central nervous system (CNS), has been highlighted as key molecule of neuroinflammation and has a very heterogeneous functional level.[5] Glial fibrillary acidic protein (GFAP) is a protein expressed in astrocytes widely described for having a relationship with neurodegenerative disease progression and CNS injuries,[6] as well as dysregulation of nervous system homeostasis.[7] Recently, research on neurodegenerative disorders has focused on understanding the role of astrogliosis in the disease pathophysiology, and has also been seem as a promising cellular source not only to study CNS pathologies initiation and progression, but also as a therapeutic target.[8]

In addition, structural proteins, such as microtubules and neurofilaments, are also important to be evaluated due to their importance for neuronal integrity and function. Previous studies revealed that, in neurons, microtubules maintain the integrity of axons by forming stable bundles and facilitate the transport of synaptic vesicles. One of the mechanisms used by cells to regulate the stability and dynamics of microtubules involves the interaction of microtubules with microtubule-associated proteins (MAP), including microtubule-associated protein-2 (MAP2). Interaction between MAP have either stabilizing or destabilizing effects on the microtubules.[9] MAP2 is the major neuronal component, providing structural support for the axon and regulating its diameter, therefore, dysfunction in their synthesis can directly affect neurotransmission.[9] Abnormal patterns of MAP2 in PD brain tissue have also been observed, and can be responsible for the destabilization of microtubule structures.[10] In neurodegenerative diseases, including PD, microtubules destabilization may be a vital step in the pathogenesis.[11]

Neurofilaments, whose subunits have different domain structures and function, are the only neuron-specific intermediate filaments.[12] They are important to give shape to cells; to determine axonal caliber, which controls signal conduction; to regulate the transport of synaptic vesicles; and to modulate synaptic plasticity.[13] On the other hand, the accumulation of neurofilament proteins can develop aggregates, being one of the responsible for the formation of Lewy bodies in PD.[13]

Several studies have investigated interventions aimed to improve the quality of life of PD patients. Physical activity in older people is important to prevent the disease,[14] as was seen in a recent longitudinal study with self-reported physical activity that revealed a decline in the clinical progression of PD.[15] In PD animal models, we have previously shown that exercise protocols promoted a reduction in inflammatory markers,[16] and an increase in dopamine function.[17] Despite the symptomatic improvements found in clinical trials, studies of human postmortem brains correlating physical activity with morphological changes are lacking.

Therefore, we aimed to evaluate, in a human postmortem brain tissue with proven Lewy body pathology classified as PD by Braak criteria, the association between active or non-active lifestyle and structural proteins (MAP2 and neurofilaments) and astrogliosis, evaluated by GFAP. The dopaminergic system function was also investigated by measuring the TH protein expression in these individuals.

METHODS

Participants

From 2004 to 2016, the Brain Bank from the Biobank for Aging Studies (BB-BAS) included 1,123 participants. The inclusion criteria is to be 50 years old or older. Exclusion criteria included acute brain lesions (*e.g.*, infarctions, hemorrhages, cancer, or trauma); severe chronic conditions that could interfere in brain homeostasis (*e.g.*, severe heart failure and dialytic chronic kidney failure); subjects without a reliable next-of-kin to answer the clinical interview; and subjects with acidosis due to severe agonal status (cerebrospinal fluid pH<6.5).[18] For this study, all participants with a neuropathological diagnosis of LBP classified as Braak PD stage≥III were included. Participants with incomplete information about lifestyle and bedridden were excluded. The deceased's

next-of-kin signed an informed consent to donate the brain. All procedures were approved by local and national human research ethics committees (Certificate number 285/04, and 1181 CEPSH/ICB/USP).

Postmortem clinical evaluation

Clinical assessment was obtained through a clinical interview with the next-of-kin. The protocol included semi-structured questionnaires that assessed clinical-functional and neuropsychiatric abilities, which were validated for postmortem interviews.[19] The interview included the Tanner questionnaire, a brief, sensitive and specific screening questionnaire for parkinsonism, and the Clinical Dementia Rating (CDR) scale for cognitive evaluation. The Tanner questionnaire contains nine questions about parkinsonism symptoms (one point for each symptom). The CDR evaluates the presence and severity of cognitive impairment by assessing six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Because of the nature of this postmortem study, only the informant section of the CDR was used. Participants were then classified into five categories: normal cognition (CDR=0); questionable dementia (CDR=0.5); mild dementia (CDR=1); moderate dementia (CDR=2); and severe dementia (CDR=3). Subjects with CDR>0 were characterized with cognitive impairment. Participants were considered to have an active lifestyle if the next-of-kin reported that the subject had a walking routine of at least three times a week in the last 12 months before death, and was active in household activities. The non-active individuals were paired with active ones based on age, gender, and PD Braak staging.[18] These information were obtained from the BB-BAS database.

Neuropathological evaluations

Brain tissue was obtained within 24 hours after death. One hemisphere was fixed in 4% buffered paraformaldehyde and specific areas were embedded in paraffin: middle frontal gyrus, middle and superior temporal gyri, angular gyrus, superior frontal, anterior cingulate gyrus, visual cortex, hippocampal formation at the level of the lateral geniculate body, amygdala, basal ganglia at the level of the anterior commissure, thalamus, midbrain, pons, medulla oblongata, and cerebellum. Blocks were sectioned into 5-μm-thick sections stained with hematoxylin and eosin. Immunohistochemistry was performed with antibodies against β-amyloid (4G8, 1:10,000; Signet Pathology Systems, Dedham, Massachusetts), phosphorylated tau (PHF-1, 1:2,000; gift from Peter Davies, New York), TDP-43 (1:500, Proteintech, Chicago, Illinois), and α-synuclein (EQV-1, 1:10,000; gift from Kenji Ueda, Tokyo, Japan).[20] Internationally accepted neuropathological criteria were used to stage and diagnose the brain pathologies.[21-25] We considered the diagnosis of Lewy body disease or PD when Braak PD stage≥3.[25]

The neuropathological classification was performed on all brains donated to BB-BAS. Based on the neuropathological classification, 100 participants were diagnosed with PD. Among these participants, 12 subjects were classified as active, and 34 were non-active. From the non-active group, 12 cases were selected and paired by age and gender with the active group. Therefore, this study included 24 subjects divided between active (n=12) and non-active groups (n=12) (Figure 1). The two groups had similar Braak PD staging (p=1.00). In addition, some participants also had Alzheimer disease (AD) neuropathology, but Braak staging for AD was similar between groups (p=1.00).

Selected samples were submitted to immunohistochemistry to evaluate structural proteins (neurofilaments and MAP2), astrogliosis (GFAP), and dopaminergic system (TH) in the midbrain (including the SN) and the basal ganglia (Caudate and Putamen nuclei). For that, slides with brain tissue were submitted to antigenic-retrieval treatment by immersion in citrate buffer pH 6.0 in a steamer at 95°C for 45 min.[26] The sections were incubated overnight at 4°C with primary antibodies, namely: TH (Millipore, MAB5280, 1:2,000), neurofilaments (Zymed, 18-0171, 1:2,000); MAP2 (Millipore, MAB3418, 1:2,000) and GFAP (Sigma, G3893, 1:2,000). After secondary antibody incubation (Jackson ImmunoResearch Laboratories, 715-065-151, 1:200), the sections were incubated for 1 h at 37°C with avidin-biotin-peroxidase complex (Vectastain® ABC Kit; Vector Laboratories, 1:100), and the slices were incubated with 0.05% 3,3'-diaminobenzidine tetrahydrochloride and a 0.01% solution of hydrogen peroxide in phosphate buffer. Intensification of the reaction was performed using 0.05% osmium tetroxide in water. The sections were dehydrated, cleared with xylol, and coverslipped with Permount (Fisher).

Five selected digital images with 10x magnification were acquired using a Nikon E1000 microscope (Melville, NY, USA) and a Nikon DMX1200 digital camera (Nikon Imaging Software ACT-U). An independent researcher blinded to the subject's physical activity status analyzed the integrated optical density of immunolabeling in five areas of 0.58 mm^2 from each digital image, totaling an analysis area of 3 mm^2 for each sample. Digital images were analyzed using the ImageJ software, version 1.52a (NIH, USA). For image analysis, the digital

image was opened, a square of 0.58 mm^2 was drawn, and the analysis instrument was used (Set Measurements – Integrated Density – Measure).

Statistical analysis

Data are represented as mean and standard deviations for continuous variables and frequencies for categorical variables. As the active and non-active groups were paired, we used paired *t*-tests to compare protein expression between groups. The McNemar test was used to compare categorical variables. $P<0.05$ was adopted.

RESULTS

Table 1 describes the characteristics of the samples. Tanner scores showed fewer parkinsonism symptoms among active participants compared to non-active ones (p=0.03). The non-active group revealed four subjects classified as CDR 0, three classified as CDR 0.5, one as CDR 1, two subjects as CDR 2, and two subjects as CDR 3. For the active group, there were seven subjects classified as CDR 0, one classified as CDR 1, one subject as CDR 2, and three as CDR 3 (p=0.45).

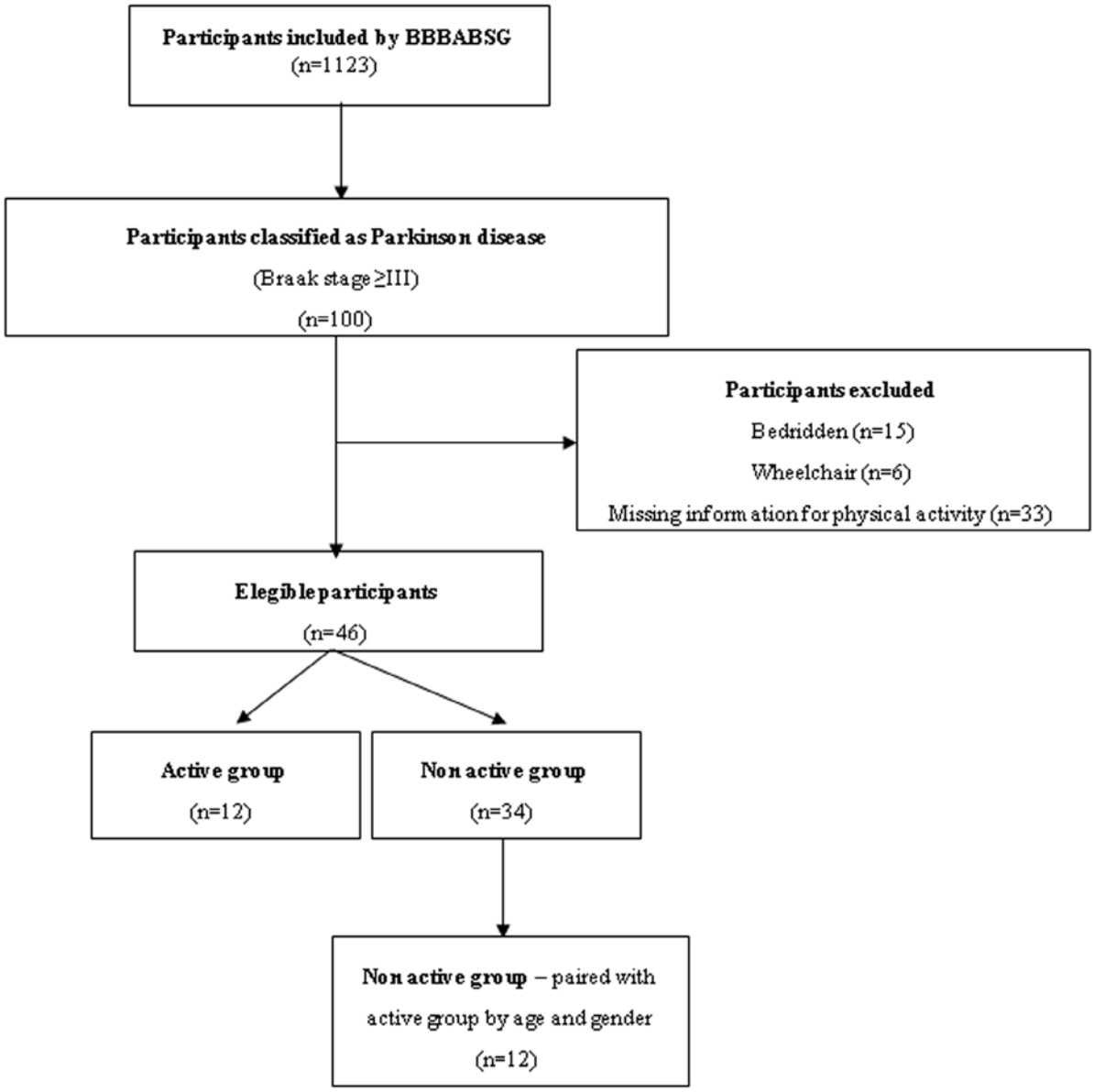


Figure 1. Flowchart of the inclusion process of the study participants.

Table 2 describes the mean and standard deviation of integrated density for each protein analyzed. TH was more highly expressed in the active group than in the non-active one in the SN (p=0.04) (Figures 2A and 2C) and in the basal ganglia (p=0.04) (Figures 2B and 2D). On the other hand, astrocyte was decreased in the substantia nigra of the active group compared to the non-active one (p=0.03) (Figures 2E and 2G) and increased in the basal ganglia among the non-active participants compared to the active participants (p<0.001) (Figures 2F and 2H).

For MAP2, there were no differences between the groups in the substantia nigra (p=0.46) (Figures 3A and 3C), while the expression was higher in the non-active group than in the active group in the basal ganglia (p=0.003) (Figures 3B and 3D). Neurofilaments were more highly expressed in the non-active group than in the active one in the SN (p=0.006) (Figures 3E and 3G), while no differences were observed between groups in the basal ganglia (p=0.24) (Figures 3F and 3H).

DISCUSSION

The present study is the first to correlate protein expression in individuals with proved LBP classified as PD, with an active lifestyle using human brain tissue. The active group, which included participants who walked at least three times a week during the year prior to death, showed higher expression of TH and lower expression of astrocytes in the midbrain and basal ganglia areas. On the other hand, MAP2 and neurofilament expression were higher in non-active subjects. Thus, this study can help explain the effects of physical activity on clinical progression improvement in PD patients.

It is important to reinforce that despite the small sample of subjects, all tissue samples analyzed in our study included only PD subjects with Braak stage≥III, and with the same Braak AD between groups confirmed by neuropathological classification. In addition, the Braak staging for PD was similar between groups, however the Tanner scale revealed more parkinsonism symptoms in the non-active participants, corroborating previous studies.[27]

Table 1. Characteristics of the sample (n=24).

	Non-active (n=12)	Active (n=12)	p-value
Age (years), mean±SD*	80.8±2.42	81.2±2.52	0.71
Male, n (%)†	7 (58.3)	7 (58.3)	1.00
Braak PD staging≥III, n (%)†	12 (100)	12 (100)	1.00
Clinical Dementia Rating CDR>0, n (%)†	8 (66.7)	5 (41.7)	0.45
Braak AD staging≥III, n (%)†	9 (75)	9 (75)	1.00
Tanner score, mean±SD*	3.42±3.20	0.67±1.07	0.03

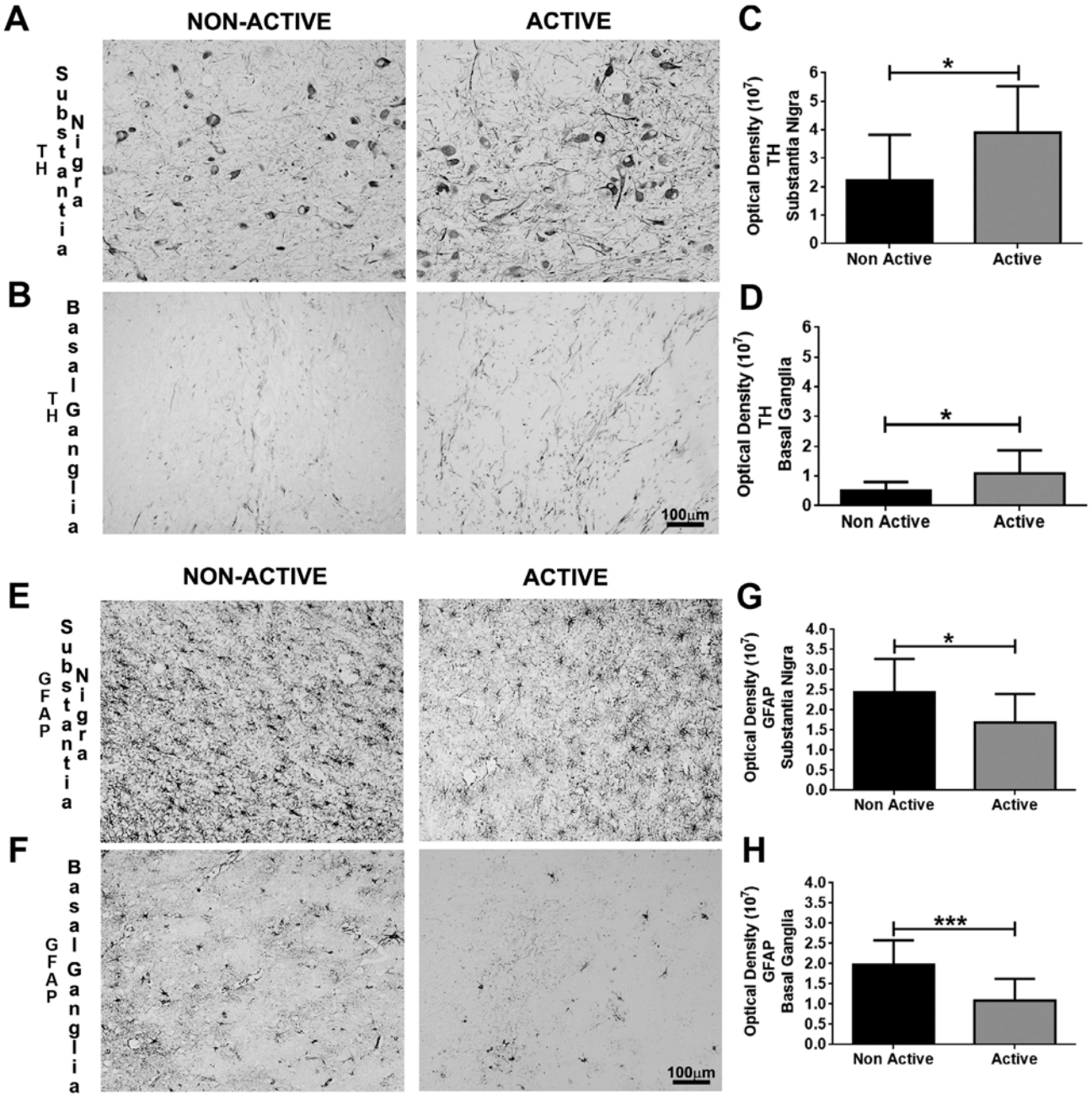
*paired t-test; †McNemar test; PD: Parkinson's disease; AD: Alzheimer's disease; SD: standard deviation.

Table 2. Protein expression in the substantia nigra and basal ganglia according to physical activity status (n=24).

	Substantia Nigra		Basal Ganglia	
	Non-active (n=12)	Active (n=12)	Non-active (n=12)	Active (n=12)
Tyrosine hydroxylase mean±SD (10^7)*	2.21±1.62	3.90±1.63	0.51±0.28	1.09±0.77
Microtubule-associated protein 2 mean±SD (10^7)*	1.86±1.05	1.54±0.81	1.57±0.73	0.73±0.41
Neurofilaments mean±SD (10^7)*	1.07±0.43	0.58±0.24	2.53±1.32	3.28±1.43
Glial fibrillary acidic protein mean±SD (107)*	2.44±0.83	1.69±0.70	1.99±0.60	1.09±0.54

*paired t-test. Data are expressed as the integrated density mean in an area of 0.58 mm^2.

Physical activity can slow down the aging process, which involves astrocytic,[28] as well as promotes better motor learning capacity, through increased plasticity in motor-related structures.[29] Progressive resistance exercise in PD patients with akinesia and rigidity can improve static posturography, gait, and quality of life.[30] Comparisons between patients with PD who self-reported regular exercise (≥2.5 hours per week) and people who exercise <2.5 hours per week revealed positive effects of exercise on health-related quality of life and mobility changes over two years. The benefit of exercise on health-related quality of life was greater in advanced than mild PD.[31] A recent clinical trial with 128 PD patients, followed for 3 years and with half the subjects undergoing exercise protocols, demonstrated that a high-intensity treadmill exercise protocol was

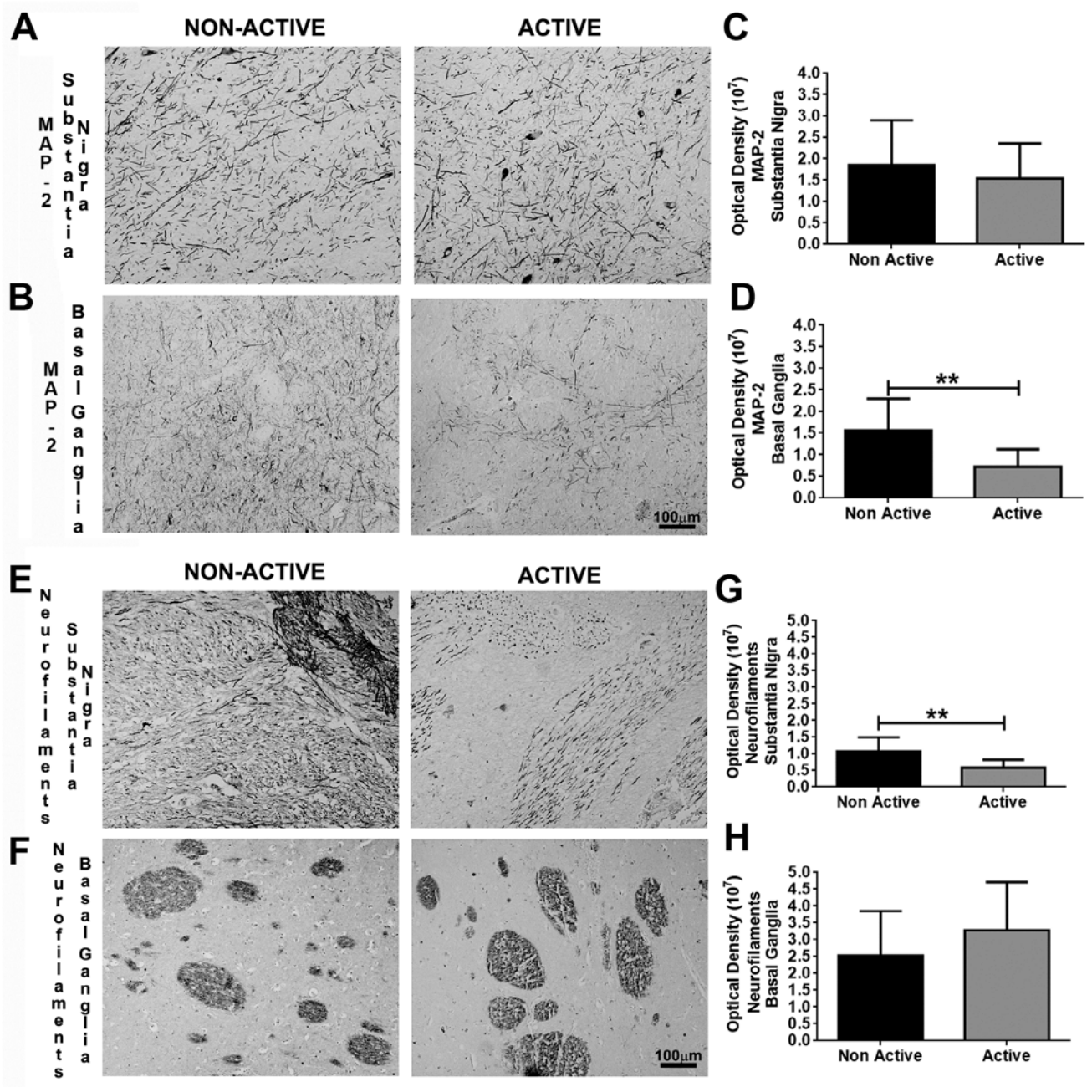


*p<0.05; ***p<0.001.

Figure 2. Digital images and graphics for tyrosine hydroxylase in the substantia nigra (A, C) and basal ganglia (B, D); and for glial fibrillary acidic protein in the substantia nigra (E and G) and basal ganglia (F and H).

able to promote improvement in Unified Parkinson's Disease Rating Scale motor scores.[32]

The current findings on TH expression in human postmortem material corroborate our previous studies with a 6-hydroxydopamine PD-like animal model. In animal models, treadmill exercise 3 times/week for 40 minutes led to the neuroprotection of the dopaminergic system with high TH expression in exercised animals, regardless of the exercise protocol.[16,17] Despite the ability of different exercise protocols to protect the dopaminergic system and benefit the nervous system, better effects are found when the exercise begins earlier.[15] In addition to high TH expression in the postmortem material from active participants, it was possible to observe that astrocytic activation was related to an increase in GFAP expression, which was also found in a previous study.[33] Astrocyte dysfunction has been described in LBP given the critical role of this



MAP2: microtubule-associated protein 2; **p<0.01

Figure 3. Digital images and graphics for microtubule-associated protein 2 in the substantia nigra (A, C) and basal ganglia (B, D); and for neurofilaments in the substantia nigra (E, G) and basal ganglia (F, H).

glial subtype in the metabolic and structural support of the nervous system.[7]

Studies suggest that astrocytes play an important role in the pathology and propagation of PD, since they sustain a hazardous environment and further promote dopaminergic neurodegeneration. The pathology of PD is not limited to neurons but extends to astrocytes, since the accumulation of α-synuclein is not only found in neurons, but also extends to astrocytes, which are capable of clearing α-synuclein deposits from neurons. After taking up α-synuclein, astrocytes are proposed to release cytokines including tumor necrosis factor and interleukin-6, thereby causing inflammatory responses, which can promote PD progression.[5] However, the exact role of these cells on the pathophysiology of PD is still controversial, since they can also be active anti-inflammatory pathways.[8] Nevertheless, the findings from PD postmortem studies on GFAP expression are inconsistent, since some have revealed GFAP upregulation and typical reactive morphology and others, minimal or mild astrogliosis in patients with PD.[5] The finding of decreased GFAP expression in active participants corroborated with studies in PD-like rat models that have described reduced GFAP, dopaminergic neuron protection, and improvements in motor behavior after a treadmill exercise protocol.[16]

In human postmortem material, there is a decrease in axonal transport in subjects in early phases of PD when compared to subjects without dopaminergic degeneration. In contrast, in the symptomatic phase of PD, there is an increase in MAP2 and neurofilaments.[34] These proteins, in the presence of α-synuclein protein, worsen clinical symptoms.[10] In addition, the present study evidenced reduced expression of these proteins in the active group, which could be related to fewer symptoms of parkinsonism and better TH expression. AD-brain-isolated tau protein was also observed to co-stain with both endogenous tau and MAP2, suggesting sequestration of these proteins, and α-synuclein also binds MAP2 *in vitro*. The sequestration of other MAPs may play an important role in the ability of the hyperphosphorylated Tau protein to cause microtubules instability and neurodegeneration, suggesting that the non-active group may have worse stability of microtubules in the basal ganglia.[11]

The majority of neurodegenerative disorders are proteinopathies, *i.e.*, they are diseases of protein homeostasis with proteins misfolding and accumulating in aggregates, including PD.[13] The high expression of neurofilaments in the non-active group when compared to the active one can suggest an increase in protein aggregation and PD progression, evidenced in our study with worsening of TH levels in non-active group. The mechanism by which neurofilaments aggregate is still unknown, but hyper-phosphorylation, which is the overexpression of neurofilaments, is considered one of the main triggers for neurofilaments (NF) aggregation,[13] including higher levels of neurofilaments in the cerebrospinal fluid.[12]

A major limitation of this study is that there was no information on exercise intensity and duration per session, as well as information on how many years the participant walked for. This information could be relevant because in animal models, the type, duration, and frequency of exercise are associated with plastic responses in the nervous system.[35,36] In our cross-sectional study, questionnaires were evaluated postmortem, which can cause information bias, though they were also validated for postmortem interview,[19] and used before by other studies.[20,37,38] Another limitation is the absence of control cases, future studies should include subjects without neurodegenerative disease neuropathology. Also a limitation is the presence of mixed neuropathology, since 75% of our sample had a significant number of neurofibrillary tangles. However, it is important to note that the Braak score for AD was similar between the non-active and active groups.

Despite the fact that our sample contains subjects with cognitive impairment defined as CDR≥0.5, there was no statistical difference between groups regarding the CDR. In a validation study of the postmortem interview, we found a high accuracy for normal cognition and moderate and advanced dementia; and lower accuracy was found for questionable and mild dementia.[19] Although the information on cognitive impairment was used to describe the sample, it is important to highlight that the main study variable was LBP based on a neuropathological examination, which is not subject to bias related to postmortem evaluation. In addition, non-active and active groups were paired by age and gender, reducing the confounding chance by these variables.

In conclusion, in participants with similar LBP burden, classified as PD, an active lifestyle may improve dopamine synthesis and structural protein expression in the nigrostriatal system as well as decrease astrocyte activation, which are associated with neuronal death and the worsening of clinical symptoms in neurodegenerative diseases. Our study showed similar results to those found in animal models of PD that could explain the benefits of physical activity in the clinical improvement of PD patients who underwent exercise protocols. Future studies in human brain samples that evaluate the frequency, duration, and intensity of exercise are

important to better understand the clinical effects of exercise on PD pathophysiology.

ACKNOWLEDGEMENTS

This study was supported by The São Paulo Research Foundation (FAPESP, Brazil), Coordination for the Improvement of Higher Education Personnel (CAPES, Brazil), Research Center on Applied Neuroscience (NAPNA, Brazil) and The National Council for Scientific and Technological Development (CNPq, Brazil). Thanks are also due to Adilson S. Alves for technical assistance. CCR and KHB were the recipient of a fellowship from FAPESP (2013/25049-2 and 2016/16166-3, respectively).

Authors' contribution. CCR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Visualization, and Writing – original draft; CKS: Conceptualization, Formal analysis, Resources, Visualization, and Writing – review; KHB: Formal analysis, Investigation, and Writing – review; LTG: Resources, and Writing – review; CAP: Resources, and Writing – review; WJF: Resources, and Writing – review; RELFR: Resources, and Writing – review; RN: Resources, and Writing – review; REPL: Conceptualization, Resources, and Writing – review; Luiz R Britto: Conceptualization, Funding acquisition, Supervision, Resources, and Writing – review.

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Dement Neuropsychol 2021 March;15(1):51-59

Original Article

https://doi.org/10.1590/1980-57642021dn15-010005

Impact of cognitive intervention on cognitive symptoms and quality of life in idiopathic Parkinson's disease: a randomized and controlled study

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ABSTRACT. Pharmacological treatments for mild cognitive impairment (MCI), are lacking, and alternative approaches have been implemented, including cognitive training (CT). **Objective:** To determine the impact of CT on cognitive and quality of life measures in patients with Parkinson's disease (PD) who were seen a hospital neurorehabilitation program. **Methods:** Thirty-nine individuals with MCI-PD, according to the Movement Disorder Society, were randomly distributed into two groups: experimental and control group, matched for demographic and clinical characteristics. Both groups were assessed for cognition and quality of life at the beginning of the study and at the end of the intervention protocol. The following instruments were used to assess cognition and quality of life: Addenbrooke's Cognitive Examination III, Digit Span, Trail Making Test (TMT, A and B) and Parkinson disease quality of life questionnaire. The experimental group (EG) engaged in CT, whereas the control group (CG) underwent activities of the general rehabilitation program. **Results:** No baseline evaluation differences were found. Intergroup analysis showed differences in measures, such as total score (1.977, p=0.0480) and visuospatial domain (-2.636, p=0.0084) of the ACE-III, with the EG performing better, in addition to better performance in TMT-B mistakes (-1.928, p=0.0439). Intragroup analysis revealed that the EG showed significant improvement in almost all the cognitive variables, well as in self-reported quality of life (total score and mobility, activities of daily living, body discomfort dimensions). **Conclusion:** Engagement in cognitive activities was associated with better cognitive abilities in PD-MCI. Future studies should consider the long-term effect of this type of intervention and impact on functional activities.

Keywords: Parkinson's disease, cognition, rehabilitation, quality-of-life.

O IMPACTO DA INTERVENÇÃO COGNITIVA NOS SINTOMAS COGNITIVOS E NA QUALIDADE DE VIDA NA DOENÇA DE PARKINSON IDIOPÁTICA: UM ESTUDO RANDOMIZADO E CONTROLADO

RESUMO. A falta de evidência de tratamentos farmacológicos, especificamente para pacientes com comprometimento cognitivo leve na doença de Parkinson (CCL-DP), leva à implementação de abordagens alternativas, incluindo a reabilitação cognitiva. **Objetivo:** Determinar o impacto do treino cognitivo (TC) em medidas cognitivas e da qualidade de vida em pacientes com DP, que participavam de um programa de reabilitação neurológica hospitalar. **Métodos:** Total de 39 indivíduos com CCL-DP, de acordo com a Sociedade de Distúrbios do Movimento, foram distribuídos aleatoriamente em dois grupos: experimental e controle, pareados por características demográficas e clínicas. Ambos os grupos foram avaliados quanto à cognição e qualidade de vida no início do estudo e ao final do protocolo de intervenção. Os seguintes instrumentos foram utilizados para avaliar a cognição e a qualidade de vida: Exame Cognitivo III de Addenbrooke, teste de dígitos, TMT (A e B) e questionário de qualidade de vida da doença de Parkinson. O grupo experimental foi submetido ao treino cognitivo, ao passo que o grupo controle passou por atividades do programa de reabilitação. **Resultados:** Não foram encontradas diferenças na avaliação basal. A análise intergrupo mostrou diferenças em medidas, como escore total (1,977, p=0,0480) e domínio visuoespacial (-2,636, p=0,0084) da ACE-III, tendo o grupo experimental melhor desempenho, além de desempenho superior em TMT-B erros (-1,928, p=0,0439). A análise intragrupo revelou que o grupo experimental mostrou melhora significativa em quase todas as variáveis cognitivas, assim como na percepção de qualidade de vida (escore total e dimensões de mobilidade, atividades da vida diária e desconforto corporal). **Conclusão:** O envolvimento em atividades cognitivas foi associado a melhores habilidades cognitivas em pacientes com CCL-DP. Estudos futuros devem considerar o efeito a longo prazo desse tipo de intervenção e o impacto nas atividades funcionais.

Palavras-chave: doença de Parkinson, cognição, reabilitação, qualidade de vida.

This study was conducted at the Rede SARAH de Hospitais de Reabilitação – Reabilitação Neurológica, Unidade de Salvador, Salvador, BA, Brazil.

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Disclosure: The authors report no conflicts of interest.

Funding: none.

Received on March 23, 2020. Accepted in final form on October 26, 2020.

INTRODUCTION

The original description by James Parkinson mentioned a condition characterized by motor features, which included bradykinesia, tremor and gait impairment, but he also described other symptoms, without the same accuracy, such as bowel dysfunction, somnolence, delirium and constipation, which now constitute the spectrum of nonmotor symptoms (NMS) associated with Parkinson's disease (PD).[1,2] Such symptoms were neglected for many years but in many cases, especially in more advanced stages, may dominate the clinical picture and impair functional performance and quality of life. It is important to improve long-term outcomes by delivering therapeutic interventions earlier in the clinical course of cognitive dysfunction, although the best therapeutic decision is not precisely defined.[3]

Mild cognitive impairment (MCI) is considered an intermediate stage between normal cognition and the presence of dementia, having been initially recognized in patients with Alzheimer's disease, but it can be present in individuals with Parkinson's disease since diagnosis. Recommendations from the National Institute on Aging-Alzheimer's Association workgroup defined the symptomatic pre-dementia phase of Alzheimer's Disease and proposed a set of criteria to establish the diagnosis. Recently, the DSM 5 recognized the clinical entity of minor neurocognitive disorder (NCD) for different disorders including PD.[4] In contrast to amnestic MCI as a prodrome to Alzheimer's disease (AD), the Parkinson's disease-mild cognitive impairment (PD-MCI) is more heterogeneous and may affect diverse cognitive domains. This heterogeneous clinical presentation is related to a great variety of available tests to assess cognitive functions in PD patients. The clinical diagnostic criteria were defined by the Movement Disorder Society (MDS) that proposed standardized diagnostic criteria. Routine cognitive screening is important for the optimal management of patients with PD, to assess cognition functions, and to define the diagnosis of MCI or Parkinson's disease dementia (PDD). The Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE),[5] and Addenbroke's Cognitive Examination (ACE) were evaluated in different studies and populations, but even a positive screen frequently requires additional assessment through standardized neuropsychological tests, to assess the whole heterogeneity of cognitive impairment in PD patients. Patients who present deficits in semantic language, figure drawing/copying and visuospatial tasks have a higher risk to develop dementia.[6,7]

Although PD is considered a motor control disorder, deterioration in cognitive functions is a common complication, occurring in approximately 40% of cases. Half of the patients without dementia have MCI, and such changes can impair the patient's quality of life, as well as being a risk factor for the development of dementia.[8] Other studies report that a quarter of newly diagnosed patients already have some cognitive impairment and can affect 26.7% of patients without dementia.[9,10] Cognitive decline, especially in executive functions, is more associated with worsening gait performance and risk of falls.[11] Cognitive changes are characterized mainly by deficits in executive functions, visuospatial skills and attention.[12,13]

Single domain and multiple domain MCI are the most observed in this population, mainly the dysexecutive subtype; however, the criteria for defining MCI in PD are not yet fully established.[14] Therefore, cognitive assessment and use of functional scales should be taken into account for this diagnosis. There are brief batteries that assist in the differential diagnosis of MCI and dementia in PD, such as ACE, in addition to cognitive screening instruments (such as MMSE) and standardized neuropsychological tests, to assess function cognitive.

Non-pharmacological approaches are essential for the management of cognitive symptoms, and their importance becomes even more significant in view of the lack of evidence of the effectiveness of pharmacological approaches. Recent studies have shown the effectiveness of cognitive training (CT) programs (individual or group) and cognitive-specific rehabilitation approaches have been tested in this population, due to the specificity of the neuropsychological disorder, in which impaired attention functions predominate.

Therapeutic approach in cases of PD-MCI or PDD may involve medications, such as cholinesterase inhibitors, CT, physical exercise which may include tango and/or treadmill training, brain stimulation, or combined interventions. The best therapeutic strategy is yet to be defined and the treatment of patients presenting these conditions is frequently a challenge to health professionals.[15]

There was an increase in publications on this topic not only in PD but in healthy elderly people and those with other neurological conditions.[16] Neuroimaging studies have shown changes in activation in brain regions,[17-19] and also a systematic review study showed that there was an improvement in global cognition and ability for planning.[20] The studies used different assessment and intervention protocols (format of interventions and assessment instruments, sample size, follow-up time and therapeutic dose), which can interfere in the comparative and homogeneous analysis of the results. These aspects interfere in the comparison

between studies and in the ability to generalize the results. Thus, there are studies with computerized CT,[21] paper-pencil tasks[22] and even combined with transcranial direct current stimulation.[23] Most of these studies show that CT has a positive effect on cognitive performance and should be considered as an adjunctive therapy in PD.[24,25]

Limitations of existing research include diverse methodologies and CT programs, small samples, insufficient focus on functional outcomes, sustainability and generalization of effects of this treatment.

A study, performed in Brazil, determined the effectiveness of physiotherapy associated with CT to improve cognition and quality of life in individuals with PD, involving 58 individuals with mild to moderate PD, randomly distributed into two groups: motor group and cognitive-motor group. Intragroup analysis revealed that both groups showed improved cognition (memory and visuospatial function domains) and quality of life after execution of the protocols, but without statistically significant intergroup differences.[22]

We evaluated the therapeutic effects of non-pharmacological interventions (CT) on cognitive symptoms in PD, including control group (CG) and randomization.

The group intervention, the modality of cognitive intervention chosen for this study, allows a more direct and efficient approach to issues common to most patients, providing a moment of learning and the search for shared solutions.

Our main objective was to determine the effectiveness of a 4-week, randomized and controlled CT program in improving cognition performance and quality of life of individuals with PD.

METHODS

This was a randomized, placebo-controlled study.

Recruitment and treatment protocol were conducted at the rehabilitation hospital from January 2019 to November 2019, at the SARAH Network of Rehabilitation Hospitals (Salvador/Bahia Unit, Brazil). A total of 39 patients (24 in the experimental group (EG) and 15 in the CG) were enrolled in this study, according to UK Parkinson's Disease Brain Bank criteria.

Participants and recruitment

The following inclusion criteria were applied:

- MCI according to the Movement Disorders Society (MDS) PD-MCI Level II diagnostic criteria;[23]
- presence of a stable response to antiparkinsonian medication in the pre-intervention and during the course of the intervention;
- Hoehn and Yahr (H&Y) stages I–III;
- the Beck Depression Inventory scores, with minimal to light intensity (BDI≤16); and
- not having participated in CT protocols in the year prior to enrollment.

The ACE-III battery and executive function tests (Digit Span and Trail Making Test, A and B) were used; in addition to the application of a quality-of-life questionnaire (PDQ-39), before the intervention/baseline (T0) and immediately after the intervention (T1).

The patients were divided into two groups (EG and CG), according to simple randomization. Candidate files were forbidden as to the identification and numbered in their verses from 1 to 8, after which the numerals were drawn and their respective allocation in each group: control or experimental. At the end of the allocation, professionals were made aware of the identifications to inform candidates of their respective modality of participation in the study.

The study was approved by the local Ethics Committee (CAAE: 88364618.8.0000.0022). All participants received the research details and signed on the informed consent line. Participation was carried out during "on" medication stage.

Neuropsychological assessment

The tests were administered in a fixed order by a neuropsychologist. The following tests were administered during the "on" phase of the patients: Digit Span, TMT-A and TMT-B and short battery ACE-III.

After cognitive evaluation and application of the quality-of-life questionnaire (PDQ-39), patients who fulfilled the inclusion criteria were referred to specific groups, according to randomization.

All participants (EG and CG), during this study, participated in the general activities of the rehabilitation program for four weeks: physiotherapy, dance, reeducation in writing, speech therapy, information groups, manual skills workshops, physical activity.

Experimental group

Participants in the EG additionally received the CT program conducted by two professional cognition experts, twice a week for 120 minutes each, totaling 8 sessions. The intervention emphasized the specific areas of cognitive deficit in this population, attention and executive dysfunction.

The CT program consisted of paper-and-pencil tasks, focused on the repeated practice of structured exercises, organized at a level of complexity and aimed to the specific cognitive domain(s), with the purpose of improving cognitive function.

Each session contemplated a function more explicitly: attention, visual memory, working memory, planning, and visuospatial and visuoconstructive abilities. The tasks involved find and mark equal figures among other similar ones, follow instructions to solve a problem, observing scenes and after evoking their details, planning and building geometrics puzzles, matching shadows between themselves focusing on the details, and reading and evoking information in a text.

The participants were asked to explore and find solutions to the initial task of each meeting, to resolve it and, after discussion with the other participants, to select the most effective strategies, being encouraged by professionals to use them for the next tasks of the same session. In the same session, three levels of difficulty were offered (easy to difficult).

Control group

The participants participated only in the various activities of the general rehabilitation program by four weeks: physiotherapy, dance, reeducation in writing, speech therapy, information groups, manual skills workshops, and physical activity, except for activities that involved CT itself.

Statistical analysis

Descriptive statistics (total value/percentage, mean, standard deviation and confidence interval) and inferential statistics were used. The chi-square test for nominal data and the *t*-test were used to compare demographic and clinical data between groups.

The paired-sample Student's t-test (repeated measurement) was used to evaluate the effect of time (T0 and T1) in each group. The Student's t-test for independent-samples was used to evaluate the effect of group (EG and CG) in T0 and T1. Correlation analyses between cognitive variables and quality of life, were performed by Spearman's correlation.

Statistical significance was set at $p<0.05$. All analyses were performed using *Statistical Package for the Social Sciences* (SPSS) software, version 22.0.

RESULTS

Twenty-four patients and fifteen controls participated in the study, matched for age, gender, education, age and disease severity, global cognition. All patients received stable drug treatment throughout this period.

The EG had a mean age of 60 (±7.5) years, and there was a higher proportion of men than women; mean years of education was 12.4 (±3.1). In relation to clinical data, patients had a mean time of disease evolution of 5.7 (±3.3) years and 87.5% were in stage I-II on the Hoehn & Yahr (H&Y) scale.

The CG had a mean age of 58.5 (±9.8) years, and there was a higher proportion of men than women; mean years of education was 12.8 (±3.4). Regarding the clinical data, patients had a mean time of disease evolution of 6.8 (±8.8) years and 93.3% were in stage I-II on H&Y (Table 1).

In Table 2, we can see that there was an improvement in measures in the post-intervention period (T1) in both groups, with better performance, in relation to the mean values for the EG.

As seen in Table 3, the baseline evaluation (T0) did not show any difference in the cognitive variables between the groups. In the T1 evaluation, there were differences in measures, including total score (1.977, p=0.0480*) and visuospatial domain (-2.636, p=0.0084*) in the ACE-III, with the EG performing better, in addition to better performance in TMT-B mistakes (-1.928, p=0.0439*).

To compare and measure the effect of the intervention, in relation to the EG, parametric statistics were used paired-sample Student's t-test after normality analysis (Shapiro-Wilk $p>0.05$). Table 4 presents the

Table 1. Demographic and clinical data at baseline of patients in the control and experimental groups.

	Experimental group (n=24)	Control group (n=15)	p-value
	Mean (SD) or n (%)	Mean (SD) or n (%)	
Age, years	60.0 (7.5)	58.5 (9.8)	0.6980[a]
Gender	4 (16.67%) females and 20 (83.33%) males	2 (13.33%) females and 13 (86.66%) males	0.779[b]
ACE-III (total score)	87.5 (6.6)	87.1 (6.9)	0.2354[a]
Education, years	12.4 (3.1)	12.8 (3.4)	0.3495[a]
Duration of disease (years)	5.7 (3.3)	6.8 (8.8)	0.3309[a]
H&Y scale, n	Stage 3=3	Stage 3=1	0.6804[b]

SD: standard deviation; ACE-III: Addenbrooke's Cognitive Examination III; [a]chi-square test; [b]Student's t-test for independent samples.

results showing improvement in attention/orientation subscores (-2.228, p=0.0259*), memory (-3.221, p=0.0013*), verbal fluency (-2.133, p=0.0329*) and visuospatial function (-2.562, p=0.0104*), in addition to the total score (-3.686, p=0.0002*) in the ACE-III battery. Regarding the standardized neuropsychological tests, improvement was observed in tests that evaluate alternate attention and visuomotor processing speed (TMT-B errors -1.646, p=0.0398*; TMT-A seconds -0.700, p=0.0484*). In the CG, improvement was observed in domains including verbal fluency (-2.020, p=0.0434*) and visuospatial function (-2.227, p=0.0260*) in the ACE-III.

Regarding quality of life (PDQ-39 values), there was an improvement in the total score, mobility, activities of daily living and body discomfort dimensions in the EG. The CG showed improvement only in the total score (Table 5).

Correlations between quality-of-life data (PDQ-39) and cognitive scores showed significant interaction between the total score of the PDQ-39 questionnaire and TMT-B (r=0.3724, p=0.0358) and activities of daily living of PQD-39 and TMT-B (r=0.4453, p=0.0106) in the post-intervention group.

No adverse effects were reported during treatment in either group.

DISCUSSION

Cognitive dysfunctions are common non-motor symptoms in PD and are generally associated with a worse

Table 2. Neurocognitive performances in the control and experimental groups at baseline (T0) and retest (T1).

n=39	Control group T0 Mean (SD)	Confidence interval	Control group T1 Mean (SD)	Confidence interval
ACE-III (total score)	87.07 (7.19)	83.0872–91.0461	89.83 (6.38)	85.7800–93.8866
Attention/orientation	17.20 (1,21)	16.5315–17.8684	16.50 (1.73)	15.3995–17.6004
Memory	20.87 (4.05)	18.6233–23.1099	22.25 (4.31)	19.5121–24.9878
Verbal fluency	10.00 (1.51)	9.1627–10.8372	11.25 (1.48)	10.7837–26.0496
Language	24.93 (1.83)	23.9193–25.9472	25.42 (1.00)	24.7837–26.0496
Visuospatial function	14.07 (1.33)	13.3276–14.8057	14.42 (1.00)	13.7837–15.0496
Digit span (forward)	5.27 (0.59)	4.9379–5.5954	5.64 (0.81)	5.0928–6.1798
Digit span (backward)	3.93 (0.59)	3.6045–70.2185	4.00 (1.18)	3.2051–4.7948
Trail making test (A)	59.13 (20.02)	48.0480–70.2185	55.33 (12.94)	45.3850–65.2815
Trail making yest (B)	174.20 (122.05)	106.611–241.788	214.33 (162.58)	89.3603–339.306
n=39	**Experimental group T0 Mean (SD)**	**Confidence interval**	**Experimental group T1 Mean (SD)**	**Confidence interval**
ACE-III (total score)	87.50 (6.76)	84.6442–90.3557	92.26 (5.17)	90.0244–94.4973
Attention/orientation	16.71 (1.46)	16.0922–17.3244	17.13 (1.25)	16.5880–17.6728
Memory	20.75 (3.74)	19.1688–22.3311	22.96 (2.62)	21.8237–24.0892
Verbal fluency	9.92 (2.36)	8.92116–10.9121	11.61 (3.77)	9.9763–13.2410
Language	25.54 (0.72)	25.2371–25.8461	25.22 (3.33)	23.7775–26.6572
Visuospatial function	14.58 (1.50)	13.9494–15.2172	15.35 (1.07)	14.8848–15.8108
Digit span (forward)	5.33 (1.20)	4.82498–5.8416	5.65 (0,98)	5.2275–6.0768
Digit span (backward)	3.83 (0.76)	3.51182–4.15483	3.91 (1.08)	3.4445–4.3815
Trail making test (A)	63.71 (19.57)	55.4426–71.9740	61.52 (25.38)	50.5456–72.49781
Trail making test (B)	193.38 (126.62)	139.909–246.8403	188.74 (93.14)	148.4612–229.0171

Mean (standard deviation [SD]); ACE-III: Addenbrooke's Cognitive Examination III.

prognosis. The current study aimed to evaluate cognitive intervention (CT) in cognitive and quality of life measures in patients with PD-MCI.

The current intervention program, in a group format, was beneficial in these patients.

The results showed improvement, after this intervention program in aspects, mainly attention (especially test of shifting attention and processing speed), executive (verbal fluency) and global measures in the ACE-III battery, in agreement with other studies that have shown the benefits of this type of intervention in Parkinson's patients.

Regarding quality of life, the results showed a significant improvement in the total score and in

Table 3. Inferential analysis — experimental x control.

Cognitive tasks	Baseline (T0)		Post-intervention (T1)	
	t-test	p-value	t-test	p-value
Digit span forward	-0.456	0.6487	-0.039	0.9685
Digit span backward	0.360	0.7191	0.268	0.7887
TRAIL A second	-0.867	0.3862	-0.482	0.6297
TRAIL A mistakes	1.265	0.2059	-0.626	0.5316
TRAIL B second	-1.039	0.2987	-0.231	0.8177
TRAIL B mistakes	1.634	0.1022	-1.928	0.0439*
Total score (ACE-III)	-1.187	0.2354	1.977	0.0480*
Attention/orientation	-1.072	0.2838	-1.327	0.1844
Memory	0.174	0.8616	0.000	1.0000
Verbal fluency	-0.117	0.9069	0.177	0.8594
Language	-1.150	0.2503	-1.395	0.1631
Visuospatial function	-1.276	0.2018	-2.636	0.0084*

Student's t-test for independent samples (group effect); *p<0.05; **p<0.01.

Table 4. Inferential analysis — baseline x post-Intervention evaluations.

Cognitive tasks	Control group		Experimental group	
	t-test	p-value	t-test	p-value
Digit span forward	-1.414	0.1573	-1.384	0.1664
Digit span backward	0.000	1.0000	-0.113	0.9103
TRAIL A second	-0.178	0.8590	0.700	0.0484*
TRAIL A mistake	1.000	0.3173	-1.000	0.3173
TRAIL B second	-0.059	0.9528	-0.532	0.5945
TRAIL B mistake	0.914	0.3609	1.646	0.0398*
Total score (ACE-III)	-0.029	0.9769	-3.686	0.0002*
Attention/orientation	1.386	0.1657	-2.228	0.0259*
Memory	-1.327	0.1844	-3.221	0.0013*
Verbal fluency	-2.020	0.0434*	-2.133	0.0329*
Language	-1.379	0.1677	-1.335	0.1819
Visuospatial function	-2.227	0.0260*	-2.562	0.0104*

Paired-sample *t* test (baseline and post-intervention) in each group (intragroup analysis); *p<0.05; **p<0.01.

the dimensions of mobility, activities of daily living and body discomfort. The results, therefore, are in line with data from the literature demonstrating that cognitive interventions are effective in patients with PD.[24-26]

In the CG, improvement was observed in the domains verbal fluency (-2.020, p=0.0434*) and visuospatial function (-2.227, p=0.0260*) in the ACE-III (Table 2), as was also observed in the CG, but with a slightly lower level of significance.

The CG also showed improvement after CT, but the intervention group showed improvement in more cognitive and quality of life measures. It is worth mentioning that the groups were homogeneous in demographic and clinical aspects, making the analysis of the intervention effect with less bias, such as interference from the learning effect.

Despite the PDQ-39 instrument being the most used in this population, we observed few items that assess the cognitive dimension, while others have a higher quantity. These aspects may have interfered with the results observed in this study.

The maintenance of the effects of CT over time has also been the object of investigation. However, there are few studies that maintain longitudinal monitoring.[27] A study that maintained longitudinal monitoring for 3 months after the intervention observed persistent results in language, attention and executive functions.[28] In turn, the maintenance of benefits after one year of participation in a structured and consistent training program was observed.[10]

Studies that contemplate a more systematic follow-up may help in the design of training programs more useful to this population.

The improvement observed also in the CG could be attributed to the benefit that motor activity can have for cognition, since the general activities of the rehabilitation program carried out in both groups have a greater character of motor training, and as its execution demands cognitive skills (attention and executive functions), it is possible that they offer cognitive challenges to individuals with PD and this has also been reflected in the CG.[22]

The methodological variability of the training programs established in the studies can include sample size, therapeutic dose (number and duration of intervention sessions), evaluation and intervention protocols, absence of follow-up and variable follow-up times, which are some of the aspects that hinder the more precise definition of the effects of CT and which demand more and more investigations in this area. Moreover, most of the studies included a cognitively mixed PD group in terms of cognitive decline; these studies might have less ability to detect treatment effects, as ceiling effects may play a role in cognitively unimpaired individuals.

Despite the methodological improvement of studies with group CT, it is difficult to compare them and generalize the results.

This study, even though on a small study sample, showed differential treatment effects for a PD-MCI group.

The results of our study showed the importance of early cognitive assessment and intervention in the PD-MCI population. There is a greater benefit and effectiveness of the CT as they have more preserved skills. Most of our sample consisted of patients who were still working or had an active routine of activities. In this study, however, it was not possible to assess the persistence of cognitive gain after training (follow-up),

Table 5. Inferential analysis — baseline x post-intervention evaluations.

PDQ-39	Control group		Experimental group	
	t test	p-value	t test	p-value
Total score	1.889	0.0588*	2.275	0.0229*
Mobility	1.916	0.0554	2.680	0.0074**
Activities of daily living	0.905	0.3656	3.317	0.0009**
Emotional well-being	1.560	0.1188	1.326	0.1848
Stigma	1.882	0.0599	0.335	0.7379
Social support	-0.771	0.4406	-0.957	0.3386
Cognition	0.884	0.3768	0.405	0.6853
Communication	0.159	0.8733	-0.217	0.8283
Body discomfort	0.666	0.5057	2.847	0.0044**

Paired-sample *t* test (baseline and post-intervention); *p<0.05; **p<0.01.

and only the assessment was carried out immediately after the intervention. However, the demographic and clinical homogeneity between the groups (EG and CG) at baseline (T0) contributed to the analysis of the effectiveness of cognitive intervention.

The current study had as strengths:

- neuropsychological assessment with global and cognitive and sensitive and standardized assessment tests for this population;
- groups with homogeneous profile;
- systematization and standardization of the mediation/intervention process; and
- CG matched by demographic and clinical characteristics.

The limitations were:

- the progressive characteristic of the pathology increases the risk of cognitive worsening and development of dementia, which may influence the results of the reassessment;
- the reduced intensity of interventions (therapeutic dose) of cognitive training when compared with previous studies on neuropsychological intervention; and
- absence of follow-up.

Although more controlled studies are needed to demonstrate the effectiveness of CT interventions, the current study did highlight that a CT treatment can be useful to improve cognitive functioning in PD patients. Future studies should consider the long-term effect of this type of intervention and impact on functional activities of this treatment. These findings support the integration of CT into the standard of care for patients with PD.

Authors' contributions. NMFS, ACMN, IVBB and SMDB: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing — original draft, writing — review & editing.

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Dement Neuropsychol 2021 March;15(1):60-68

Original Article

https://doi.org/10.1590/1980-57642021dn15-010006

Changes in executive function and gait in people with mild cognitive impairment and Alzheimer disease

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ABSTRACT. Changes in executive function and motor aspects can compromise the prognosis of older adults with mild cognitive impairment (MCI) and favor the evolution to dementia. **Objectives:** The aim of this study was to investigate the changes in executive function and gait and to determine the association between changes in these variables. **Methods:** A 32-month longitudinal study was conducted with 40 volunteers: 19 with preserved cognition (PrC), 15 with MCI and 6 with Alzheimer disease (AD). Executive function and gait speed were assessed using the Frontal Assessment Battery, the Clock-Drawing test and the 10-meter walk test. For data analysis, the Pearson product-moment correlation, two-way repeated-measures ANOVA, and chi-square were conducted. **Results:** After 32 months, an improvement in the executive function was found in all groups (p=0.003). At baseline, gait speed was slower in individuals with MCI and AD compared to those with PrC (p=0.044), that was maintained after the follow-up (p=0.001). There was significant increase in number of steps in all groups (p=0.001). No significant association was found between changes in gait speed and executive function. **Conclusion:** It should be taken into account that gait deteriorates prior to executive function to plan interventions and health strategies for this population.

Keywords: walking speed, longitudinal studies, cognition, cognitive dysfunction, aging.

ALTERAÇÕES NA FUNÇÃO EXECUTIVA E NA MARCHA EM PESSOAS COM COMPROMETIMENTO COGNITIVO LEVE E DOENÇA DE ALZHEIMER

RESUMO. Alterações na função executiva e nos aspectos motores podem comprometer o prognóstico de idosos com comprometimento cognitivo leve (CCL) e favorecer a evolução para demência. **Objetivos:** O objetivo deste estudo foi investigar alterações na função executiva e na marcha e determinar a associação entre alterações nessas variáveis. **Métodos:** Foi realizado um estudo longitudinal de 32 meses com 40 voluntários: 19 com cognição preservada (PrC), 15 com CCL e 6 com doença de Alzheimer (DA). A função executiva e a velocidade da marcha foram avaliadas por meio de bateria de avaliação frontal, do teste de desenho do relógio e do teste de caminhada de 10 metros. Para a análise de dados, o coeficiente de correlação produto-momento de Pearson, ANOVA de medidas repetidas bidirecional e o qui-quadrado foram realizados. **Resultados:** Após 32 meses, houve melhora na função executiva em todos os grupos (p=0,003). No início do estudo, a velocidade da marcha foi mais lenta nos indivíduos com CCL e DA em comparação com os PrC (p=0,044), que foi mantida após o acompanhamento (p=0,001). Houve aumento significativo no número de etapas em todos os grupos (p=0,001). Não foi encontrada associação significativa entre alterações na velocidade da marcha e função executiva. **Conclusão:** Deve-se levar em consideração que a marcha se deteriora antes da função executiva para planejar intervenções e estratégias de saúde para essa população.

Palavras-chave: velocidade de caminhada, estudos longitudinais, cognição, disfunção cognitiva, envelhecimento.

This study was conducted at the Department of Physical Therapy, Universidade Federal de São Carlos, São Carlos, SP, Brazil.

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Funding: National Council for Scientific and Technological Development (CNPq) - process number 426666 / 2016-0; Coordination for the Improvement of Higher Education Personnel (CAPES) - Finance Code 001; Amparo Foundation Research of the State of São Paulo (FAPESP).

Disclosure: The authors report no conflicts of interest.

Received on April 15, 2020. Accepted in final form on December 16, 2020.

INTRODUCTION

Older adults with mild cognitive impairment (MCI) and Alzheimer disease (AD) experience changes in executive function (EF),[1,2] which are more pronounced in the latter group.[3] EF is a broad term related to planning, working memory, cognitive flexibility, monitoring, decision-making, and the ability to solve novel problems.[4]

A study that monitored older adults with preserved cognition (PrC), MCI, and mild to moderate AD for three years found that EF scores were significantly worse in those with AD compared to those with MCI, who, in turn, had worse scores than those with PrC.[5] Considering the heterogeneous sample of the AD group (patients in the mild and moderate phases), studies assessing only older adults with mild AD are needed, since this population differs greatly from the population in the moderate phase of the disease with regard to cognitive and motor aspects.[6-8]

A relationship has been found between changes in gait and EF in older adults with cognitive impairment[9,10] and those with AD in the mild and moderate phases.[6] A poorer performance regarding EF measures is associated with a shorter step length and width as well as slower gait.[11] In a study with a 23-month follow-up, reductions in cadence (number of steps per minute) and gait speed (GS) were associated with global cognitive decline and diminished EF in older adults with PrC.[12]

Slow GS is a strong predictor of dementia.[13] Older adults with MCI who have lower limb impairment are more likely to develop AD than those with MCI and preserved lower limb function.[14] Moreover, GS is a potential marker for the early identification of MCI.[15,16]

Few longitudinal studies have analyzed the relationship between gait and EF in older adults with and without cognitive impairment or have performed comparative analyses of older adults with PrC, MCI, and mild AD. As early diagnosis is important to the prognosis of older adults with MCI and its progression to dementia, the present study was conducted to identify changes in motor aspects and EF in this population and determine which ones declines first. The prompt identification of cognitive and gait changes enables the establishment of preventive actions. Therefore, the results of the present longitudinal analytical study can contribute to the planning of future interventions to mitigate such changes and their consequences.

Therefore, the aim of the present study was to investigate changes in EF and gait in older adults with PrC, MCI, and mild AD over a 32-month period and to analyze the correlation between the changes in these two variables. The hypothesis was that those with greater cognitive impairment would demonstrate a greater worsening in EF and GS after 32 months. It was also believed that the 10-meter walk test would be strongly correlated with EF tests.

METHODS

The present longitudinal analytical study was conducted with data from the "Brazilian longitudinal study about motor alterations in older adults with cognitive disorders". This study received approval from the local Human Research Ethics Committee (certificate number: 72774317.7.0000.5504). All volunteers signed a statement of informed consent.

Sample

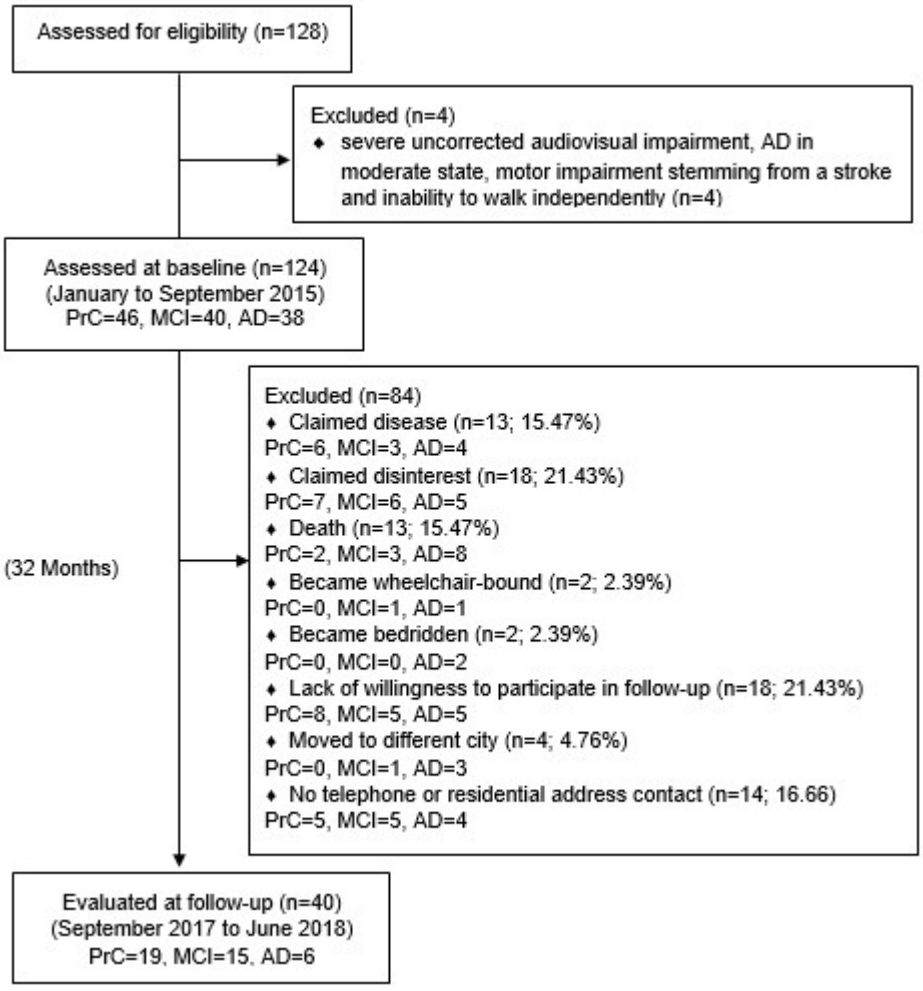
The subjects were recruited through leaflets, posters, and local radio and television channels. In addition, older people attending the Center for Medical Specialties, Universidade Aberta da Terceira Idade (São Carlos – SP), and School Health Unit (Universidade Federal de São Carlos) were contacted. This is a convenience sample.

Community-dwelling adults aged 65 years old or older who could be contacted by telephone or at their residential address were eligible for the study. Inclusion criteria included ability to walk at least 12.4 m with or without the aid of gait-assistance device, availability to participate in the evaluations, and admission to one of the three groups: PrC, MCI or mild AD. Exclusion criteria were: other neurological diseases that interfered in cognition or mobility and associated medications(such as motor alterations after stroke, Parkinson disease, multiple sclerosis, Huntington disease, epilepsy, traumatic brain injury, and advanced or moderate-stage of dementia), and severe uncorrected audiovisual impairment that would hinder test performance. Moreover, after the 32-month follow-up, participants with unsuccessful telephone or residential contact, those who died, became wheelchair-bound or bedridden, were unable to continue in the study due to illness (*i.e.*, influenza, deep vein thrombosis, acute lumbosacral pain, etc.), those who moved to a different city, and those not interested in continuing the evaluations were also excluded from the study. The massive loss of the initial sample may have caused a significant bias in the research. This type of loss is commonly observed in longitudinal studies with this population. We sought to reduce losses by offering transportation to participants, telephone contact with participants during the period between assessments, obtaining contact information from family or friends in case of a change of address or telephone number. Three attempts were made when trying to contact participants before they were considered a dropout.

The diagnosis and phase of AD was confirmed by a single neurologist trained in the field of behavioral neurology, based on the National Institute on Aging and Alzheimer's Association criteria.[17] Only individuals with a score of 1 on the Clinical Dementia Rating (CDR) scale were included in the mild AD group.[18] Participants classified as PrC obtained a normal score on the Mini-Mental State Examination (MMSE)[19] and did not meet the criteria for MCI or dementia. For the diagnosis of MCI: cognitive complaint manifested by the participant or a caregiver (person who cares for the older adult for at least 12 h per day, four times a week); objective cognitive decline with a score of 0.5 on the CDR;[18] normal general cognitive function for level of schooling assessed by the MMSE;[19] and preserved functioning evaluated by the Pfeffer Scale.[20,21] After 32 months, the participants were reclassified.

Evaluations

Evaluations were performed on two occasions: baseline and follow-up (Figure 1). As there are studies research with shorter[22] and intermediate[12,23] follow-up, this study approached the longer period of 32 months. Participants were evaluated in the laboratory wearing comfortable clothes, closed-toe shoes, hearing aid and/or glasses, and no physical activity in the previous 24 hours. The tests were administered in a closed environment with a flat floor and minimal external visual and auditory stimuli. Evaluators were properly trained and explained all the tests to the participants in a simple, objective, and standardized way. When necessary, the participants had the help of a caregiver for the recording of the patient's history (socio-demographic and health characteristics, such as age, gender, body mass index, schooling, use of medications in general



PrC: preserved cognition; MCI: mild cognitive impairment; AD: Alzheimer disease.

Figure 1. Sample flowchart.

and psychotropic drugs, and presence of disease in general, depression, and anxiety) and for the screening of depressive symptoms.[24]

The assessment of the EF was performed using the Frontal Assessment Battery (FAB) and clock-drawing test (CDT). The FAB is employed to evaluate frontal cognitive function, including EF. The maximum score is 18.[25,26] Its inter-rater reliability is 0.87 and discriminant validity is 89.1%.[25] The CDT is used to assess EF based on the design of an analog clock, for which the maximum score is 10. Its inter-rater reliability is 0.86.[27] CDT has been translated, adapted, and validated for use in older adults in Brazil.[28] In addition, CDT has good inter-examiner and test-retest reliability, high sensitivity and specificity, concurrent validity and predictive validity.[29] The FAB and CDT were chosen because these tests detect changes in EF and are fast and easy to administer. Moreover, a strong association has been reported between frontal function and kinetic gait variables.[6]

GS was determined using the 10-meter walk test (10mWT) by video and stopwatch. On the 10mWT, participants are instructed to walk 12.4 m in a flat corridor at their usual pace. The initial and final 1.2 m are discarded to eliminate the components of acceleration and deceleration.[30] The test was performed only once. The elements analyzed were the number of steps, GS, and cadence. Walk tests ranging from six to 15 m have good reliability and reproducibility and are valid for assessing physical mobility in a clinical or home setting.[30] Inter-rater reliability for the walk test is 0.985.[31] The 10mWT was chosen because it is widely used in the literature for the evaluation of GS. The minimal detectable change with 90% confidence for GS is 0.21 m/s.[32]

Data analysis

Statistical tests were performed using the SPSS software, with a significance level of α=0.05. The Kolmogorov-Smirnov test was used to determine the normality of data distribution. One-way analysis of variance and the chi-square test were used to determine differences among the groups regarding the initial clinical and sociodemographic characteristics. When an overall group difference was significant, a post hoc independent Student's t-test was performed.

Two-way repeated-measures ANOVA was used to determine the interaction between group and time with regard to EF and performance on the 10mWT. When a significant interaction was identified, analyses of the main simple effects were performed. Pearson's correlation test was used to determine the correlation between the change in EF and GS between evaluations.

RESULTS

One hundred and twenty-four volunteers were evaluated at baseline: 46 with PrC, 40 with MCI, and 38 with mild AD. After a 32-month follow-up, the dropout rate was 67.74% (n=84) due to deaths (15.47%), lack of willingness to participate in the follow-up evaluation (21.43%), change of address to a different city (4.76%), having become bedridden (2.39%), having become wheelchair-bound (2.39%), claimed disease (15.47%), disinterest (21.43%), and loss of contact via telephone or residence (16.66%). Thus, the final sample was composed of 19 older adults with PrC, 15 with MCI, and six with AD (Figure 1). There was a progression of two PrC participants to MCI and three MCI to DA, as well as a regression of six MCI to PrC after a 32-month follow-up.

Regarding sociodemographic characteristics at baseline, significant differences among the groups were found only for gender, total number of medications, and diseases. The MCI group had a higher number of women (93.3%) in comparison to the other groups. The MCI and mild AD groups took more medications and had more diseases compared to the PrC group (Table 1).

In the intragroup analysis of the change in GS on the 10mWT over time, a significant group versus time interaction was found (p=0.019). In the analysis of the main simple effects, both the PrC and mild AD groups had a worse performance after 32 months compared to baseline. A significant difference was found between the PrC and MCI groups at baseline (p=0.024), with a worse performance in the MCI group. Regarding the number of steps required to complete the 10mWT, no significant group versus time interaction was found, but a significant increase in the number of steps was found at follow-up in all groups (p=0.001) (Table 2).

Regarding the frontal functions, the analysis of the FAB results revealed no significant group versus time interaction. Improvements in FAB scores were found at follow-up in all groups (p=0.003). Moreover, significant differences were found between the PrC and MCI groups and between the PrC and mild AD groups at both evaluation times (p=0.006). No significant group versus time interaction was found with regard to cadence on the 10mWT or the CDT and no main significant group-time effect was found in these analyses (Table 2).

No significant correlation was found between the change in EF (FAB) and change of GS in any of the groups. A correlation was found between the change in the FAB and the number of steps in the mild AD group and between the change in the FAB and cadence in the PrC group (Table 3).

DISCUSSION

In the present study, 32 months was not enough time for EF impairment in older adults with PrC, MCI, and mild AD. However, a decrease in GS at follow-up was found in those with PrC and mild AD. The findings suggest that the slowing of gait in individuals with PrC and mild AD is due to aging and cognitive impairment, respectively.

The deceleration in GS over time has been described in previous studies[33] and GS has been associated with cognitive impairment.[13] These findings are in agreement with Ojagbemi et al.,[23]

Table 1. Descriptive characteristics of the sample.

Characteristics (M±SD)	PrC group (n=19)	MCI group (n=15)	AD group (n=6)	p-value
Age (years)	72.7±6.7	72.8±5.4	77.6±4.1	0.195
Female gender, n (%)	10 (52.6)	14 (93.3)	3 (50.0)	**0.026***
Body mass index (kg/m^2)	28.5±5.7	29.8±3.9	26.1±4.0	0.296
Schooling (years)	7.9±4.2	5.2±3.9	6.5±5.0	0.207
Total number of medications	2.0±1.5	5.5±3.1$^{\#}$	5.5±2.9$^{\#}$	**<0.001***
Use of psychotropics, n (%)	1 (5.3)	5 (33.3)	5 (83.3)	**<0.001***
Total number of diseases	1.7±1.3	3.1±1.4$^{\#}$	3.8±1.3$^{\#}$	**0.003***
Diagnosis of depression, n (%)	0 (0)	0 (0)	0 (0)	-
Diagnosis of anxiety, n (%)	1 (5.3)	1 (6.7)	0 (0)	0.816
GDS (0–15)	1.8±1.6	3.5±2.4	2.8±1.8	0.057

M±SD: mean±standard deviation; n (%): number of individuals (percentage); PrC: preserved cognition; MCI: mild cognitive impairment; AD: Alzheimer disease; kg/m^2: kilogram/square meter; GDS: Geriatric Depression Scale; >5 points is suggestive of depression; ≥10 points is almost always indicative of depression; >5 points should warrant follow-up comprehensive assessment; *p<0.05 between groups; #p<0.05 in comparison to PrC Group.

Table 2. Performance on 10-meter walk test, Frontal Assessment Battery and clock-drawing test tests in older adults with preserved cognition, mild cognitive impairment and mild Alzheimer disease over 32 months (n=40).

Characteristics (M±SD)	PrC group (n=19)		MCI group (n=15)		AD group (n=6)		Time-group interaction p-value*	Time-group interaction Power*	Time p-value	Group p-value
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up				
10mWT	Mean and SD		Mean and SD		Mean and SD					
N. of steps	16.4±2.6	17.5±2.7	17.7±2.8	18.7±1.6	16.2±2.6	20.0±7.5	0.147	0.391	0.001*	0.354
GS (m/s)	1.2±0.2	1.1±0.2	1.0±0.1	1.0±0.0	1.1±0.2 $^{+\#}$	0.9±0.2 $^{\#}$	**0.019***	0.727	<0.001*	0.044*
Cadence (steps/min)	113.0±13.6	113.2±11.8	103.9±15.5	108.8±7.9	106.0±14.7	102.4±13.1	0.285	0.264	0.828	0.123
FAB (maximum score=18)										
Score	11.0±3.5	13.1±3.1	8.7±2.6$^{\#}$	10.1±3.1$^{\#}$	7.2±2.7$^{\#}$	9.5±5.2$^{\#}$	0.745	0.094	0.003*	0.006*
CDT (maximum score= 10)										
Score	7.7±2.4	7.2±3.0	6.5±2.9	6.6±3.4	7.0±2.8	5.0±3.7	0.471	0.171	0.217	0.343

M±SD: mean±standard deviation; PrC: preserved cognition; MCI: mild cognitive impairment; AD: Alzheimer disease; GS: gait speed; 10mWT: 10-meter walk test; nº: number; FAB: Frontal Assessment Battery; CDT: clock-drawing test; +p<0.05 in comparison to PrC group at baseline; #p<0.05 in comparison to PrC group; *p<0.05; high score on FAB and CDT: high score on executive function.

which reports a substantial change in GS associated with a reduction in cognitive performance after a 24-month follow-up.

In six-month follow-up studies of gait changes,[34-36] no significant differences in GS were found in older adults with MCI. However, a 30-month follow-up study reports slower walking in older adults with amnestic MCI,[15] which differs from the sample in the present investigation.

A slower GS was identified in older adults with MCI compared to those with PrC at baseline, but not at follow-up, possibly because GS in the PrC group has become slower over time, reflecting the influence of aging.[33,37-40] It is believed that MCI participants have already reached a plateau in the GS decline. In addition, maybe changes on GS in the MCI group were not significant enough to be detected in a small sample size like this. Furthermore, possibly due to the heterogeneous evolution in the MCI group during follow-up, as some may have resumed normal cognition, remained stable or progressed to dementia. Although not confirmed by our data, studies suggest that the slowing of gait in individuals with PrC and mild DA is due to aging[33] and cognitive impairment,[13] respectively. The difficulty in assessing gait in older people is highlighted.

Although no significant difference was found among the groups, the AD group took the most number of steps on the 10mWT. As the power of this test is low, a larger number of individuals in the sample could have resulted in a significant p-value.

Regarding EF, no differences among groups or between times were found on the CDT and the change in FAB results over time was similar in all three groups. Moreover, significant differences in relation to FAB were found between the PrC and MCI groups as well as between the PrC and mild AD groups at baseline, whose differences were maintained at follow-up. The change in FAB was an improvement in the EF for all groups. Therefore, the CDT and FAB do not seem to be good markers to differentiate the evolution of cognition in these groups.

The FAB has discriminant validity as well as good internal consistency, interobserver reliability and convergent validity.[25] However, there are no Minimum Detectable Change analyses to determine whether the change in score was clinically relevant. The standard deviations of the three groups ranged from 2.6 to 5.2 points and were reasonably high in the follow-up period compared to the values reported in other studies.[41,42] Studies with larger samples may facilitate the conclusion of the findings.

In addition, the increase in the FAB was believed to have occurred for four reasons:

- It was a group with mild AD, which mainly affects the temporal lobes.
- It was AD rather than another form of dementia that affects the frontal lobe more.
- The introduction of new pharmacological treatments (37.5%), physical activity (65%), and physical therapy interventions (57.5%) among the participants during the period between evaluations, given that some received their diagnosis during the study.
- Due to possible learning of the instruments, since improvements were found in all groups (with no difference among groups).

Table 3. Correlation between change in Frontal Assessment Battery and clock-drawing test tests and change in gait speed among older adults with preserved cognition, mild cognitive impairment, and mild Alzheimer disease.

Correlation measurements	PrC group (n=19)	MCI group (n=15)	AD group (n=6)
DFAB with DGS	p=0.146	p=0.108	p=0.851
DFAB with DSTEPS	p=0.730	p=0.129	**p=0.001** r= -0.978
DFAB with DCADENCE	**p=0.042** r=0.472	p=0.627	p=0.664
DCDT with DGS	p=0.819	p=0.635	p=0.747
DCDT with DSTEPS	p=0.696	p=0.434	p=0.119
DCDT with DCADENCE	p=0.569	p=0.104	p=0.968

PrC: preserved cognition; MCI: mild cognitive impairment; AD: Alzheimer disease; FAB: Frontal Assessment Battery; CDT: clock-drawing test; GS: gait speed; Δ: final value–initial value; r: correlation coefficient.

In studies by Ansai et al.,[43] changes in EF were found at baseline and gait alterations were found at follow-up. However, changes in EF and GS do not go hand in hand, since motor decline precedes that of EF. GS is a good early marker of the development of MCI.[15,16]

No significant association was found between changes in the FAB and GS. However, associations were found between changes in the FAB and both the number of steps in the mild AD group and cadence in the PrC group. These findings are in agreement with the data reported by Pedroso et al.[44] and Melo et al.,[45] respectively. At follow-up, a decline in GS was found, while EF remained stable. Taylor et al.[22] found an association between baseline GS and decline in EF in a 12-month period among older adults with dementia. In contrast, the present study included MCI and mild AD. Coelho et al.[6] also found an association between GS and EF, but in a heterogeneous sample that included individuals with both mild and moderate AD. As these groups differ significantly in terms of cognitive and motor impairment,[6-8] it is necessary to study them separately.

Two studies found an association between changes in gait and EF,[12,46] however, the divergent results of the present investigation may have occurred because the authors used instruments to assess EF and gait variables different from those used in this study investigation. The literature shows that in addition to the consistency in the results and quality of the studies, there seems to be variations in the results according to the instrument chosen for the evaluation, sample size, population studied, and the evolution of cognitive impairment in the volunteers.[12,22,46,47]

As MCI and dementia become more prevalent with the increase in age, early diagnosis is essential. The results of the present study seem to indicate that slowing GS is a potential early marker of cognitive decline. Thus, rehabilitation professionals should perform periodic assessments of GS in older adults. Once decreased GS over time is detected, such individuals should be screened for cognitive decline to obtain an early diagnosis and timely intervention. Therefore, rehabilitation professionals should prioritize attention to gait variables during the clinical care of older adults with the aim of preventing their decline. If older adults with slower gait are admitted to a rehabilitation clinic, the main intervention of the care should be to promote an increase in GS.

A limitation of the present study was the use of a convenience sample. However, the diagnostic criteria were rigorous and based on the current literature.[17,21] Moreover, the stringent, sophisticated methodology, extensive evaluation, and use of clinical instruments widely employed in the clinical practice strengthened the study. Another limitation was the small number of volunteers who participated in the follow-up evaluation. Longitudinal studies with this type of population pose a challenge, since the older adults with MCI and AD can exhibit physical and cognitive frailty, which makes data collection more difficult. In addition, caregivers are often over-burdened and may have little time and/or interest in participating in studies. However, the small sample size may have some impact on the lack of significance in some results.

Future researches should carry out population-based studies in developing countries, which have socioeconomic inequalities and different health conditions, in order to offer greater reliability in the characterization of cognitive and motor impairment in these populations. It is fundamental to perform selective sampling that differentiates older adults with preserved cognition, those with subjective memory complaints, those with MCI and its subtypes and those with AD and its different phases. It is also important to standardize the use of other common evaluation instruments of gait and/or EF to compare cognitive profiles, such as the Timed up and Go test. Finally, it is necessary to reproduce these analyses in larger samples so that loss to follow-up does not interfere with the results.

As conclusion, gait of older adults with PrC and mild AD slowed down in 32 months and, over the years, this group needs to take more steps to cover the same distance. The same period was insufficient to detect deficits in EF in the PrC, MCI, and AD groups, suggesting that gait changes occur in older adults before EF are affected. This study contributes to the field of research in older adults with cognitive impairment and offers a theoretical foundation for the planning of interventions and health promotion strategies for this population.

ACKNOWLEDGMENTS

This study was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

Authors' contributions. NOCC: conceptualization, data curation, formal analysis, funding acquisition, investigation, visualization, writing – original draft, review & editing. JHA: conceptualization, formal analysis, investigation, methodology, supervision, writing – review & editing. LPA: formal analysis, investigation, project administration, supervision, writing – review & editing. MPBO, DCPS, FACV, ACMT: investigation, writing – review & editing.

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Dement Neuropsychol 2021 March;15(1):69-78

Original Article

https://doi.org/10.1590/1980-57642021dn15-010007

Vascular mild cognitive impairment and its relationship to hemoglobin A1c levels and apolipoprotein E genotypes in the Dominican Republic

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ABSTRACT. Dementia and vascular mild cognitive impairment (VaMCI) currently impose a tremendous human and economic burden on patients from aging populations and their families worldwide. Understanding the interplay of cardiometabolic risk factors and apolipoprotein E (APOE) may direct us to a more personalized medicine and preventative care in MCI and dementia. **Objective:** To evaluate the relationship of cardiometabolic risk factors with MCI and assess the APOE genotype's role in an elderly cohort in the Dominican Republic. **Methods:** We studied a cohort of 180 participants 65 years of age and older using a combined assessment of cardiometabolic risk factors, neuropsychological battery tests, and APOE genotyping. We used the number of failed tests as a proxy to predict MCI. **Results:** We found that patients with the ε3-ε4 APOE genotype had 2.91 higher number of failed cognitive tests (p=0.027) compared to patients with the ε3-ε3 genotyped. The rate of test failures increased 10% (p=0.025) per unit increase in HbA1c percentage. **Conclusions:** Increased Hemoglobin A1c levels and ε3-ε4 APOE genotypes seem to have an association with the development of VaMCI.

Keywords: vascular dementia, risk factors, apolipoproteins E, metabolic syndrome, diabetes mellitus.

COMPROMETIMENTO COGNITIVO LEVE VASCULAR E SUA RELAÇÃO COM OS NÍVEIS DE HEMOGLOBINA A1C E GENÓTIPOS APOLIPOPROTEÍNA E NA REPÚBLICA DOMINICANA

RESUMO. A demência e o comprometimento cognitivo leve vascular (VaMCI) atualmente impõem uma enorme carga humana e econômica aos pacientes de populações envelhecidas e suas famílias em todo o mundo. Compreender a interação dos fatores de risco cardiometabólicos e apolipoproteína E (APOE) pode nos direcionar para uma medicina mais personalizada e de cuidados preventivos em MCI e demência. **Objetivo:** Avaliar a relação dos fatores de risco cardiometabólicos com o MCI e o papel do genótipo APOE em uma coorte de idosos na República Dominicana. **Métodos:** Estudamos uma coorte de 180 participantes com 65 anos de idade ou mais, utilizando uma avaliação combinada de fatores de risco cardiometabólicos, uma bateria de testes neuropsicológicos e genotipagem APOE. Adotou-se o número de testes com mau desempenho para o diagnóstico de MCI. **Resultados:** Verificou-se que os pacientes com o genótipo ε3-ε4 do APOE apresentaram 2,91 vezes mais testes cognitivos com mau desempenho (p=0,027) em comparação com os pacientes com o genótipo ε3-ε3. A taxa de falhas de teste aumentou 10% (p=0,025) por aumento de unidade na porcentagem de HbA1c. **Conclusões:** Níveis mais altos de HbA1c e os genótipos ε3-ε4 do APOE parecem estar associados ao desenvolvimento de VaMCI.

Palavras-chave: demência vascular, fatores de risco, alipoproteínas E, síndrome metabólica, diabetes mellitus.

This research was conducted by School of Medicine, Pontificia Universidad Católica Madre y Maestra, and carried out at the Geriatrics Services at Hospital Regional Universitario José Maria Cabral y Baez, as well as, in Clínica Corominas, Santiago, Dominican Republic.

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Funding: This work was supported by the Dominican Republic National Funding of Technologic and scientific Development and Innovation (FONDOCYT) grant: 2013-2A3-117.

Disclosure: The authors report no conflicts of interest.

Received on May 28, 2020. Accepted in final form on December 29, 2020.

INTRODUCTION

Dementia and vascular mild cognitive impairment (VaMCI) currently impose a tremendous human and economic burden on patients from aging populations and their families worldwide.[1] VaMCI encompasses the cerebrovascular continuum from MCI to dementia,[2] beginning with cardiometabolic risk factors leading to cerebral vascular disease (CVD) of the large and small arteries. This disease will lead to different types of cognitive impairments depending on the location of the damage produced.[3-5] Associated risk factors comprise the entire cluster of classical vascular risks: Hypertension (HTN), hyperlipidemia, Diabetes Mellitus Type 2 (DM2), metabolic syndrome (MetS), smoking, and age but also the emerging risk factors:[6] high sensitivity C-reactive protein and homocysteine, behaving as pro-inflammatory markers and prothrombotic status, respectively. When vascular diseases have been associated with MCI, the incidence in patients with at least one vascular disease doubles the frequency of MCI in the healthy population.[7] HTN also seems to have a strong influence when developed during mid-adulthood as compared to its appearance in an older age.[8]

DM2 has also been associated with executive function impairment, including reasoning, mental flexibility, problem solving, and decision making; especially with high glucose levels, worst performance on executive cognitive tasks was seen when DM2 would onset in midlife.[9] Evidence for the relationship between diabetes and vascular dementia has been consistent,[10] both the American Diabetes Association (ADA) and the American Heart Association (AHA) have stated the need to develop reliable estimates of the combined cardiometabolic risks for patient care.[11] Metabolic syndrome, as well, encompasses multiple coexisting factors associated with cognitive function decline in elderly populations.[12,13] However, most cardiovascular risk factors are modifiable; genetics are also likely to play a role.[14] Understanding this interplay may unlock the promise of personalized medicine and preventive care in MCI and dementia.[15] The presence of at least one allele of apolipoprotein E (APOE) ε4 is a risk factor for cardiovascular diseases and increases the risk of dementia in subjects who have suffered a stroke,[16,17] being particularly pronounced factors in the Latino population.[18] APOE is involved in lipid metabolism and can modulate the relationship between vascular factors, diabetes, and cognitive functions.[19,20]

The geriatric neuropsychological battery (NPB) is a great tool to identify patients with MCI at risk of progressing to dementia.[21] In conjunction with NPB, early identification of vascular risk factors and treatment of associated diseases may decrease vascular cognitive impairment incidence.[17] However, the literature is still unclear about the interplay between APOE genotypes, cardiometabolic risk factors, and cognitive impairment. This research group investigated cardiometabolic risk factors to address this gap, aiming to convey findings that may lead to the development of clinical protocols for early prevention, diagnosis, and treatment of cognitive changes in aging patients. The objective of this study was to evaluate the relationship of cardiometabolic risk factors with MCI and to assess the role of the APOE genotype in an elderly cohort in the ethnically heterogeneous Dominican Republic.

METHODS

Study description

The Cardiometabolic, Cerebral and Genetic Factors and Their Influence on Neurocognitive Functions and Depression in the Elderly (CEGENED) study, was conducted in Santiago, Dominican Republic. The cohort comprised 180 subjects aged 65 years old or older, both male and female. The study period lasted four years. For this paper, the first assessment, performed between July 2014 and May 2015, was analyzed. The purpose of the study and the participants' role were written, and verbally explained, following the evaluation of the participants' comprehension of its benefits and consequences. They proceeded to sign the consent form, per protection of human subject standards. Participants were invited from primary care consultations to community gatherings, where objectives of the study were explained. An initial interview assessed demographic variables, including age and gender, and self-reported level of education. During the visit, an in-depth medical history was also conducted, in addition to a biophysical medical evaluation, Columbia University validated neuropsychological battery tests,[22] and a Depressive Symptoms (Center for Epidemiologic Studies Depression Scale — CES-D) test.[23] Smoking for more than a month and any history of alcohol intake were self-reported.

Inclusion criteria were:

- Dominican citizens aged 65 years old or older;
- No history of CVD or depression;
- Being able to perform basic and instrumental activities of daily living autonomously (Lawton and Brody Scale,[24] and Barthel Index).[25]
- Being able to use public transportation independently and apparent normal cognition (short Blessed test[26] score).

Exclusion criteria were:

- History or evidence of stroke.
- Myocardial infarction.
- Neurological or psychiatric conditions such as psychotic disorders or bipolarity.
- Alcoholism (intake greater than 30 gr a day for men and 20 gr a day for women).
- History of brain surgery.

This study was approved by the Committee of Bioethics of the Pontificia Universidad Católica Madre y Maestra (COBE-FACS) and the National Committee on Bioethics (CONABIOS): 002-2-2013-2014.

Cardiometabolic evaluation

Cardiometabolic factors were assessed using the diagnostic criteria described in the AHA guidelines.[27] DM was considered in anyone with prior diagnosis or who is currently being treated with glucose-lowering medication. Diagnosis would be made if there was no history of diabetes, but a fasting glucose level greater than 126 mg/dL or HbA1c level greater than 6.5%. Hypertension is defined as systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥80 mmHg. Diagnosis was made according to the 24-hour Ambulatory Blood Pressure Monitoring report for anyone with prior diagnosis or currently treated with antihypertensive medications, or HTN diagnosis status unknown. The lipid profile was determined using standard enzymatic techniques. High-density lipoprotein cholesterol (HDL-C) was determined using a cholesterol laboratory standard method for CVD biomarkers. High sensitivity C-reactive protein was measured using an ultrasensitive enzyme-linked immunosorbent assay. Criteria of the Third Report of the National Cholesterol Education Program Expert Panel of Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), were used to determine the metabolic syndrome if three or more of the following criteria coexisted: Abdominal obesity determined by a waist circumference greater than 102 cm in men and 88 cm in woman, triglycerides greater than or equal to 150 mg/dL, HDL-C lower than 40 mg/dL in men and 50 mg/dL in women, HTN diagnosed previously or by the Holter during the study, and diabetes previously diagnosed or an HbA1c greater than 6.5%. Homocysteine levels were determined by the Abbott homocysteine (HCY) assay considering normal values of up to 15 µmol/L. APOE genotyping was performed at Columbia University in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain using a polymerase chain reaction-based method. APOE genotype was determined by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) using the enzyme HhaI.[28-30]

Neuropsychological assessment

All participants were cognitively normal according to the initial Short Blessed Test assessment. The neuropsychological battery[22] was then applied, including the following tests and their cut-off values:

- Memory (Selective Reminding Test total recall <25, Selective Reminding Test long-term recall <15, Selective Reminding Test delayed recall <4, Delayed recognition <8, Benton Visual retention Test multiple choice recognition <7).
- Orientation <8.
- Construction (Benton Visual retention test multiple-choice matching <7).
- Abstract reasoning (Mattis identities and oddities <12).
- Language (Boston Diagnostic Aphasia Evaluation repetition of high probability phrases <7, Boston Diagnostic Aphasia Evaluation complex ideation material <5, Boston Naming Test <11).
- Controlled Oral word association <16 percentile.

Subject differences were explored along two dimensions: patients who scored below the tests' cutoff values classified as MCI patients *versus* not along with the raw number of failed cognitive tests per patient. All participants underwent brain magnetic resonance imaging (MRI) to determine vascular brain damage status.

Imaging techniques

Noninvasive cardiologic and brain imaging studies included: Electrocardiogram and echocardiogram, brain magnetic resonance with Brain MRI (Toshiba 1.5 tesla): Coronal section cuts of 0.3 mm. Axial and sagittal section cuts of 4 mm in T1, T2, and FLAIR. Also, white matter hyperintensities and brain atrophy were assessed by the FAZEKAS visual scales. Anterior and posterior extracranial circulation was evaluated by carotid Doppler using Mindray M7 Duplex Scan equipment of high-resolution 3D/4D color images, B-mode, with 7L4sMHZ transducer. Thickening of the medial intima greater than or equal to 1.0 mm was considered stenotic and associated with atherosclerosis.

Diagnosis of vascular mild cognitive impairment

The diagnosis of VaMCI was based on the new criteria proposed by the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG)[31] comprising two main categories:

- The cognitive deficits are not sufficient to interfere with independence (*i.e.*, instrumental activities of daily living are preserved), but greater efforts, compensatory strategies, or accommodation may be required to maintain independence.
- Determining that vascular disease is the dominant or exclusive cause of cognitive deficits.

Cognitive performance impairment in neuropsychological assessment was considered when between 1 and 2 standard deviations below the norm, or between the 3rd and 16th percentile in individuals of similar age, gender, education, and sociocultural backgrounds. One of the exclusion criteria was the history of known stroke. Subjects with large vessel disease or atherothrombotic diseased patients were also excluded. For the deemed VaMCI, we have considered silent infarcts, small vessel disease: multiple lacunar infarcts in the white substance or the gray matter of the basal nuclei, extensive and confluent vascular leukopathy (Fazekas II-III scale), microinfarcts, and cortical microhemorrhages.

Statistical analysis

For this analysis, the number of test failures were assessed as a proxy to predict the intensity of VaMCI in each patient, as done in previous studies.[32,33] A test was considered failed when its cognitive test score was below the cut-off value. We explored initial associations with univariate models predicting VaMCI in patients with a binomial regression and the number of failed tests with count regressions. Multivariate count regressions were built to predict the number of neuropsychological tests failed using R's generalized linear model (GLM).[34] We tested our datasets for zero inflation using the Van den Broek's zero-inflation test[35] and for overdispersion by comparing means and standard deviations in our primary outcome variable (*i.e.*, number of failed tests). We selected classic Poisson regressions to fit our non-zero-inflated, non-over-dispersed data. For all the models, the number of failed tests was this study's primary outcome variable. Models were built using a forward selection process. Specifically, there was a pre selection of variables based on predictive power according to Harell's variable selection approach,[36] setting the p-value variable inclusion threshold at 0.1. Then, each pre-selected variable's relationship to VaMCI and APOE genotypes were explored. The Akaike's information criterion was used to select the final model by maximizing each model's goodness of fit.[37] All models were tested for variable interactions and collinearity effects with more than one variable. Adjustments for multiple comparisons were made using R's p. adjust function, selecting Holm's correction method.[38] Statistical significance was set at p=0.05 for all models.

RESULTS

180 participants were recruited, two died before completing data collection, and two were lost to follow up. This study's final cohort contained 176 participants, with 70.5% of the total sample affected by Non-VaMCI (Table 1). Age ranges from 65 to 77 years, with 30.11% males and 69.3% females. 58.86% of patients had a history of HTN, 25.5% had a history of diabetes, and 68.18% completed primary education. Mean systolic blood pressure

Table 1. Demographics, cardiometabolic risk factors, genetic, and neuropsychological assessments.

Characteristics	Non-VaMCI (n=127)	VaMCI (n=49)	p-value
Age (years)	71±6.03	73±6.28	0.863
Female (%)	88 (69.3)	35 (71.4)	0.0649
Education (years)	5.49±3.31	4.95±2.67	0.992
Diabetes mellitus	31 (24.4%)	12 (24.5%)	0.901
Hypertension	70 (55.1%)	33 (67.3%)	0.0996
Systolic blood pressure (mmHg)	153.39±24.88	154.47±26.62	0.189
Diastolic blood pressure (mmHg)	78.68±10.67	79.80±11.81	0.568
MAP (mmHg)	100.53±16.60	99.06±22.29	0.480
BMI (kg/m^2)	27.6±6.99	26.29±3.96	0.413
Waist circumference (cm)	95.1±12.3	97.06±9.96	0.457
Total cholesterol (mg/dL)	198.42±41.71	196.28 ±40.96	0.968
Triglyceride (mg/dL)	138±80.84	138.69±63.22	0.980
LDL-C (mg/dL)	122.6±36.7	122.5±36.4	0.715
HDL-C (mg/dL)	46.66 ±10.85	45.63±10.75	0. 646
HbA1c (%)	6.56±1.18	6.69±1.18	0.619
C-reactive protein	5.50±8.06	4.39 ±6.12	0.217
Homocysteine	17.9±6.77	19.7±9.46	0.856
Smoking	55 (47.02%)	20 (45.26%)	0.562
MetS	54 (49.09%)	21 (48.84%)	0.348
CES-D	92 (83.64%)	14 (12.73%)	0.490

Continue...

Table 1. Continuation.

Characteristics	Non-VaMCI (n=127)	VaMCI (n=49)	p-value
Neuropsychological Battery			
Memory			
SRT total recall	37.69±9.69	36.24±9.15	0.373
SRT long-term recall	24.96±12.55	23.26±10.93	0.451
SRT delayed recall	5.48±2.35	5.59±2.28	0.709
Delayed recognition	11.19±1.30	11.16±1.32	0.991
BVRT multiple-choice recognition	5.60±2.30	5.18±2.26	0.338
Orientation	8.16±1.40	8.02±1.24	0.571
Construction			
BVRT multiple-choice matching	7.31±2.34	7.26±2.06	0.950
Abstract reasoning			
Mattis identities and oddities	14.90±1.26	14.26±1.61	1
Language			
BDAE repetition of high probability phrases	7.80±0.50	7.79±0.45	0.756
BDAE complex ideation material	4.44±1.18	4±1.59	0.071
Boston Naming Test	13.32±1.70	12.65±2.86	0.105
CFL	24.65±20.65	20.44±18.18	0.202
APOE genotype			
ε2-ε2	1 (0.79%)		0.996
ε2-ε3	10 (7.97%)	7 (14.29%)	0.991
ε2-ε4		1 (2.04%)	0.988
ε3-ε3	82 (65.08%)	35 (71.43%)	0.992
ε3-ε4	30 (23.81%)	6 (12.24%)	0.992
ε4-ε4	3 (2.38%)		0.992
Indeterminate	1 (0.85%)		1

APOE: apolipoprotein E; VaMCI: vascular mild cognitive impairment; MAP: mean arterial pressure; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; MetS: metabolic syndrome; CES-D: Center for Epidemiologic Studies Depression Scale; SRT: Selective Reminding Test; BVRT: Benton Visual Retention Test; BDAE: Boston Diagnostic Aphasia Evaluation; CFL: Controlled Oral Word Association.

was at stage I hypertension (153.4 mmHg), but the mean diastolic blood pressure was normal (78.7 mmHg). Mean cholesterol was (198.42 mg/dL), mean triglycerides was (138 mg/dL), and mean low-density lipoprotein cholesterol (LDL-C) was (122.6 mg/dL), while the mean glycated hemoglobin was 6.6%, characterizing diabetes. Exploring group differences and statistically significant relationships between our variables and VaMCI groups, no statistically significant relationships were observed, likely due to the limited cohort size.

Demographic data of all aged patients comparing VaMCI and non-vascular cognitive impairment. MAP: mean arterial pressure; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; MetS: metabolic syndrome; CES-D: Center for Epidemiologic Studies Depression Scale; SRT: Selective Reminding Test; BVRT: Benton Visual Retention Test; WAIS-R: Wechsler Adult Intelligence Scale-Revised; BDAE: Boston Diagnostic Aphasia Evaluation; CFL: Controlled Oral Word Association; APOE: apolipoprotein E genotypes. Even though there was genotype variability among participants, we chose to focus on APOE ε3-ε3 and ε3-ε4 due to data availability. Statistical differences were evaluated with univariate logistic regression models predicting patient's belonging to the VaMCI group or not. Values are mean ± standard deviations or n (%).

Our population presented a high rate of cognitive test failures (*i.e.*, a cognitive test score below its cut-off value) for patients with both APOE genotypes of interest (Table 2). We report the overall number of failed tests for each cognitive category tested; therefore, the number of failed tests is higher than the number

Table 2. Number of patients with failed cognitive tests and number of test failure. Statistical differences were evaluated with univariate logistic regression models predicting patient's belonging to each apolipoprotein E group.

Area impaired	APOE ε3-ε3 n=117	APOE ε3-ε4 n=36	p-value
Memory	6 (5.08%)	4 (11.11%)	0.231
Orientation	29 (24.58%)	16 (44.44%)	0.0608
Construction	117 (100%)	36 (100%)	1
Abstract reasoning	117 (100%)	36 (100%)	1
Language	80 (67.80%)	28 (77.78%)	0.280
Overall number of failed tests (% of total tests)	578(32.9%)	207(38.7%)	0.0609

APOE: apolipoprotein E.

of patients in the cohort. Construction and Abstract reasoning tests had close to 100% failure rates for both genotypes, whereas language tests showed no differences (67.80 *vs*. 77.78% for ε3-ε3 and ε3-ε4 genotypes, respectively). Nevertheless, we found significant differences for orientation tests (24.58 *vs*. 44.44% for ε3-ε3 and ε3-ε4, respectively). Memory tests, however, presented low failure rates: 6 *vs*. 4 test failures overall, corresponding to 5.08 *vs*. 11.11% failure rates of ε3-ε3 and ε3-ε4, respectively. The mean failure rates were relatively similar, with 4.92+-2.25 and 5.75+-2.26 for APOE genotypes ε3-ε3 and ε3-ε4, respectively. Near-significant group differences were found between ε3-ε3 and ε3-ε4 APOE groups for orientation tests and the overall number of test failures.

Our preliminary cardiometabolic risk factor variable screening based on their relationships with the number of failed cognitive tests revealed statistically significant relationships for mean arterial pressure, waist circumference, weight, and HbA1c (Table 3).

This study's final model predicting overall test failures disclosed statistically significant relationships between the number of failed tests, the APOE genotype, and the patients' HbA1c levels at the day the tests were administered (Table 4). HbA1c, waist circumference, weight,

Table 3. Statistical association between individual cardiometabolic risk factors and the number of failed cognitive tests using a count model using the full cohort sample.

Term	Rates ratio (exp(ß))	Estimate (ß)	95% confidence interval		Standard error	p-value
Gender	1.053	0.0524	(-0.099,	0.201)	0.076	0.493
Age	1.005	0.0055	(-0.005,	0.016)	0.005	0.335
Hypertension	1.114	0.1080	(-0.033,	0.251)	0.072	0.137
Diabetes	1.089	0.0859	(-0.0827,	0.249)	0.084	0.310
HbA1c*	1.054	0.0533	(-0.0054,	0.109)	0.029	0.069
Waist circumference*	0.747	-0.2905	(-0.545,	-0.035)	0.130	0.025
BMI	0.994	-0.0055	(-0.020,	0.009)	0.007	0.474
Weight*	0.993	-0.0060	(-0.011,	-0.0005)	0.002	0.031
Triglyceride	0.999	-7.90E-05	(-0.001,	0.0008)	0.000	0.870
HDL-C	0.995	-0.0048	(-0.011,	0.001)	0.003	0.147
LDL-C	1.000	0.0007	(-0.001,	0.0026)	0.000	0.428
MAP*	1.132	0.1242	(-0.017,	0.266)	0.072	0.086

HbA1c: glycated hemoglobin; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MAP: mean arterial pressure. Variables presenting a relationship with the number of failed cognitive tests are marked with an asterisk. Statistical differences were evaluated with univariate count regression models predicting the number of failed tests for each patient.

Table 4. Final count regression model predicting the number of overall failed tests for the full patient cohort.

Regression term	Rates ratio (exp(ß))	Estimate (ß)	Confidence interval (95%)		Standard error	p-value	Adjusted p-value
Intercept	2.59	0.95	(0.470,	1.45)	0.249	0.0001	0.0005
APOE ε3-ε3 (Reference)	1	1	-		-	-	-
APOE ε3-ε4	2.91	1.07	(0.228,	1.93)	0.434	0.013	0.027
HbA1c	1.10	0.098	(0.0238,	0.170)	0.037	0.008	0.025
APOE ε3-ε4: HbA1c	0.87	-0.138	(-0.264,	-0.016)	0.063	0.028	0.028

APOE: apolipoprotein E; HbA1c: glycated hemoglobin.

and MAP were pre-selected for modeling in accordance with the previously defined variables selection strategy[36] that sets our p-value variable inclusion threshold at 0.1. This model was selected based on our candidate variables (*i.e.*, MAP, waist circumference, and HbA1c). Though MAP and waist circumference showed a relationship with the number of failed tests, they failed to show a joint relationship mediated by APOE genotypes (p=0.14 and 0.24, respectively). In contrast, HbA1c presented a relationship with the APOE genotype and evidence of statistically significant interaction, revealing a strong interrelation. Specifically, we found that patients with the ε3-ε4 genotype have a 2.91 rate ratio for failed cognitive tests (Adj-p=0.027) compared to patients with the ε3-ε3 genotype. The number of failed tests would increase by a rate of 10% (Adj-p=0.025) for each one-unit increase in a patient's HbA1c values. Finally, we found a statistically significant interaction between the APOE genotype and the HbA1c, revealing that the effect of the HbA1c was lower by 13% (Adj-p=0.028) in patients with the ε3-ε4 APOE genotype compare those with the ε3-ε3 genotype. The number of failed tests for patients in the APOE ε3-ε3 genotype group was more susceptible to being affected by HbA1c values than those in the APOE ε3-ε4 group, which already had much higher rates of failed test. We explored the effect of cardiometabolic factors such as prior diagnoses of hypertension and diabetes, weight, BMI, waist circumference and lipid values, and relevant variable interactions during the model building phase. However, it was not possible to find any other statistically significant relationships in multivariate models that included the APOE groups of interest. We would, therefore, provide the appropriate evidence to test our hypothesis.

This finding was explored further by predicting the counts of failed cognitive and memory tests rather than overall failures in our patient population (Table 5). Our final model predicting cognitive test failures only included the APOE variables, revealing a 19.4% higher number of failed cognitive tests for patients with the ε3-ε4 genotype compared to patients with the ε3-ε3 genotype (Adj-p<.0001). The univariate model predicting the number of failed cognitive tests based on the HbA1c did not reveal a statistically significant relationship (Adj-p=0.172). Still, the same model developed for the overall number of failed tests returned similar estimate values with near-significance before p-adjustment. For example, the APOE group differences returned a rates ratio of 2.55 (p=0.040) compared to 2.91 (Adj-p=0.027) and the HbA1c returned a rate ratio of 1.08 (p=0.052) compared to 1.1 (Adj-p=0.025). This may be due to the reduced number of tests (*i.e.*, cognitive tests only) and may be overcome with additional data. Other cardiometabolic factors were explored to predict the number of failed cognitive tests and relevant variable interactions during model building and development. For this model, we also explored the effect of the cardiometabolic factors stated above and relevant variable interactions. Still, it was not possible to find other statistically significant relationships for the models, including the APOE group variable. The possibility of modeling the number of failed memory tests only was also explored. However, no statistically significant relationships were found for the variables of interest. Our dataset presented zero-inflation (69.3% of patients failed no memory tests), reducing our dataset variability and the potential for reliable statistical modeling.

Table 5. Final count regression results predicting the number of failed *cognitive and memory tests* for the full patient cohort.

Model	Regression term	Rates ratio (exp(ß))	Estimate (ß)	Confidence interval (95%)		Standard error	p-value	Adjusted p-value
Full model	Intercept	2.676	0.984	(0.469,	1.515)	0.267	0.0002	0.001
	APOE ε3-ε4 (Ref. 3-3)	2.55	0.936	(0.052,	1.838)	0.455	0.040	0.119
	HbA1c	1.08	0.078	(-0.003,	0.155)	0.040	0.052	0.119
	APOE ε3-ε4: HbA1c	0.892	-0.114	(-0.247,	0.014)	0.066	0.085	0.119
APOE only	Intercept	4.444	1.492	(1.404,	1.576)	0.044	<.0001	<.0001
	APOE ε3-ε4 (Ref. 3-3)	1.194	0.177	(0.009,	0.341)	0.085	0.036	0.036

APOE: apolipoprotein E; HbA1c: glycated hemoglobin.

DISCUSSION

We found that the number of failed cognitive tests in geriatric patients with cardiovascular risk factors was related to their APOE genotype and their HbA1c levels. Statistically significant differences were observed in the number of failed neuropsychological tests and APOE genotypes ε3-ε3 and ε3-ε4. ε3-ε4 genotype patients seemed to fail more cognitive tests. The HbA1c values at the time of testing appeared to affect the overall number of failed tests, but mostly in ε3-ε3 genotype patients. No HbA1c effect was found for cognitive tests alone.

Previous research established that the APOE gene is associated with the development of Alzheimer disease (AD).[39] The E allele is also associated to code for the regulation of sugar and lipid metabolism. AD and MCI have a common pathway with diabetes and other metabolic disorders that could influence mechanisms for deterioration of cognitive functions.[40] Significant positive association has been found in APOE ε4 carriers, increasing the risk of developing vascular dementia as compared to ε2 and ε3 carriers.[41] Our findings showed further differences in APOE alleles, underscoring an increased number of test failures in the ε3-ε4 as compared to the ε3-ε3 group. Furthermore, the length of time patients have diabetes is associated with greater cognitive decline after 20 years; this association is dependent on HbA1c levels, and greater cognitive decline observed with HbA1c >7%.[9] Non-adherent diabetics also had worse performance in executive functions, memory tasks, and mental planning.[42] The impairments were accentuated in cognitive domains such as information processing speed, executive function,[9] memory loss,[43] and visual construction skills, suggesting diabetes damages microvasculature of the subcortical gray matter or other pathways. Similarly, we found a strong association between HbA1c levels and VaMCI for the ε3-ε3 genotype in particular. In other investigations, cognitive performance was decreased in people with diabetes when educational differences were considered;[42] in our study, we found no association.

In previous studies, attention, executive function, and speed performance showed a decline when assessing for cognitive functions on patients with a continued hypertensive state,[44] with daily pressure variabilities associated with worse cognition and decreases in global cognitive functions.[45] Our data did not provide enough evidence to confirm the association between HTN and VaMCI. Similarly, two other studies observed that for every 10 mg increase in small-dense low-density lipoprotein cholesterol (sdLDL-C), there was an accelerated cognitive deterioration.[46] A high concentration of total cholesterol and LDL-C in late life was associated with a rapid cognitive impairment. On the contrary, another study found that MCI patients had a significant amount of small HDL when compared to the Alzheimer group,[47] higher midlife HDL-C halve the risk of developing MCI and lowered risk of dementia later in life,[48] suggesting an association between HDL subclasses and MCI. Whereas the components of MetS were not independently associated with cognitive impairment, MetS as a whole comprised a greater risk of developing accelerated cognitive decline at 10 years,[49] we did not find such association.

Limitations and strengths

Limitations included:

- The study population was relatively small and the resulting limited statistical power prevented the direct analysis of the relationship between cardiometabolic risk factors, APOE and MCI.
- Enrolled patients were from a single segment of the city.
- Our sample had a greater proportion of female participants.
- Participants were not matched according to educational level or age.
- Trial Making Test and Digit Span Tests were not included in the protocol due to financial limitation. There was a "floor effect" of the construction and abstract reasoning tests. The neuropsychological battery was developed to be used in Dominicans in New York, and we have implemented it in the Dominican Republic population; the years of education differences in these populations may have cause this floor effect.
- We analyzed only two of the APOE genotype groups with relatively different sizes due to limited proportion in some groups.

Study strengths:

- This is the first study in this population, and no comparisons of APOE 3-3 and 3-4 are available;
- The number of failed cognitive test allowed us to understand the magnitude of the impairment instead of encoding the presence or absence of VaMCI diagnosis.

Hemoglobin A1c and APOE genotypes seem to have an association with the development of VaMCI. Patients with APOE genotypes ε3-ε3 and ε3-ε4 are affected differently by A1c levels. In this sense, tight glucose control must be encouraged in the clinical consults for elderly patients at risk for developing VaMCI, in particular those with an ε3-ε3 and ε3-ε4 genotypes.

Routine APOE genotyping and neuropsychological evaluation may be beneficial in the at-risk aged population of Latin-American and Dominican heritage. We found differences that should be explored in future research with larger patient cohorts to uncover further details about the relationship between APOE genotypes, cardiometabolic risk factors and MCI.

ACKNOWLEDGEMENT

Genotyping for this project was supported by the Genetic Studies of Alzheimer's disease in Caribbean Hispanics (EFIGA) funded by the National Institute on Aging (NIA) and by the National Institutes of Health (NIH) (5R37AG015473, RF1AG015473, R56AG051876). We acknowledge the EFIGA research and support staff for their contributions to this study.

Author's contributions. MM: conceptualization, methodology, funding acquisition, investigation, project administration, supervision, writing – original draft, writing - review & editing. RL: conceptualization, methodology, investigation. GS: conceptualization, methodology, investigation. SD: conceptualization, methodology, investigation. GCT: data curation, writing – original draft, writing - review & editing. PM: data curation. FDG: formal analysis, writing - review & editing. All authors reviewed the manuscript for final approval.

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Dement Neuropsychol 2021 March;15(1):79-87

Original Article

https://doi.org/10.1590/1980-57642021dn15-010008

Feasibility of action observation effect on gait and mobility in idiopathic normal pressure hydrocephalus patients

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ABSTRACT. Action observation (AO) has been proved to be of benefit in several neurological conditions, but no study has previously been conducted in idiopathic normal pressure hydrocephalus (iNPH). **Objective:** This study aimed to investigate the feasibility of AO in iNPH patients. **Methods:** A single-group pretest-posttest design was conducted in twenty-seven iNPH patients. Gait and mobility parameters were assessed using the 2D gait measurement in the timed up and go (TUG) test for two trials before and after immediate AO training. The outcomes included step length and time, stride length and time, cadence, gait speed, sit-to-stand time, 3-m walking time, turning time and step, and TUG. In addition, early step length and time were measured. AO consisted of 7.5 min of watching gait videos demonstrated by a healthy older person. Parameters were measured twice for the baseline to determine reproducibility using the intraclass correlation coefficient ($ICC_{3,1}$). Data between before and after immediately applying AO were compared using the paired t-test. **Results:** All outcomes showed moderate to excellent test-retest reliability ($ICC_{3,1=}$0.51-0.99, $p<0.05$), except for the step time ($ICC_{3,1}$=0.19, p=0.302), which showed poor reliability. There were significant improvements ($p<0.05$) in step time, early step time, gait speed, sit-to-stand time, and turning time after applying AO. Yet, the rest of the outcomes showed no significant change. **Conclusion:** A single session of AO is feasible to provide benefits for gait and mobility parameters. Therapists may modify this method in the training program to improve gait and mobility performances for iNPH patients.

Keywords: hydrocephalus, normal pressure, observation, movement, gait, walking.

VIABILIDADE DO EFEITO DE OBSERVAÇÃO DA AÇÃO NA MARCHA E MOBILIDADE DE PACIENTES COM HIDROCEFALIA DE PRESSÃO NORMAL IDIOPÁTICA

RESUMO. A observação de ação (OA) teve benefícios comprovados em diversas condições neurológicas, mas nenhum estudo foi conduzido anteriormente em Hidrocefalia de Pressão Normal idiopática (HPNi). **Objetivo:** O presente estudo teve como objetivo investigar a viabilidade da OA em pacientes com HPNi. **Métodos:** Um projeto de pré-teste e pós-teste de grupo único foi realizado em 27 pacientes com HPNi. Parâmetros de marcha e mobilidade foram avaliados por meio de parâmetros 2D para a medida da marcha com o teste timed up and go (TUG) com duas tentativas antes e imediatamente depois do OA. Os resultados incluíram comprimento e tempo do passo, comprimento e tempo da passada, cadência, velocidade da marcha, tempo para sentar-e-levantar, tempo de caminhada de 3 metros, tempo de virada e passo, e tempo do teste (TUG). Além disso, o comprimento do passo inicial e o tempo da etapa inicial foram medidos. A OA consistia em assistir 7,5 minutos de vídeos de marcha demonstrados por um idoso saudável. Os parâmetros foram medidos duas vezes para a linha de base para determinar a reprodutibilidade usando o coeficiente de correlação intraclasse ($CCI_{3,1}$). Os dados entre antes e depois da aplicação imediata de OA foram comparados com o teste *t* pareado. **Resultados:** Todos os resultados mostraram confiabilidade teste-reteste moderada a excelente ($CCI_{3,1=}$0,51-0,99, $p<0,05$), exceto para o tempo do passo ($CCI_{3,1=}$0,19, p=0,302), que apresentou confiabilidade pobre. Houve melhorias significativas ($p<0,05$) no tempo do passo, tempo do passo inicial, velocidade da marcha, tempo sentar-e-levantar e tempo de virar após a aplicação de OA. Os demais resultados não mostraram nenhuma mudança significativa. **Conclusão:** Uma única sessão de aplicação de OA é viável para proporcionar benefícios aos parâmetros de marcha e mobilidade. Os terapeutas podem modificar esse método no programa de treinamento para obter desempenho de marcha e mobilidade para pacientes com HPNi.

Palavras-chave: hidrocefalia de pressão normal, observação, movimento, marcha, deambulação.

This study was conducted at the Surgery Unit, Outpatient Department, Siriraj Hospital – Bangkok, Thailand.

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Disclosure: The authors report no conflicts of interest.

Funding: This study was supported by Norway scholarship (Mahidol-Norway Capacity Building Initiative for Myanmar) and Faculty of Physical Therapy, Mahidol University.

Received on June 02, 2020. Accepted in final form on November 13, 2020.

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH), also known as Hakim-Adams syndrome, is a potentially reversible neurodegenerative disease that is increasing steadily nowadays.[1] However, it could be possible that recovery from this disease is related to the disease's duration, severity, early diagnosis, and treatment.[2] iNPH is caused by cerebrospinal fluid (CSF) retention in the ventricle leading to its enlargement and expanding to the related brain tissue areas.[2,3] The iNPH prevalence reported in Sweden during 1986-2000 was 0.2% for ages of 70-79 years and 5.9% for 80 years and older.[4] From the population-based study, 3.7% of elderly over 65 years had a greater iNPH prevalence than the other age groups. Furthermore, the study reported four times higher prevalence in older people 80 years and older than the ones 65-79 years old.[5] It was concluded that the prevalence of iNPH increases with age.[4,5] However, the reported number is likely to be underestimated due to the patients not having received an accurate diagnosis.[4] In a hospital-based study, by using clinical symptoms, neuroimaging, and released CSF pressure in the diagnosis, the estimation of prevalence was 21.9/100,000.[2]

The clinical presentation triad of iNPH is defined as; 1) progressive gait and balance disturbance, 2) urinary incontinence, and 3) cognitive impairment.[1,2,6-8] In these symptoms, gait and balance disturbance and cognitive impairment were detected for 88% in the patients.[9] Approximately 12-60% of the patients showed all of the three clinical symptoms.[9,10] Abnormal gait pattern was characterized as a magnetic gait with difficulty to initiate the step and disequilibrium, which is usually known as a crucial feature of frontal gait disturbance.[1,9] Abnormal characteristics of iNPH frequently consist of small steps, short stride, slowness, decreased step height, and *en bloc* gait and turning, and some individuals have a broad-based gait pattern, imbalance, and outward foot rotation.[9] These disturbances are supposed to be the result of malfunction of the cortical and subcortical brain areas[9] and low perfusion in the periventricular white matter and prefrontal regions.[11] Also, the increase of intracranial pressure leading to the stretch and compression of the nerve fibers of the corticospinal tract that supplies the lower limb muscle.[11]

Cognitive deficits in iNPH patients are often associated with impaired short-term memory, speech difficulty, and loss of interest in surrounding people and environment.[1] Cognitive and behavioral disturbances are caused by fronto-subcortical dysfunction involving executive dysfunction, inattention, slow mental processing, and apathy.[2,12,13] Among these disturbances, apathy is the most common behavioral disturbance associated with gait disorders and may affect the improvement of functions and activities in iNPH patients after CSF release.[14] For the memory and orientation functions, greater preservation was found in iNPH patients than in patients with Alzheimer's disease.[12,15]

Currently, a standard treatment for iNPH is CSF drainage with different types of shunt surgery such as the ventriculoperitoneal (VP), ventriculoatrial (VA), and lumboperitoneal (LP) shunts.[6,16] It is utilized in patients who respond to CSF drainage, intended to improve clinical symptoms while avoiding over-drainage complication.[6,16] Among various clinical symptoms, gait responded to surgery the most[17] and is often used as a prognostic factor for disease progression.[17] Although the symptoms were dramatically improved after shunt surgery, the extent of gait abnormality was still the same.[18] The effectiveness of shunt surgery may last longer, ranging between 3-5 years in 28-91% of iNPH patients.[2] However, there are few reports about the rehabilitation benefit in iNPH patients after shunt surgery.[2]

Action observation (AO) has become a unique rehabilitation tool to date for both neurological and non-neurological disorders.[19-23] AO is based on the mirror neuron system (MNS), used in the rehabilitation program to recover motor control and learning by recruiting the neural structures that can perceive and execute the actions.[19] Mirror neurons can be responsible for the mechanism linking to observing the action and its understanding and imitation.[24] These neurons are active throughout movement initiation to complete execution after observing the movement by reorganizing existing motor skills and cortical changes for the muscles involved in the observed action.[24] Observing the other person's dynamic action can use couple action-perception systems closely and influence motor performance planning of their own equivalently.[25] It can activate the specific cerebral areas such as the premotor cortex and inferior parietal lobule, which are connected together to form the fronto-parietal circuits in organizing the actions.[26]

The actual or imagined locomotion tasks can activate the central locomotion control system, which includes the action observation network (AON) and other corresponding brain areas.[27] According to a review of neuroimaging study, the premotor cortex, prefrontal cortex, and superior and inferior parietal lobules are the activated brain areas involved in AON. This was the higher level of activation occurring when the individuals were asked to observe the movements immediately after its observation.[28] In addition, AON was also likely to be activated prominently during the observation of

familiar movements compared with unfamiliar movements.[28] Walking and other kinds of mobility function such as sit-to-stand and turn are dynamic familiar movements that we behave in our daily life and that can shape perception stimuli through the visual system.[29]

Observation of other person's performance can activate representational areas where AON exists. This can be activated more when the observer performs the actual movement together during watching[28,30] and the attention of observers' on stimuli can have control over the currently perceived movement.[29] AO has usually been used and demonstrated to be of benefit for improving motor function and learning in several conditions.[19-24,26,28,30-34] It can be practiced by observing the action alone (action observation; AO) or observing combined with movement execution (action observation-execution; AOE). From a recent study by Zhu et al.[35] that investigated the effect of AO and AOE on motor-cortical activation using magnetoencephalography in stroke patients. They concluded that AOE likely provides a good strategy to stimulate more brain activation at the primary motor cortex (M1), rather than AO alone as observed by a significant reduction of M1 beta oscillatory activity.

From a systematic review article,[32] there are a quite number of studies of AO in patients with chronic and acute stroke, Parkinson's disease (PD), cerebral palsy, and other orthopedic conditions. However, none of the studies investigated the effect of AO in iNPH patients. Therefore, the objective of this study was to investigate the feasibility of an acute effect of AO on gait and mobility parameters in iNPH patients after shunt surgery. We hypothesized that significant improvement of gait and mobility parameters would be found after applying AO.

METHODS

This study was the first study designed as a single group, pre- and post-test design. Participants were informed about study details and signed an informed consent form prior to participating in the study. The study was approved by the university ethical review board (MU-CIRB COA No, 2019/179.0907) and the hospital ethical review board (SIRB COA No. 691/2019). In addition, this study has also been approved by the Thai Clinical Trials Registry, and the clinical registration number is TCTR20191104003.

Participants

Ninety-six participants were recruited from the surgery unit, outpatient department, Siriraj Hospital, Bangkok, Thailand. For medical safety, participants were initially examined by the responsible neurosurgeon who provided the treatment before. They were then referred to screening following the study criteria with a well-trained physiotherapist. The inclusion criteria were age over 60 years, male or female, had received any kind of shunt surgery, able to follow the instructions, had no visual or auditory impairments after correction by glasses or hearing aid, and could walk with or without assistive device at least 10 m. Exclusion criteria were non-responsive to shunt surgery, unstable vital sign (blood pressure more than 160/90 mmHg and heart rate <59 beats/min or >90 beats/min), severe musculoskeletal problems such as severe osteoarthritis, deformities, and contractures in the lower limbs, severe pain that could affect gait performance and mobility, significant cognitive impairment, and unable to follow the instructions. Sixty-nine iNPH patients were excluded by the neurosurgeon (n=51) or physiotherapist (n=18). Hence, twenty-seven patients who met the selection criteria were left and took part in this study. They were checked for demographic characteristics, including age, weight, height, sex, and level of schooling. Afterwards, the clinical data were recorded, including the iNPH grading scale, Montreal Cognitive Assessment (MoCA), and time of shunt surgery. The flow chart diagram of the study is presented in Figure 1.

Data collection placement and setting

Before collecting the data, the placement was prepared in a quiet room at the outpatient department of Surgery Unit, Siriraj Hospital, Bangkok, Thailand. Gait and mobility parameters were captured by the 2D measurement method modified from the previous study.[36] Because some iNPH patients walked with a broad-based gait pattern, the walkway was created using five different referenced lines, each line was 50 cm in length. They were placed 7.2 cm apart, covered in the middle of the 3-m-long walkway. A video camera (Sony, HDR-CX210E, China) was placed at 1.75 m from the walkway perpendicularly. A standard chair was placed at the start point of the walkway. The data collection scenario is shown in Figure 2.

Data collection protocol

Gait parameters were collected before and immediately after applied AO by a video camera. Prior to data collection, a research assistant who was a physiotherapist explained the details and demonstrated the timed up and go (TUG) test over the walkway. TUG is a widely used assessment tool to measure the effect of treatment on lower limb function and mobility[37-39] and proposed to use in diagnosis criteria[40] for iNPH. It demonstrated

excellent reliability in elderly and chronic stroke.[41,42] To ensure that the participants understood the gait capture protocol but avoided muscle fatigue, participants practiced their walking for one trial before collecting the real data. For the test-retest reliability analysis, gait data were collected for the first and second baselines with the two trials each, with a 10 min break or more between baseline capturing. Data between before and after immediately training were compared to investigate the training effect of AO. During testing, a physiotherapist walked behind the patient to prevent any hazardous situation such as a trip or fall and provide assistance in the required cases.

Intervention

After finishing the second baseline measurement, participants received stretching and relaxation exercises together with the breathing exercise for 10–15 min for refreshment. Next, watching the video clips of AO which lasted 7.5 min, in which a healthy elderly person demonstrated the separated sequences of TUG which were captured from the front, back, left lateral, and right lateral views. The right lateral view captured a whole TUG movement. A video was edited by the combination of those demonstrated sequences with 30 s break between sequences. In addition, the model inside the videos performed the walking on the markers of the floor mat for each step.

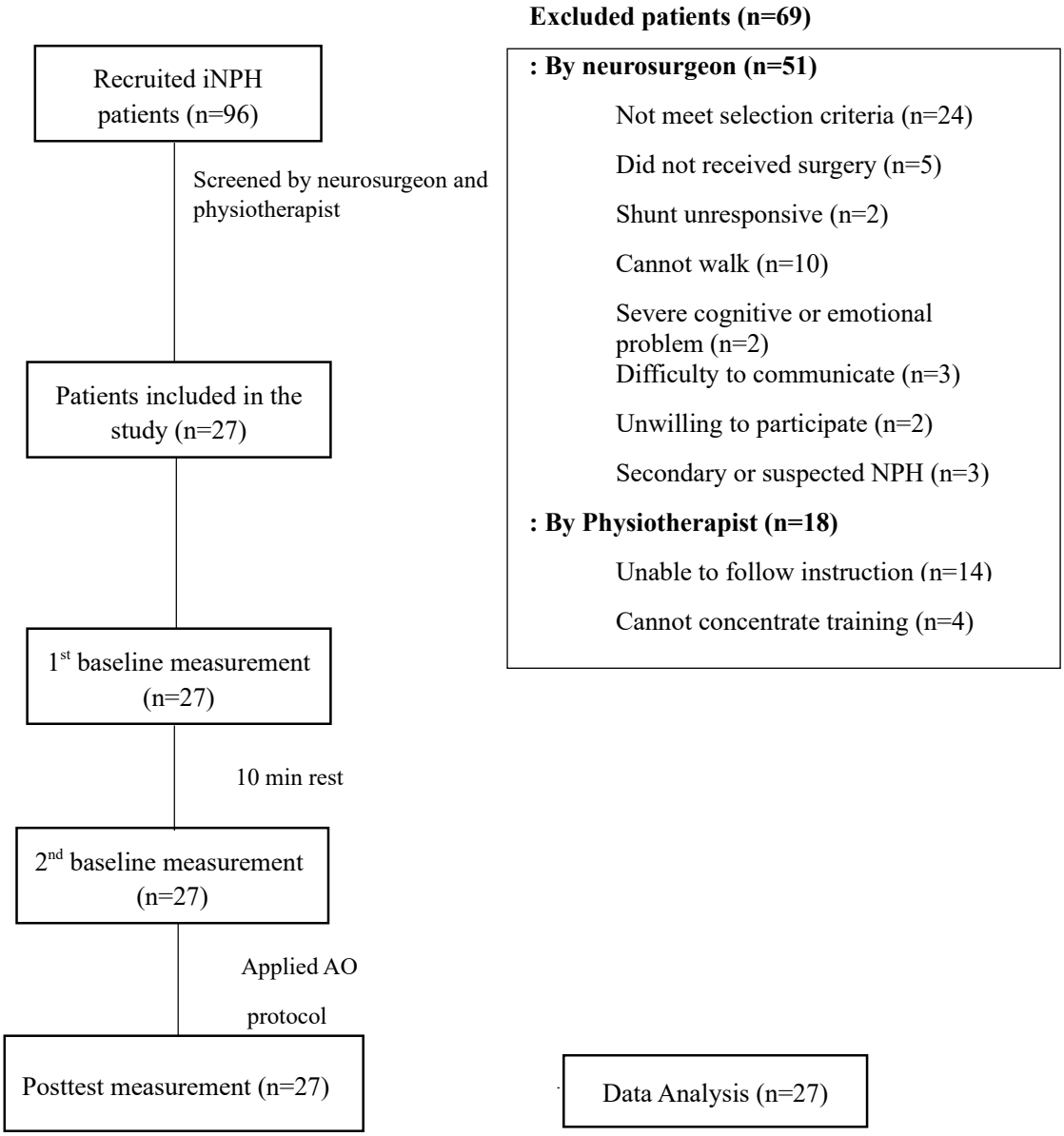

Figure 1. Flowchart of the study.

The videos were prepared with different speeds, embedded with the sound from metronome at the frequency of 80, 85, 90, 95, and 100 beats/min (bpm). Each frequency can be attributed to different gait speeds: 0.65 m/s for 80 bpm, 0.75 m/s for 85 bpm, 0.85 m/s for 90 bpm, 0.9 m/s for 95 bpm, and 1 m/s for 100 bpm. The video was chosen at proper gait speed based on individual ability testing at the baseline, simply calculated over 3 m distance by using a stopwatch to record the time. It was selected with a minor challenging method by increasing speed by about 10–15% than the ability of the individual. The video was opened by a laptop computer (Lenovo, 15 inches), and then the participant was asked to sit on a chair at a place where they could clearly see the video. They were instructed to watch the video carefully and continuously and move their legs like marching in a sitting position, following the demonstrator in the video.

Data tracking process

Spatiotemporal gait parameters and mobility parameters were collected at two time points (pre- and post-test). They included step length, step time, stride length, stride time, cadence, gait speed, early step length, early step time, sit-to-stand time, 3-m walking time, turning time, turning step, and TUG.

The data were analyzed by using the Kinovea Video Software, Windows Vista 10, version 0.8.15. The videos were opened inside the software and a 50-cm reference line nearest to the stepping foot was calibrated. According to the reference line, step length was tracked from a distance between the contact of opposite heel strike, the stride length from a distance between two successive points of the same heel contacts. These parameters were picked up from one or two gait cycles in the middle part of the walkway. While the early step length and early step time were extracted from the step first appearing on the screen.

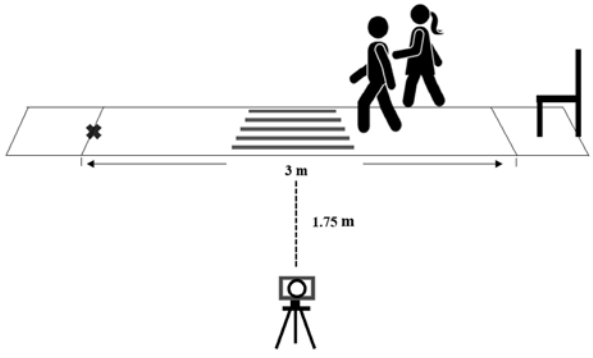

Figure 2. Data collection simulation.

Time concerning parameters were tracked by using a stopwatch item inside the software. The step time and stride time were tracked by the time taken of the step length and stride length. Sit-to-stand time was measured from sitting to standing up still, 3-m walking time was timed walking over 3-m walkway, turning time and step were captured while turning over 180 degrees, and TUG was the total time started from rise from a chair, walk 3 m, turn around, walk back to the chair, and sitting down. Gait speed was calculated over 3-m walkway divided by time spent, and cadence was calculated from 120 multiplied by gait speed and divided by stride length.

Statistical analyses

Data were analyzed using the *Statistical Package for the Social Sciences* (SPSS) software (version 23) with the statistical significance level set at $p<0.05$. The Kolmogorov-Smirnov Goodness of Fit test was used and showed normal distribution. The descriptive statistic was used to describe demographic data and reported using mean and standard deviation. The intraclass correlation coefficient ($ICC_{3,1}$) was used to determine the reproducibility of the testing protocol between the first and second baselines. The ICC values could be indicated as poor (0.00-0.50), moderate (0.50-0.75), good (0.75-0.90), and excellent (0.90-1.00) reliability.[43] The data between before and immediately after AO training were compared using the paired t-test.

Sample size calculation

The sample size was estimated from our pilot study (n=10) on the representative parameters for gait and sit-to-stand by the times to perform a step and sit-to-stand. A sample number was calculated using the G*Power software (version 3.1.9.2) with the t-tests function of comparing the difference between two dependent means (matched pairs). Determination of the alpha error probability 0.05 and power of 0.80 was set. The total sample sizes for step time, sit-to-stand time, and early step time were 7, 14, and 10, respectively. Hence, twenty-seven participants recruited in this study should cover and be sufficient to answer the research question.

RESULTS

Demographics and clinical characteristics of the participants are presented in Table 1. Twenty-seven participants with mean age of 76.81±5.53, ranging from 65 to 85 years, including twenty-one males and six females, participated in the study. The mean weight and height were 63.34±12.89 kg and 162.59±7.21 cm. Most of the patients completed high school, and many patients had hypertension and diabetes mellitus as comorbidities.

For the iNPH grading scale, all patients had gait disturbance (n=27) and most had cognitive impairment (n=24) and urinary problems (n=22). They were able to walk independently but were unstable (n=10) or walked with assistive devices (n=17). The mean MoCA score was 20.44±4.07, with scores ranging 12 to 28, and time post-shunt surgery was 1.84±2.35, ranging 0.06 to 11 years.

Test-retest reliability of the gait and mobility parameters between the first and second baseline measurements

Table 2 presents the reproducibility of gait and mobility parameters between the first and second baseline measurements. All parameters showed moderate to excellent test-retest reliability ($ICC_{3,1=}$0.51-0.99, p<0.05), except for the step time, which showed no reliability ($ICC_{3,1=}$0.19, p=0.302).

Comparison of the gait and mobility parameters between before and immediately after action observation

Table 3 shows the comparison of gait and mobility parameters between before and immediately after AO. Significant differences were found in step time (p=0.002), gait speed (p=0.044), early step time (p=0.005), sit-to-stand time (p<0.001), and turning time (p=0.049), whereas the other parameters showed no change.

DISCUSSION

From our knowledge, this was the first study that investigated the effect of a single session of AO training on gait and mobility enhancement in iNPH patients post-shunt surgery. Except for the step time, the data showed test-retest reliability with a moderate degree in early step time, stride time, and cadence ($ICC_{3,1}$=0.51–0.67), good in turning time and early step length ($ICC_{3,1}$=0.85–0.86), and excellent in the other parameters ($ICC_{3,1}$=0.92–0.99). This helps confirm to a certain extent that the findings may not come from testing repeatedly or the practice effect. As a result of the test-retest reliability results, we found that there was a variation for the step time, whereas the others showed relatively constant values in this patient population. This inconsistency may be linked to the common abnormal characters demonstrated in iNPH patients; freezing, shuffling or magnetic, and hesitant gait.[9,44,45]

After applying AO, significant improvements were found in step time (p=0.002), gait speed (p=0.044), early step time (p=0.005), sit-to-stand time (p<0.001), and turning time (p=0.049), and no change was found for the rest parameters. From a previous study, it was found that a single session of AO can induce an increase in spontaneous finger movement rate in PD.[22]

Table 1. Demographic data and clinical characteristics of the participants (n=27).

Parameters	Values
Age (years), mean±SD, range	76.81±5.53, 65.00–85.00
Weight (kg)	63.34±12.89, 44.50–92.60
Height (cm)	162.59±7.21, 148.00–176.00
Gender (male/female), n	21/6
Education, n	
No study	1
High school	14
Bachelor's degree	11
Master's degree	1
Comorbidities, n	
Hypertension	19
Diabetes mellitus	13
Heart disease	4
Parkinson's disease	2
iNPH grading scale (scores), n	
Gait	
0: Absent	0
1: Unstable, but independent gait	10
2: Walking with one cane	12
3: Walking with two canes or walker frame	5
4: Walking not possible	0
Cognition	
0: Absent	3
1: No apparent dementia, but apathetic	16
2: Socially dependent, but independent at home	6
3: Partially dependent at home	2
4: Totally dependent	0
Urinary	
0: Absent	5
1: Absent, but with pollakisuria or urinary urgency	9
2: Sometimes only at night	7
3: Sometimes, even during the day	6
4: Frequent	0
MoCA (scores), mean±SD, range	20.44±4.07, 12.00–28.00
Time since post-shunt surgery (years), mean±SD, range	1.84±2.35, 0.06–11.00

iNPH: idiopathic normal pressure hydrocephalus; MoCA: Montreal Cognitive Assessment.

Furthermore, a systematic review about AO in various populations showed evidence that 5–6 min AO could be reasonable to sustain participants' attention and enable training efficacy to improve motor function.[26] In our study, we modified the AO protocol, which consisted in stretching and breathing exercises for refreshment and allowed the patients to execute the lower limb movement together with observing the video in a sitting position. These steps of the protocol were provided to prevent injury from walking tests and to maximize the effect of AO in brain stimulation but avoid fatigability in iNPH patients due to a frail body.

As the iNPH patients were older adults with kinds of locomotion deficit, most of them may not cope with long duration or heavy intensity of physical practice. A previous study demonstrated that AO alone could provide a beneficial effect on movement execution[46] and increase walking performance in elderly people[47] as well as in iNPH, which

Table 2. Test-retest reliability of gait and mobility parameters between the first and second baseline measurements.

Parameters	First baseline (mean±SD)	Second baseline (mean±SD)	$ICC_{3,1}$	95%CI	p-value*
Step length (cm)	35.07±8.75	35.67±8.11	0.98	0.955–0.991	**<0.001**
Step time (s)	0.61±0.09	0.62±0.06	0.19	0.786–0.629	0.302
Stride length (cm)	71.64±16.36	72.70±16.19	0.99	0.968–0.993	**<0.001**
Stride time (s)	1.26±0.16	1.22±0.11	0.67	0.286–0.852	**0.003**
Cadence (steps/min)	86.21±11.77	86.84±13.33	0.63	0.181–0.830	**0.007**
Gait speed (m/s)	0.51±0.11	0.53±0.11	0.95	0.890–0.977	**<0.001**
Early step length (cm)	31.24±10.18	32.17±10.17	0.86	0.696–0.937	**<0.001**
Early step time (s)	0.63±0.09	0.60±0.08	0.51	0.078–0.776	**0.038**
Sit-to-stand time (s)	2.21±1.17	1.94±0.84	0.92	0.829–0.965	**<0.001**
3 m walking time (s)	6.24±1.58	5.96±1.51	0.96	0.903–0.980	**<0.001**
Turning time (s)	3.19±1.03	3.08±1.07	0.85	0.678–0.933	**<0.001**
Turning step (steps)	5.31±2.04	5.07±2.31	0.94	0.875–0.974	**<0.001**
Timed up and go (s)	22.83±7.01	22.22±6.57	0.98	0.948–0.989	**<0.001**

*Statistical significance was tested by the $ICC_{3,1}$ at $p<0.05$ (bold); SD: standard deviation; ICC: intraclass correlation coefficient; 95%CI: 95% confidence interval.

Table 3. Comparison of gait and mobility parameters between before and immediately after applied with action observation.

Parameters	Before (mean±SD)	Immediately after (mean±SD)	p-value*
Step length (cm)	35.37±8.35	35.22±7.81	0.769
Step time (s)	0.62±0.06	0.57±0.08	**0.002**
Stride length (cm)	72.17±16.15	73.09±16.14	0.206
Stride time (s)	1.24±0.12	1.21±0.13	0.238
Cadence (steps/min)	86.52±10.73	89.07±8.83	0.101
Gait speed (m/s)	0.52±0.11	0.54±0.12	**0.044**
Early step length (cm)	31.70±9.54	32.03±10.49	0.660
Early step time (s)	0.62±0.07	0.57±0.09	**0.005**
Sit-to-stand time (s)	2.08±0.98	1.74±0.79	**<0.001**
3 m walking time (s)	6.10±1.51	5.92±1.74	0.270
Turning time (s)	3.13±0.98	2.90±1.21	**0.049**
Turning step (steps)	5.19±2.12	4.94±2.37	0.095
Timed up and go (s)	22.53±6.72	22.07±8.11	0.366

*Significant difference tested by the paired t-test at $p<0.05$ (bold); SD: standard deviation.

was shown in the present study. The results showed statistically significant improvements in time during walking (step and early step), sit-to-stand, turning, and gait speed, while other gait parameters such as step length, stride length, cadence, and timed capturing from a long distance as stride or TUG were not significant. This may be caused by the pathology of the ventricle enlargement and compress periventricular areas such as the internal capsule, corticospinal tract, and corpus callosum.[48] Furthermore, as AO can only activate central mechanisms rather than peripheral, this can probably affect more the time parameters rather than the spatial.[47]

Relating to the characteristics of the participants, a wide range of post-shunt surgery duration (0.06-11 years) could affect the benefit of the intervention. The outcome of the efficacy of shunt surgery can be maintained for the short range between three and six months for 64–96% until one year for 41–95%, and a long term of three to five years for 28–91% of the patients. It showed that shunt surgery is predominantly effective up to five years at least. Taken together, the shunt surgery duration was not limited in this study; thus, the benefit of AO may also have been affected by this factor.[2]

On the other hand, we would expect that more sessions of AO in combination with strengthening exercise may be required to gain improvement noticeably on the temporospatial gait parameters for iNPH patients. There were different findings among the studies, depending on which parameters were selected and different training protocols.[20,31,33] Step length, stride length, single support, cadence, and gait velocity were improved four weeks after AO in stroke patients.[20,33] However, a study conducted in PD patients showed no significant improvement in stride length and walking speed after AO.[31] Apart from the difference in training protocol, the controversial results among studies may result from the factors of different pathologies, brain changes, and clinical symptoms.

The study may have been limited by having only a single training session, small sample number, varied clinical symptoms relating to cognitive level and post-shunt surgery duration, and a single group without comparing to an age-matched control. Hence, an additional session of AO with a combined effect with another strengthening exercise program and a long-term assessment with randomized controlled trial should be conducted in future studies on iNPH patients.

In conclusion, this study shows that AO may be used in an iNPH population. A single session of AO slightly improved the temporal parameters of gait, sit-to-stand, and turn. Therapists may apply this strategy in the training program to enhance gait and mobility functions in iNPH patients.

ACKNOWLEDGEMENTS

This study was supported by the Norway scholarship (Mahidol-Norway Capacity Building Initiative for Myanmar) and Faculty of Physical Therapy, Mahidol University. The authors would like to thank all iNPH patients and juniors and seniors who assisted in the study.

Authors' contributions. HHH: data curation, investigation, writing — original draft. SB: conceptualization, data curation, writing — original draft, writing — review & editing. TW: conceptualization, investigation; RV: conceptualization. RA: investigation.

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Dement Neuropsychol 2021 March;15(1):88-97

Original Article

https://doi.org/10.1590/1980-57642021dn15-010009

Memory complaints at primary care in a middle-income country:
clinical and neuropsychological characterization

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ABSTRACT. There are different causes of memory complaints in the elderly, such as subjective cognitive decline (SCD), mild cognitive impairment (MCI) or dementia. **Objective:** 1) To characterize individuals with memory complaints in a mid-sized city in Brazil, through clinical, cognitive and functional assessment; 2) to compare SCD individuals with MCI and dementia patients in terms of clinical and cognitive variables. **Methods:** We consecutively included individuals aged ≥50 years, with memory complaints (spontaneous or inquired). Subjects who scored ≥25 on the Memory Complaint Questionnaire or who had spontaneous memory complaints were selected. Participants underwent a semi-structured interview, the Mini-Mental State Examination, Figure Memory Test for visual episodic memory, Clock Drawing Test, Category Fluency (Animals), Neuropsychiatric Inventory, and functional assessment. Individuals were classified as SCD, MCI or dementia. We did not include individuals with previous diagnosis of dementia. **Results:** The final sample consisted of 91 subjects (73.6% women; mean age 67.6±9.8 years): 14.3% had spontaneous complaints and 85.7% had inquired complaints. The most common comorbidities were hypertension (69.2%), diabetes (36.3%), and dyslipidemia (24.2%). Low levels of vitamin B12 and hypothyroidism were found in 26.4 and 16.5%, respectively. Regarding cognitive diagnosis, 16.5% of the sample were classified as SCD, 49.4% as MCI and 34.1% as dementia. MCI and dementia were identified in five (38.5%) and seven (53.4%) patients with spontaneous complaint, respectively. **Conclusions:** MCI and dementia are frequently underdiagnosed. Potential reversible causes of cognitive decline are common. The diagnosis of dementia is highly frequent among individuals with spontaneous memory complaints.

Keywords: memory, primary health care, cognitive dysfunction, dementia.

QUEIXAS DE MEMÓRIA NA ATENÇÃO PRIMÁRIA EM UM PAÍS DE RENDA MÉDIA: CARACTERIZAÇÃO CLÍNICA E NEUROPSICOLÓGICA

RESUMO. Há diferentes causas de queixas de memória nos idosos, como declínio cognitivo subjetivo (DCS), comprometimento cognitivo leve (CCL) ou demências. **Objetivo:** 1) Caracterizar indivíduos com queixa de memória em uma cidade de médio porte do Brasil, por meio de avaliação clínica, cognitiva e funcional; 2) comparar indivíduos com DCS, com CCL e pacientes com demência em termos de variáveis clínicas e cognitivas. **Métodos:** Incluiu-se, de modo consecutivo, indivíduos com idade ≥50 anos, com queixas de memória (espontânea ou inquirida). Foram selecionados participantes que pontuaram ≥25 no Questionário de Queixa de Memória ou que apresentaram queixa de memória espontânea. Todos foram submetidos à entrevista semiestruturada, Miniexame do Estado Mental, Teste de Figuras (teste de memória episódica visual), Teste do Desenho do Relógio, Fluência Semântica (Animais), Inventário Neuropsiquiátrico e avaliação funcional. Os indivíduos foram classificados em declínio cognitivo subjetivo (DCS), CCL e demência. **Resultados:** A amostra final foi composta por 91 indivíduos (73,6% mulheres; média de idade 67,6±9,8 anos); 14,3% apresentaram queixa espontânea e 85,7%, queixa inquirida. As comorbidades mais comuns foram hipertensão (69,2%), diabetes (36,3%) e dislipidemia (24,2%). Baixos níveis de vitamina B12 e hipotireoidismo foram encontrados em 26,4 e 16,5%, respectivamente. Quanto ao diagnóstico cognitivo, 16,5% foram classificados como DCS, 49,4% como CCL e 34,1% como demência. CCL e demência foram respectivamente identificados em cinco (38,5%) e sete (53,4%) pacientes com queixa espontânea de memória. **Conclusões:** CCL e demência são frequentemente subdiagnosticados. Causas potencialmente reversíveis de declínio cognitivo foram frequentes na amostra. O diagnóstico de demência foi muito frequente entre indivíduos com queixas espontâneas de memória.

Palavras-chave: memória, atenção primária à saúde, comprometimento cognitivo, demência.

This study was conducted at the Patos de Minas, Minas Gerais, Brazil.

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Disclosure: The authors report no conflicts of interest.

Funding: none.

Received on June 23, 2020. Accepted in final form on October 26, 2020.

INTRODUCTION

Cognitive complaints are frequent among older adults.[1] Some cognitive functions tend to decrease with age, such as attention and executive functions.[2] During normal aging, episodic memory may also be affected by encoding or recall deficits, which depend on executive functions.[3] Indeed, declining processing speed, reduced processing resources, and decreased cognitive control may account for age-related memory complaints.[2]

On the other hand, memory loss is a frequent symptom in different neuropsychiatric disorders, including dementias and psychiatric disorders,[4] and is also found in systemic conditions (e.g., hypothyroidism and vitamin B12 deficiency).[5]

Previous studies investigated the prevalence of memory complaints in different populations. The frequency of memory complaints is variable across studies, ranging from 8 to 50%.[6-8] Older age, female sex, depressive and anxious symptoms and low educational level are generally associated with a higher prevalence of memory complaints.[3,9,10] Moreover, memory complaints can predict dementia, particularly in patients with mild cognitive impairment (MCI).[11,12] Despite their clinical relevance, memory complaints are not always reported to the general practitioner.[12]

Complaints of memory loss may be associated with subjective cognitive decline (SCD), which is currently defined by two hallmark features: 1) self-experience of continuous deterioration in cognitive status, in comparison with the individual's preceding level and; 2) normal performance on standardized neuropsychological tests, considering education, age and gender.[13] SCD is not merely an age-related phenomenon but is recognized as an important risk factor for MCI and Alzheimer's disease (AD).[14]

Considering that cognitive disorders may be due to reversible causes, it is crucial that health professionals perform proper cognitive screening at primary care. Moreover, as SCD and MCI are risk factors for AD, the detection of these conditions at primary care can contribute to early interventions, thus changing the outcome of clinical conditions related to memory loss.

Despite this clinical relevance, there are few studies of SCD in primary health care,[15] and most of them were conducted in populations from high-income countries, with high educational level.[16] There is scarce data about cognitive impairment and memory complaints in low- and middle-income countries,[10,16-19] especially in primary health care. As a matter of fact, the number of patients with dementia is globally increasing, especially in low and middle-income regions, such as Latin America,[20] making it crucial to provide data about SCD and memory complaints in these populations.

The objective of this study was to characterize individuals with memory complaints in a mid-sized city in Minas Gerais State, Brazil, through a comprehensive clinical, cognitive and functional assessment. We also aimed to compare SCD individuals with MCI and dementia patients in terms of clinical and cognitive variables.

METHODS

This was an observational, cross-sectional study. Data collection was carried out from March to September 2016, at the Lagoa Grande Basic Health Unit in Patos de Minas. Patos de Minas is located in Minas Gerais (Southeast region, Brazil), with a population of 152,488 inhabitants. The Human Development Index (HDI, 2020) of the municipality of Patos de Minas is 0.765, which is slightly higher than that of Brazil (0.755, world rank 75th). Patos de Minas' gross domestic product (GDP-2019) per capita is about US$ 5,182, which is lower than Brazil's index in 2019 (US$ 6,155).

This study was proposed for individuals over 50 years of age who were consecutively seen at a general practice visit. Importantly, we did not include participants with previously established diagnosis of dementia. Figure 1 shows the flowchart of the study.

Subjects who spontaneously presented with memory complaints (as the main reason for the consultation, hereafter referred to as "spontaneous memory complaints") were submitted to neuropsychological and laboratory investigation. In turn, subjects who had no spontaneous complaint of memory deficits were asked about the functioning of memory with an open question ("How is your memory?"). Those who answered with memory complaints completed the Memory Complaint Questionnaire (MAC-Q),[16] and those who scored 25 points or more on the MAC-Q were referred for neuropsychological and laboratory investigation. Individuals with no spontaneous memory complaints but who scored 25 or more on the MAC-Q are hereafter referred to as subjects with "inquired memory complaints".

Participants underwent a semi-structured questionnaire, describing sociodemographic and medical variables (comorbidities, use of medications, alcohol use, smoking, physical activity). Next, the Brief Cognitive Battery[21] was applied, which includes the Mini-Mental State Examination (MMSE)[22], the Figure Memory Test (FMT, a Visual Episodic Memory Test),[18] the Clock Drawing Test[23] and Verbal Fluency (Animal Category).[24] Participants were also submitted to the Neuropsychiatric Inventory (NPI)[25] and Functional Activity Questionnaire (FAQ)[26] (Figure 1). All participants were submitted to laboratory tests to investigate cognitive decline, according to current recommendations.[27]

Based on clinical and neuropsychological data, subjects were classified into three clinical categories: 1) SCD (MAC-Q ≥25, with no change in neuropsychological tests and no functional decline, FAQ ≤5); 2) MCI, with abnormal score in one of the cognitive tests (abnormal MMSE, FMT-Recall 5',<7, abnormal Verbal Fluency or Clock Drawing Test, <4), and preserved functional capacity, FAQ ≤5; and 3) dementia, with abnormal cognitive scores and functional impairment — FAQ >5). The normal cut-off scores for the MMSE[22,24] and for Verbal Fluency were extracted from normative data for the Brazilian population, considering the educational level as follows: MMSE:[22] 20 — illiterate; 25 — 1 to 4 years of schooling; 26 — 5 to 8 years of schooling; 28 — 9 to 11 years of schooling and 29 — more than 11 years of schooling; Verbal Fluency Test – Animals:[24] 11 for illiterate, 13 for 1 to 4 years of study and 14 for more than 5 years of study.

Patients of the MCI and dementia groups were referred to brain computerized tomography (CT), without contrast, to investigate structural brain lesions. We did not include patients with structural brain lesions (e.g., brain tumor, subdural hematoma).

The study was approved by the Local Ethics Committee of the University Center of Patos de Minas (No. 1.733.241). All participants or their relatives, when necessary, signed an informed consent form after clarification.

Statistical analyses

All statistical analyses were performed using *Statistical Package for the Social Sciences* (SPSS) 22.0 (SPSS Inc.,

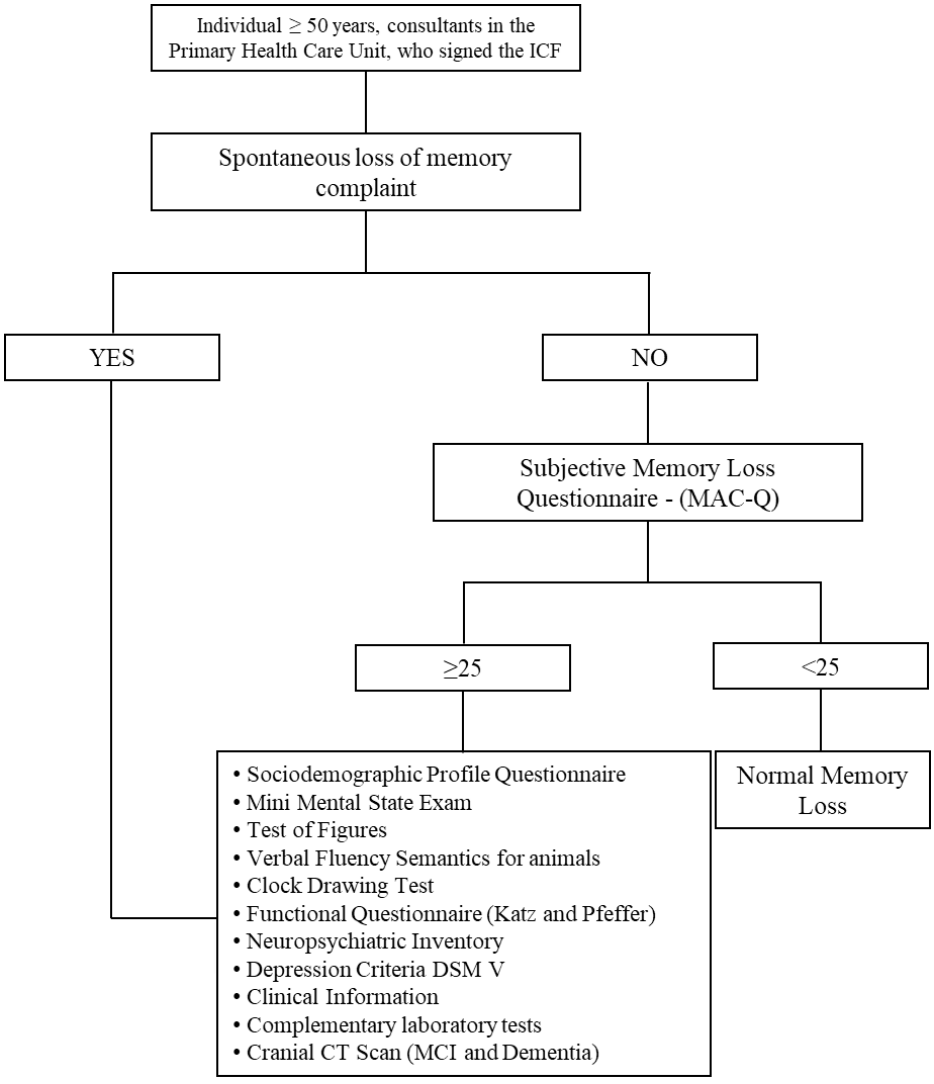


Figure 1. Study design.

Chicago, IL). Qualitative variables were described according to frequencies and percentages. The normality of the quantitative variables was verified with the Shapiro-Wilk test, after visual inspection of the histograms. The chi-square test was used for comparing frequencies between groups. Comparisons between continuous variables with normal distribution were analyzed by ANOVA, followed by the Tukey test. For non-normal distribution continuous variables, the Mann-Whitney test (for two independent groups) or the Kruskal-Wallis test (for comparison of multiple groups, followed by the Dunn post-test, when appropriate) was used. We adopted Bonferroni's correction for multiple comparisons and the level of significance (α) was set at 0.004.

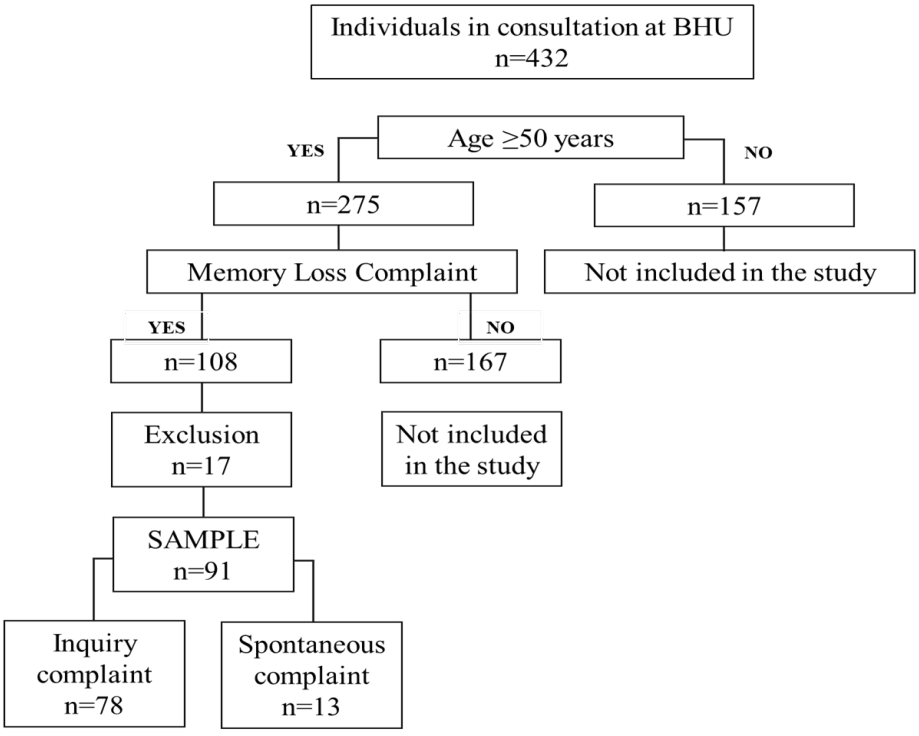
RESULTS

Descriptive analysis (total population)

During the study period, 432 individuals were referred for medical consultation at the Lagoa Grande Basic Health Unit, with 275 of them considered "initial sample" with age equal to or greater than 50 years. Among these, 167 subjects did not present with memory complaints (either spontaneous or inquired), while 108 (39% of the initial sample) had either spontaneous or inquired memory complaints. Seventeen subjects were excluded for the following reasons: (refused to undergo cognitive tests) (n=8), brain tumor (n=1), changed area covered by the health unit (n=3) and score <25 on MAC-Q (n=5). The final sample of the study consisted of 91 participants (Figure 2), being 13 (14.3%) with spontaneous memory complaints and 78 (85.7%) with inquired memory complaints.

Table 1 presents the demographic data of the sample. Women (74.7%), with mean age of 67.6 years (±9.8), composed most of the study population. Most individuals had low educational level (4–8 years of schooling — n=47, 51.7%).

Table 2 shows comorbidities and medications in use for the study population. Systemic arterial hypertension was present in 69%; diabetes, dyslipidemia and hypothyroidism were found in 36.3, 25.3 and 22%, respectively. Regarding medications, 33% of participants used antidepressants or anxiolytics (mainly selective serotonin reuptake inhibitors) and 23% used a proton pump inhibitor. Laboratory analyses found that 26.4% had low levels of vitamin B12, and 16.5% had thyroid-stimulating hormone (TSH) levels above normal. None of the individuals tested positive for



BHU: Basic Health Unit.

Figure 2. Sample flowchart

human immunodeficiency virus (HIV) or syphilis. Most patients (MCI and dementia) did not show abnormalities on CT scan. Leukoaraiosis was found in 7.6% of MCI or patients with dementia, being more frequent in the dementia group.

Comparison of groups: spontaneous vs inquired memory complaints

Among subjects with memory complaints (n=91), 13 (14.3%) had spontaneous memory complaints and 78 (85.7%) had inquired memory complaints. Individuals

Table 1. Demographic data (n, %) for the study population, according to clinical group.

		SCD (n=15)	MCI (n=45)	Dementia (n=31)	Total (n=91)
Sex¥	Female	8 (53.3%)	35 (77.8%)	25 (80.6%)	68 (74.7%)
	Male	7 (46.7%)	10 (22.2%)	6 (19.4%)	23 (25.3%)
Age (mean±standard deviation)§		64.9±9[a]	66.4±8.9	70.6±10.8	67.6±9.7
Schooling (years)¥	Illiterates	1 (6.7%)	2 (4.4%)	4 (12.9%)	7 (7.7%)
	1 to 3	5 (33.2%)	11 (24.5%)	8 (25.8%)	24 (26.4%)
	4 to 8	7 (46.7%)	24 (53.3%)	16 (51.6%)	47 (51.6%)
	9 to 11	1 (6.7%)	3 (6.7%)	1 (3.2%)	5 (5.5%)
	>11	1 (6.7%)	5 (11.1%)	2 (6.5%)	8 (8.8%)
Family income (in Brazilian minimum wage)¥	1 to 2	11 (3.3%)	27 (60.0%)	16 (51.6%)	54 (59.3%)
	3 to 5	4 (26.7%)	16 (35.6%)	14 (45.2%)	34 (37.4%)
	6 to 10	0 (0.0%)	2 (4.4%)	1 (3.2%)	3 (3.3%)
	>10	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Civil status¥	Unmarried	3 (20.0%)	2 (4.4%)	3 (9.7%)	8 (8.8%)
	Married	10 (66.7%)	24 (53.3%)	17 (54.8%)	51 (56.0%)
	Widow	2 (13.3%)	12 (26.7%)	8 (25.8%)	22 (24.2%)
	Divorced	0 (0.0%)	7 (15.6%)	3 (9.7%)	10 (11.0%)

MCI: mild cognitive impairment; SCD: subjective cognitive decline. The p-values refer to the significance level of the comparison between the 3 groups. ¥The frequency of qualitative variables (sex, schooling, family income and civil status) was compared between groups with the chi-square test. §The quantitative variable (age) between the groups was compared using the Kruskal-Wallis test. [a]p<0.05 (subjective complaint vs dementia).

Table 2. Clinical data (medications and comorbidities) for the study population, according to clinical group (n, %).

	SCD (n=15)	MCI (n=45)	Dementia (n=31)
Medications			
Proton pump inhibitor	2 (13.3%)	9 (20%)	10 (32.2%)
Antidepressant	4 (26.7%)	12 (26.7%)	14 (45.2%)
Typical antipsychotic	0 (0%)	1 (2.2%)	1 (3.2%)
Atypical antipsychotic	0 (0%)	0 (0%)	1 (3.2%)
Benzodiazepine p<0.015	3 (20.0%)	6 (13.3%)[a]	13 (41.9%)
Comorbidities			
Alchool use	2 (13.3%)	8 (17.7%)	2 (6.4%)
Smoking	2 (13.3%)	5 (11.1%)	3 (9.7%)
Hypertension	11 (73.3%)	28 (62.2%)	24 (77.4%)
Diabetes	5 (33.3%)	17 (37.8%)	11 (35.5%)
Dyslipidemia	6 (40.0%)	12 (26.7%)	5 (16.1%)
Hypothyroidism	4 (26.7%)	9 (20.0%)	7 (22.6%)

SCD: subjective cognitive decline; MCI: mild cognitive impairment; [a]p<0.05 (dementia vs MCI).

from these groups did not differ in age, sex distribution, schooling and family income (Supplementary Table). The two groups did not differ in the frequency of clinical diseases (hypertension, diabetes, dyslipidemia, and hypothyroidism).

Regarding the cognitive diagnoses, SCD, MCI and dementia were identified in one (7.7%), five (38.5%) and seven (53.4%) subjects with spontaneous memory complaints, respectively. In the group with inquired memory complaints, 12 (15.4%), 42 (53.4%) and 24 (30.8%) had SCD, MCI and dementia, respectively.

Table 3 presents the cognitive data of all participants. Compared to subjects with inquired memory complaints, those with spontaneous memory complaints had lower scores on the MMSE, but without statistical significance (p=0.015). These groups did not differ in 5'Recall (FMT), Animal Fluency and Clock Drawing Test.

Table 3. Neuropsychological data (mean±standard deviation) for clinical groups according to complaint type.

	Spontaneous complaint (n=13, 14.3%)	Inquired complaint (n=78, 85.7%)
MAC-Q p<0.05	31.1±3.7	29.3±3.0[b]
MMSE p<0.01	19.8±3.8	22.8±4.5[a]
Figure Memory Test (Recall 5') p<0.05	5.2±3.2	7.0±2.2[b]
Verbal Fluency (Animals)	8.3±2.8	9.8±3.5
Clock Drawing Test	3.5±1.7	3.2±1.9
FAQ	3.0±2.7	2.4±2.6

FAQ: Functional Activity Questionnaire; MAC-Q: Memory Complaint Questionnaire; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; SCD: subjective cognitive decline. The comparison between groups was performed using the Mann-Whitney test; [a]p<0.01 (spontaneous vs surveyed); [b]p<0.05 (spontaneous vs respondent).

Comparison of groups: subjective cognitive decline, mild cognitive impairment and dementia

According to clinical criteria, participants (n=91) were clinically categorized as follows: 15 (16.5%) with SCD, 45 (49.4%) with MCI and 31 (34.1%) with dementia.

These three groups did not differ in age, sex distribution, schooling and family income. There was no statistically significant difference in the frequency of comorbidities (hypertension, diabetes, dyslipidemia, and hypothyroidism) between groups. The frequency of use of antidepressants, antipsychotics and proton pump inhibitors did not differ across groups, but there was a trend (p<0.015) for a higher frequency of benzodiazepine use in the dementia group, when compared to the MCI group. Participants with regular physical activity were 8.3, 31.2 and 16.1% in the SCD, MCI and dementia groups, respectively.

Table 4 presents cognitive tests and scales for the clinical groups (SCD, MCI and dementia). There was a statistically significant difference in MMSE between groups, with higher scores in the SCD group, and lower in the dementia group, with MCI showing intermediate scores (SCD<MCI<dementia). Similarly, individuals with dementia performed worse than MCI (p<0.002) and SCI (p<0.001) individuals in the 5'Recall (FMT). Compared to SCD and MCI, patients with dementia also underperformed on Animal Fluency and on the Clock Drawing Test. Individuals with SCD and MCI had similar performances on all cognitive tests, except for MMSE (p<0.001), with lower scores in the MCI group.

The scores on the NPI across the groups are shown in Table 5. The groups did not differ in the following scores: disinhibition, dysphoria, anxiety, irritability, aberrant motor behavior, euphoria and night-time behavioral disturbances. Dementia group had higher scores than SCD on the NPI total score (p<0.002). Compared to MCI group, patients with

Table 4. Neuropsychological data (mean±standard deviation) for the study population, according to clinical group.

	SCD (n=15)	MCI (n=45)	Dementia (n=31)
MAC-Q	29.3±2.9	29.0±2.8	30.4±3.7
MMSE p<0.001	26.7±1.8[a,b]	23.4±3.4[a]	18.7±4.3
Figure Memory Test (Recall 5') p<0.001	8.1±1.1[a]	7.3±2.0[a]	5.3±2.7
Verbal Fluency (Animals) p<0.001	12.4±1.8[a]	9.9±3.5	7.7±2.9
Clock Drawing Test	3.9±1.3	3.6±1.6	2.3±2.0
FAQ	1.0±1.3	1.0±1.0	12.5±7.9

FAQ: Functional Activity Questionnaire; MAC-Q: Memory Complaint Questionnaire; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; SCD: subjective cognitive decline; [a]significant difference vs dementia group (p<0.004; Mann-Whitney test); [b]significant difference vs MCI group (p<0.004; Mann-Whitney test).

dementia scored higher on apathy (p<0.001), agitation (p<0.003), appetite disorders (p<0.004) and on the NPI total score (p<0.001). The groups SCD and MCI did not differ in any of NPI scores.

DISCUSSION

This study aimed to characterize complaints of memory loss in adults in primary health care in a middle-income country (Brazil). We found that clinical diseases, such as systemic arterial hypertension and hypothyroidism, were frequently observed in patients with memory complaints. We also identified notable frequencies of underdiagnosis of dementia and of treatable causes of cognitive decline among individuals with memory complaints. Finally, as an original contribution, we provide clinical characterization of subjects with SCD at primary health care in a middle-income country.

In line with previous studies,[1,10,11,12,28] most of our sample was composed of women. The reasons for this are unclear, but both medical and sociological issues may account for this[28]. Women look for medical care more frequently than men,[28] and it is possible that the memory loss in men is underdiagnosed.

There is scarce data about cognitive impairment and memory complaints in low- and middle-income countries, especially in primary health care. Data from India and China found respectively 10.8 and 17% of patients with cognitive impairment in primary health care surveys.[17,29] The prevalence of memory complaints and cognitive impairment is heterogeneous across studies, ranging from 8 to 50%.[6-8] Methodological issues, such as the target population (primary care, secondary outpatient clinics or referral centers) and differences on cognitive screening tests may explain the variability of the results across studies. Interestingly, the frequency of memory complaints in our sample is similar to that observed in study conducted at a high-income country.[30] Waldorff and colleagues[30] reported that 24% of Danish patients seen at primary health care had memory complaints. However, that study selected patients at least 65 years-old, while our study included individuals over 50 years of age. It is possible that we would find higher frequencies of memory complaints if we had included only patients over 65.

A previous study with elderly Brazilians community-living setting found that memory complaints were associated with low schooling and depressive symptoms but did not correlate with cognitive performance.[10] Another Brazilian study found that the score on the Memory Complaints Scale correlated with the MMSE and with measures of visual-spatial abilities and orientation.[18]

This study investigated both inquired and spontaneous memory complaints. We found that inquired memory complaints (n=78; 85.7%) were more frequent than spontaneous memory complaints (n=13; 14.3%), in line with Burmester et al.,[31] who reported that the frequency of spontaneous memory complaints was lower than when actively investigated with a structured questionnaire, in a large survey with 421 individuals. Again, these results raise the problem of underdiagnosis of cognitive decline in primary care.

Table 5. Scores (mean±standard deviation) on the Neuropsychiatric Inventory, according to clinical group.

Neuropsychiatric Inventory	SCD (n=15)	MCI (n=45)	Dementia (n=31)
Hallucinations	0.0±0.0	0.0±0.0	0.4±1.7
Delusions	0.0±0.0	0.0±0.0	0.4±1.5
Apathy	0.2±0.6	1.2±2.2[a]	4.3±4.7
Dysphoria	2.5±3.2	2.5±3.55	4.9±3.9
Agitation/aggression	0.1±0.3	0.6±2.1[a]	3.2±4.3
Anxiety	3.4±4.7	2.8±3.6	5.4±4.7
Disinhibition	0.1±0.3	0.19±0.55	0.4±1.2
Irritability/lability	1.4±2.7	1.7±3.4	3.3±4.6
Aberrant motor activity	0.0±0	0.03±2.15	0.6±2.0
Euphoria	0.0±0	0.03±2.15	0.3±1.5
Appetite and eating abnormalities	0.5±1.7	0.85±2.3[a]	3.7±4.8
Night-time behavioral disturbances	0.0±0	0.6±2.26	1.3±3.4
Total score	11.1±16.5[a]	10.2±13.2[a]	28.4±21.6

MCI: mild cognitive impairment; SCD: subjective cognitive decline; [a]significant difference vs dementia group (p<0.004; Mann-Whitney test).

Interestingly, subjects with spontaneous memory complaints had similar performance than those with inquired memory complaints on the cognitive tests. However, the frequency of dementia tended to be higher among participants with spontaneous memory complaints (53.4%) than in those with inquired memory complaints (30.8%). These results suggest that individuals with spontaneous memory complaints should be carefully screened for cognitive decline and dementia.

Previous diagnosis of dementia was an exclusion criterion, but 31 patients (34.1%) with memory complaints (seven with spontaneous memory complaints and 24 with inquired complaints) fulfilled criteria for dementia. All dementia patients had mild to moderate functional impairment, and none had severe dementia. These findings are in agreement with a recent meta-analysis showing that the underdiagnosis of dementia is high, with middle-income countries showing higher rates (above 90%) than in high-income countries (around 60%).[32] These results reinforce the urgent need for dementia screening at primary care.

We identified 15 out 91 (16.5%) individuals with SCD, i.e., patients who had memory complaints but with no objective deficit on cognitive assessment.[33] To the best of our knowledge, this is one of the first reports of frequency of SCD in a middle-income country.[18] Considering that SCD is associated with increased risk for developing MCI and AD,[14] a clinical follow-up of these individuals is warranted.

In agreement with previous studies, non-communicable chronic diseases such as systemic arterial hypertension, diabetes mellitus and dyslipidemia were frequently observed in our sample.[34-36]

Interestingly, there was no difference in frequencies of these comorbidities across groups of SCD, MCI and dementia. The interactions between these conditions and cognitive performance are a matter of debate. A Brazilian study did not find a significant difference in verbal fluency between healthy controls and patients with hypertension and/or diabetes,[37] but other studies found an association between poor cognitive performance and cardiometabolic diseases such as hypertension, diabetes and obesity.[37,38] Importantly, schooling may modulate the impact of these diseases in cognitive performance, as education is associated with adherence to preventive measures.[39]

Of note, we found substantial percentages of patients with potential reversible causes of cognitive decline. For instance, 26.4% of participants with memory complaints had low levels of vitamin B12, and 16.5% had abnormal TSH levels. These data reinforce the need for comprehensive screening for non-degenerative causes of cognitive deficit at primary care settings.

Patients with dementia had higher scores on the NPI than SCD and MCI patients. The use of benzodiazepines tended to be more frequent among patients with dementia thus suggesting that these medications were prescribed for treating neuropsychiatric symptoms associated with dementia. There is evidence that long-term use of benzodiazepines is associated with an increased risk of dementia,[40-42] although this association may be considered causal.[42,43] Considering the cross-sectional design of our study, we cannot establish a causal relation between benzodiazepine use and dementia. On the other hand, these medications are associated with increased risk of falls[40] and impairment in executive abilities[41] in patients with dementia. Our data support the need for a detailed inventory of medications in use in patients with memory complaints, to avoid possible negative effects, especially in patients with established dementia.

This study has some limitations. Besides the small sample size, we did not include a control group, without memory complaints, which would be of value for comparative purposes. Considering that we employed a self-scale for screening of memory complaints, it is possible that subjects with anosognosia were not retained in the study. Moreover, the value of the MAC-Q as a screening tool is limited by the interference of the affective status,[44] but the MAC-Q has been successfully used in the Brazilian population.[10] The diagnosis was established on clinical grounds, and participants did not undergo formal neuropsychological examination and did not pass advanced investigation with brain magnetic resonance imaging and biological markers of AD. Therefore, we cannot establish the etiology for cognitive decline and dementia in our group. Finally, we adopted strict statistical correction for multiple comparisons, to avoid spurious results. It is possible that we would find more differences for clinical and cognitive variables between groups using a less strict level of significance (e.g., $p<0.05$).

Despite these limitations, this study provides relevant clinical information to general practitioners working at the primary health care level, as well as for public health programs. The early diagnosis of cognitive decline provides the best opportunities for care planning and medical assistance for patients and caregivers. In this context, physicians and the primary care team play a key role in the early recognition of cognitive impairment in their patients.[45] We detected substantial percentages of non-diagnosed MCI and dementia among individuals with memory complaints, and we also found that potentially reversible causes of cognitive impairment, such as hypovitaminosis B12 and hypothyroidism, are frequent at primary care. We also identified that the

diagnosis of dementia was very frequent among subjects with spontaneous memory complaints. Taken together, these results reinforce the central role of primary care assistance in the diagnosis and medical care of individuals with memory complaints. Finally, we suggest that physicians in primary health care be trained to diagnose MCI and dementia and to perform longitudinal monitoring of individuals with SCD as well.

Authors' contributions. MLP: conceptualization, methodology, data curation, formal analysis, visualization, writing – original draft. THFV, AARO, SBC, SOF: investigation, data curation. AFBCG: resources, data curation. MTB, LFJRM, PC: writing – review & amp; editing. LCS: supervision, conceptualization, methodology, data curation, formal analysis, writing – review & amp; editing.

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Dement Neuropsychol 2021 March;15(1):98-104

Original Article

https://doi.org/10.1590/1980-57642021dn15-010010

Evaluation of sensitivity and specificity of the INECO Frontal Screening and the Frontal Assessment Battery in mild cognitive impairment

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ABSTRACT. The Frontal Assessment Battery (FAB) and the INECO Frontal Screening (IFS) are two instruments frequently used to explore cognitive deficits in different diseases. However, studies reporting their use in patients with mild cognitive impairment (MCI) are limited. **Objective:** To compare the sensitivity and specificity of FAB and IFS in mild cognitive impairment (multiple-domain amnestic MCI subtype — md-aMCI). **Methods:** IFS and FAB were administered to 30 md-aMCI patients and 59 healthy participants. Sensitivity and specificity were investigated using the Receiver Operating Characteristic (ROC) analysis. **Results:** The area under the ROC curve (AUC) of IFS for MCI patients was .82 (sensitivity=0.96; specificity=0.76), whereas the AUC of FAB was 0.74 (sensitivity=0.73; specificity=0.70). **Conclusions:** In comparison to FAB, IFS showed higher sensitivity and specificity for the detection of executive dysfunctions in md-aMCI subtype. The use of IFS in everyday clinical practice would allow detecting the frontal dysfunctions in MCI patients with greater precision, enabling the early intervention and impeding the transition to more severe cognitive alterations.

Keywords: mild cognitive impairment, cognitive assessment screening instrument, sensitivity, specificity.

AVALIAÇÃO DA SENSIBILIDADE E ESPECIFICIDADE DO TESTE DE RASTREIO FRONTAL DO INECO E DA BATERIA DE AVALIAÇÃO FRONTAL NO COMPROMETIMENTO COGNITIVO LEVE

RESUMO. A Bateria de Avaliação Frontal (FAB) e o teste de rastreio frontal do INECO (IFS) são dois instrumentos frequentemente utilizados para explorar déficits cognitivos em diferentes doenças. No entanto os estudos que relatam seu uso em pacientes com comprometimento cognitivo leve (MCI) são limitados. **Objetivo:** Comparar a sensibilidade e especificidade da FAB e IFS em comprometimento cognitivo leve (subtipo amnéstico de múltiplos domínios [md-aMCI]). **Métodos:** O IFS e FAB foram administrados a 30 pacientes md-aMCI e 59 participantes saudáveis. A sensibilidade e a especificidade foram exploradas usando a análise ROC. **Resultados:** A área sob a curva ROC (AUC) do IFS para pacientes com MCI foi de 0,82 (sensibilidade=0,96; especificidade=0,76), enquanto a AUC de FAB foi de 0,74 (sensibilidade=0,73; especificidade=0,70). **Conclusões:** Em comparação com o FAB, o IFS apresentou maior sensibilidade e especificidade para detecção de disfunções executivas no subtipo md-aMCI. O uso do INECO Frontal Screening (IFS) na prática clínica cotidiana, permitiria detectar com maior precisão as disfunções frontais em pacientes com deficiência cognitiva leve, possibilitando a intervenção precoce, impedindo a transição para alterações cognitivas mais graves.

Palavras-chave: disfunção cognitiva, testes de estado mental e demência, sensibilidade, especificidade.

INTRODUCTION

Mild cognitive impairment (MCI) is considered a transition phase between normal cognition and Alzheimer's disease (AD).[1] The prevalence of MCI in people aged over 65 years ranges from 7 to 47.9%, with a global prevalence of 18.9% per one thousand people.[2] MCI patients can be classified in two main categories: amnestic MCI (aMCI), if patients show a poor performance on

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Funding: none.

Disclosure: The authors report no conflicts of interest.

Received on July 27, 2020. Accepted in final form on October 26, 2020.

the episodic memory test, but functioning in other cognitive domains is preserved; and non-amnestic MCI (naMCI), if patients show a poor performance on cognitive evaluation covering domains other than memory such as language, visuospatial abilities, or executive functions.[2] Additionally, aMCI patients could be classified in one of two possible clinical subtypes: (i) single-domain aMCI (sd-aMCI), when memory is the only impaired domain; and (ii) multiple-domain aMCI (md-aMCI), when besides the memory deficit, at least another cognitive domain is impaired (e.g., executive function, language, or visuospatial abilities).[3]

The annual conversion of MCI to AD is estimated between 10 and 15%.[4] Approximately 50% of people with MCI will be diagnosed with AD in the following 4 years.[1]. However, the specific conversion prognoses for each subtype may differ. In this sense, md-aMCI patients had more severe deficit in working memory and problem solving than sd-aMCI patients, leading to the assumption that this subtype, not pure amnestic MCIs, are at highest risk of dementia.[5,6] Another study sought to more systematically and comprehensively investigate predictors of rate of cognitive decline in a longitudinal sample of individuals with MCI, including age, genetic vulnerability, baseline cognitive performance, and baseline neuropsychiatric severity.[7] The results showed that participants with composite scores for lower executive functions and greater severity of memory impairment at baseline predicted faster decline on dementia severity measures.

Recently, a meta-analytic study was conducted to explore inhibitory control (IC) in patients with aMCI, using a battery of well-validated inhibition tasks.[8] According to the findings, patients with aMCI showed a generalized IC deficit, suggesting that inhibition paradigms should be routinely included in neuropsychological evaluations to obtain a more detailed overview of executive functioning in MCI patients.

Hence, early diagnosis of pathological cognitive decline becomes increasingly important in providing patients with the necessary interventions.[9] Global neuropsychological batteries, such as the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE), and the Mattis Dementia Rating Scale second edition (DRS-2), are frequently used for neuropsychological evaluation. These screening batteries are helpful for obtaining a global cognitive performance approximation; however, they do not allow researchers to delve into executive functioning.

In this sense, the Frontal Assessment Battery (FAB) and the INECO Frontal Screening (IFS) are two frequently used instruments to explore frontal dysfunctions in different pathologies.[10] FAB was designed for brief investigation of executive functioning and consists of six subtests that evaluate mental flexibility, conceptualization, inhibitory control, motor programming, resistance to interference, and environmental autonomy.[11] This instrument is fundamentally used for two purposes:[12]

1) early identification of neurodegenerative diseases, and
2) detection of executive dysfunctions in different diseases that affect the frontostriatal brain circuits.

On the other hand, IFS is a brief neuropsychological test designed to explore executive functions across neurodegenerative pathologies such as AD,[13] behavioral variant frontotemporal dementia,[14] Multiple Sclerosis (relapsing-remitting phase),[15] MCI,[16] and MCI in Parkinson's disease.[17] IFS is composed of eight subtests, organized into three main executive domains:[18]

1) inhibition and change,
2) working memory, and
3) capacity for abstraction.

Some studies have compared the clinical utility of FAB and IFS. For example, Gleichgerrcht et al.[19] evaluated the usefulness of FAB and IFS in a group of 25 patients diagnosed with behavioral variant frontotemporal dementia (bvFTD) and 25 patients with AD. Compared with FAB, IFS showed a better capacity to discriminate between both dementia subtypes, a greater sensitivity and specificity for the detection of executive dysfunctions, and a high correlation with frequently used executive tests such as the Trail Making Test (part B) and the Wisconsin Card Sorting Test.

This result was confirmed by another study carried out on Peruvian patients.[20] In this investigation, the diagnostic capacity of FAB and IFS was compared in a sample of 117 participants (35 AD patients, 34 patients with bvFTD, and 48 healthy controls [HC]). IFS showed a greater sensitivity to discriminate between AD and bvFTD, compared with FAB. The objective of the present study is to compare the sensitivity and specificity of FAB and IFS in patients with multiple-domain aMCI subtype (md-aMCI). Considering previous studies that have used both instruments, the authors' hypothesis is oriented towards a better sensitivity of IFS compared with FAB.

METHODS

Participants

A total of 89 participants were evaluated: 59 cognitively healthy controls and 30 patients with MCI

(multiple-domain aMCI subtype). The groups were selected according to the following criteria:

Healthy control group

The following criteria were used to select the control group: scoring more than 85 points on the Addenbrooke's Cognitive Examination Revised (ACE-R),[21] no subjective complaints of memory, and preserved functioning in the activities of daily living. Psychiatric history was reported by the participants during the initial interview (conducted by an experienced psychiatrist) and an experienced neurologist performed the neurological examination.

Mild cognitive impairment Group (multiple-domain aMCI subtype)

MCI patients were classified using the criteria proposed by Petersen:[2] objective impairment in formal neuropsychological measures (total score in ACE-R of at least 1.5 standard deviation [SD]below the demographically corrected mean)[21] and preservation of activities of daily living (Barthel index>95).[22] Patients with potential causes of cognitive deficits different than neurodegenerative or cerebrovascular disease (e.g., Schizophrenia, alcoholism, epilepsy, depression, head injury) were excluded. According to the standardized neuropsychological assessment, the sample was classified as multiple-domain aMCI subtype.

Patients with MCI who showed clinical signs of depression (Geriatric Depression Scale<5)[23] or anxiety (Zung Self-Rating Depression Scale<51) were excluded from the study.[24] The presence of severe sensory deficits (vision and hearing) was also considered an exclusion criterion.

Instruments

Frontal Assessment Battery

The FAB[11] is a test battery easy to administer and sensitive to frontal dysfunction. FAB consists of six subtests evaluating similarities (conceptualization), motor programming, inhibitory control, verbal fluency (mental flexibility), resistance to interference, and environmental autonomy. Each subtest is scored on a maximum of three points, with a total score of 18. High scores indicate preservation of the executive functions.

INECO Frontal Screening

INECO Frontal Screening (IFS)[14] is a brief neuropsychological test battery to explore executive functioning in neurodegenerative diseases. The subtests included in IFS are Luria's Fist-Edge-Palm task (three points), Conflicting instructions (sensitivity to interference) (three points), Inhibitory control (three points), Months backwards (verbal working memory) (two points), Digit Span Task (six points), Corsi Block Tapping Test (four points), Proverb interpretation (abstraction capacity) (three points), and Verbal inhibitory control (modified Hayling Test) (six points). IFS has a maximum possible score of 30 points. High scores indicate preservation of the executive functions.[25]

Procedure and Analysis of Data

All participants were informed of the objectives of the study and signed the informed consent form. All cognitive evaluations were done blindly (HC vs MCI) and independently by one neuropsychologist who applied the IFS and FAB tests to all the participants. IFS and FAB were applied in different sessions to reduce fatigue and potential learning effects.

Data were obtained following the regulations of the ethics committee of the Department of Psychology of Universidad Central "Marta Abreu" de Las Villas and in accordance with the Declaration of Helsinki. Data were processed using the *Statistical Package for the Social Sciences* (SPSS) for Windows, version 21. Descriptive statistics were used to explore participants' characteristics. An independent-sample Student's t-test was conducted to compare the executive functioning between groups. In all analyses, the homogeneity of variances was considered (by using the Levene's test for homogeneity of variances). The Cohen's *d* effect size was calculated to estimate effect sizes in all comparisons. Values above 0.2, 0.5, and 0.8 were considered as small, medium, and large effect size, respectively.[26] Linear regression was used to evaluate age and education effects over total scores of FAB and IFS. To investigate the sensitivity and specificity of FAB and IFS, the Receiver Operating Characteristic (ROC) curve analysis was performed.

RESULTS

Demographics of mild cognitive impairment patients and Control Group

The present study was conducted with 59 healthy participants and 30 patients with MCI diagnosis (multiple-domain aMCI subtype). The results of the comparison of demographics are summarized in Table 1. There are no significant differences in age, education years, and sex between groups. Significant differences were found

Table 1. Demographic and neuropsychological characteristics of Healthy Controls and Mild Cognitive Impairment patients.

	HC (n=59)		MCI (n=30)		p-value
	M	SD	M	SD	
Age (years)	76.25	8.08	78.63	8.26	0.84
Education level (years)	12.38	4.15	11.63	3.07	0.63
Sex (M_a:F)	29–30		15-15		0.94
Handedness (R:L)	59–0		29_1		0.15
ACE-R (/100)	89.74	4.36	68.13	11.01	<0.001
Attention and Orientation (/18)	16.67	1.67	13.96	2.31	<0.001
Memory (/26)	23.11	2.16	17.53	4.53	<0.001
Verbal Fluency (/14)	10.06	1.89	5.90	1.82	<0.001
Language (/26)	25.20	1.18	20.86	3.47	<0.001
Visuospatial (/16)	14.61	1.48	10.03	2.89	<0.001

HC: healthy controls; MCI: mild cognitive impairment patients; M: mean; SD: standard deviation; M_a: male; F: female; R: right; L: left; ACE-R: Addenbrooke's Cognitive Examination Revised.

Table 2. Performance of healthy controls and mild cognitive impairment patients in the Frontal Assessment Battery.

FAB subtests	HC (n=59) M(SD)	MCI (n=30) M(SD)	t	p-value	d
Conceptualization	2.29(0.76)	1.83(0.74)	2.66	0.009	0.61
Mental flexibility	2.51(0.67)	1.97(0.71)	3.49	0.001	0.79
Motor programming*	2.42(0.77)	2.23(1.04)	0.97	0.33	0.22
Resistance to interference*	2.66(0.63)	2.26(0.86)	2.44	0.017	0.56
Inhibitory control*	2.10(0.90)	1.36(0.96)	3.54	0.001	0.81
Environmental autonomy	2.93(0.41)	2.87(0.43)	0.69	0.48	0.14
Total	14.85(2.33)	12.47(2.78)	4.27	<0.001	0.96

*Subtests shared by both IFS and FAB tests. IFS: INECO Frontal Screening; FAB: Frontal Assessment Battery; HC: healthy controls; MCI: mild cognitive impairment patients; SD: standard deviation; M: mean, d: effect size.

between groups regarding the Addenbrooke's Cognitive Examination Revised (ACE-R).

Overall, age had no influence on FAB (r=-0.086, p=0.27) and IFS (r=-0.082, p=0.18), whereas years of education had a positive linear influence on FAB (r=0.32, p<0.001) and IFS (r=0.29, p=0.004).

Subtests shared by both INECO Frontal Screening and Frontal Assessment Battery

FAB and IFS shared three subtests:[19] Luria's Fist-Edge-Palm task, Conflicting instructions, and Inhibitory control (Go/No-go task) (Table 2). Two subtests showed differences between groups. Resistance to interference (Conflicting instructions) showed differences between groups. The MCI group showed lower scores than the HC group. The means of the scores in the Inhibitory control (Go/No-go task) also showed significant differences between groups. Patients with MCI performed worse than healthy controls. No differences between HC group and MCI patients were found in Luria's Fist-Edge-Palm task.

Frontal Assessment Battery

The results of HC participants and MCI patients concerning the FAB test is summarized in Table 2. In addition to the test shared by both instruments, the subtests Conceptualization, Mental flexibility, and Total score differed between groups. In all cases, MCI patients showed lower scores than HC participants. In Conceptualization and Mental Flexibility subtests, the effect size of the differences was medium (d>0.5). For Total Score in FAB, differences between means was large (d>0.8). No differences between MCI patients and the HC group were found in the Environmental Autonomy domain.

INECO Frontal Screening

The executive functioning of MCI patients and HC participants according to IFS is summarized in Table 3. In Backward months (Verbal working memory), Corsi Block Tapping Test (Spatial working memory), Modified Hayling Test (Verbal inhibitory control), and IFS total score showed significant differences between groups. In all cases, MCI patients showed poorer performance than HC participants. In verbal and spatial working memory domains, the effect size of the differences in the means was medium (d>0.5). For Verbal inhibitory control (Modified Hayling Test) and IFS total score, differences between means was large (d>0.8). No differences between MCI patients and the HC group group were found in the Working memory (Digit Span Task), and Abstraction capacity (Proverb interpretation) domains.

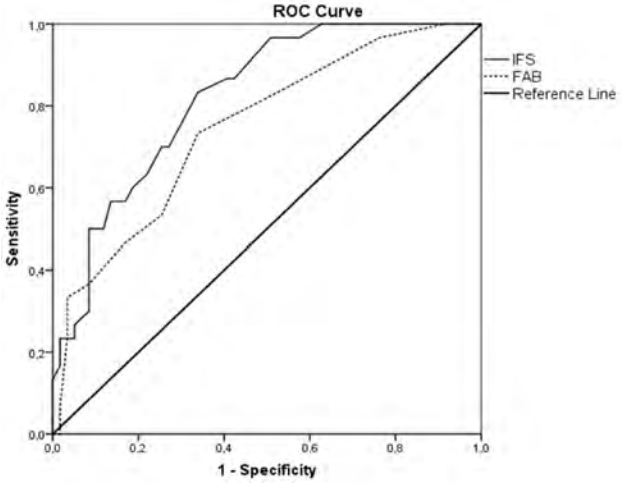
Sensitivity and specificity of Frontal Assessment Battery and INECO Frontal Screening

Figure 1 shows ROC curves of IFS (total score) and FAB (total score) for detecting MCI (multiple-domain aMCI subtype). The results showed that the area under the curve (AUC) of IFS for MCI

Table 3. Performance of healthy controls and mild cognitive impairment patients in the INECO Frontal Screening.

IFS subtests	HC (n=59) M(SD)	MCI (n=30) M(SD)	t	p-value	d
Motor series*	2.42(0.77)	2.23(1.04)	0.97	0.33	0.22
Conflicting instructions*	2.66(0.63)	2.26(0.86)	2.44	0.017	0.56
Go/No-go task*	2.10(0.90)	1.36(0.96)	3.54	0.001	0.81
Digit Span Task	2.67(1.04)	2.46(0.81)	0.96	0.33	0.21
Verbal working memory	1.69(0.50)	1.26(0.69)	3.34	0.001	0.76
Spatial working memory	2.20(0.97)	1.63(0.92)	2.64	0.01	0.60
Proverb interpretation	2.50(0.70)	2.16(0.83)	1.98	0.50	0.46
Modified Hayling Test	4.84(1.62)	2.36(1.86)	6.46	<0.001	1.42
Total	21.05(4.11)	15.6(4.28)	5.83	<0.001	1.32

*Subtests shared by both IFS and FAB tests. IFS, INECO Frontal Screening; FAB: Frontal Assessment Battery; HC: healthy controls; MCI: mild cognitive impairment patients; SD: standard deviation; M: mean; d: effect size.



ROC: Receiver Operating Characteristic; IFS: INECO Frontal Screening; FAB: Frontal Assessment Battery.

Figure 1. Receiver Operating Characteristic curves show INECO Frontal Screening (total score) and Frontal Assessment Battery (total score) for distinguishing between healthy controls and mild cognitive impairment patients.

patients was .82 (cutoff=20/21; sensitivity=0.90; specificity=0.76), whereas the AUC for FAB was 0.74 (cutoff=13/14; sensitivity=0.96; specificity=0.70) (Table 4).

Table 4. Sensitivity, specificity, area under the curve, and cutoff of Frontal Assessment Battery and INECO Frontal Screening for mild cognitive impairment patients vs. healthy controls.

	AUC	95%CI	Cutoff	Sensitivity	Specificity
MCI vs. HC					
IFS	0.82	0.73–0.90	20/21	0.96	0.76
FAB	0.74	0.64–0.85	13/14	0.90	0.70

IFS: INECO Frontal Screening; FAB: Frontal Assessment Battery; MCI: mild cognitive impairment patients; HC: healthy controls; AUC: area under the curve; 95%CI: confidence interval.

DISCUSSION

The objective of the present study was to compare the sensitivity and specificity of FAB and IFS in patients with amnestic MCI multiple-domain subtype (md-aMCI). First, it was found that years of education showed a positive effect on FAB and IFS, whereas the age of participants did not show a significant effect.

The absence of the effect of age on the IFS score has been previously reported,[18,27] although other authors have found opposite results.[16] Thus, it is worth developing more studies aimed at verifying the effect of age on IFS scores. The present results did not show an effect of age on the total FAB score, which does not correspond to the results reported in other studies that suggest an inverse effect of age on FAB performance.[28-30]

On the other hand, a positive effect of years of education on the global and dimensional scores of FAB and IFS was verified. This result is related to some studies reporting that a higher education level has a positive influence on the performance of various tests that evaluate executive functioning.[31-33] In the particular case of IFS, previous research showed significant effects of education and no significant effects for age on the scores of this instrument.[27] In another study carried out with patients with dementia, compared with healthy controls, age did not show associations with IFS scores, but with years of education.[18]

The present findings also illustrate that IFS shows better sensitivity than the FAB for distinguishing between healthy controls and MCI patients. In this study, IFS showed higher precision compared with FAB to discriminate between MCI patients and healthy participants. In a recent study, the usefulness of IFS to discriminate between healthy controls and MCI patients was also verified.[16] The cutoff point reported by the authors is very similar to that found in our study (cutoff =20; sensitivity=0.92; specificity=0.81).

In the specific case of Cuba, we did not find any previous study that explored the clinical utility of FAB; conversely, to date, only one study in the country has investigated the sensitivity and specificity of IFS in detecting cognitive deficits in MCI patients (md-aMCI).[17] Contrary to results of the present study, the previous study showed that IFS had a low capacity for discriminating between md-aMCI patients and healthy controls. This discrepancy accounts for differences in the cognitive profiles of the MCI patients included in both studies. In the study conducted by Broche-Pérez et al.[17] the md-aMCI patients did not differ from healthy controls in the following subtests: Conflicting instructions (sensitivity to interference), Months backward, and Digit Span Task (working memory). In this sense, the md-aMCI patients of the present study show a greater executive deficit, which increases the sensitivity of IFS.

It is worth noting that although the existence of executive dysfunctions in MCI patients has been previously published,[34] the evidence for the utility of brief screening neuropsychological instruments to evaluate them is limited.[16]

In spite of this limitation, the results of this study are related to other research carried out on different neurodegenerative diseases, according to which a greater discriminative capacity of IFS is evidenced compared with FAB. For example, when compared with FAB, IFS has shown greater discriminatory capacity in frontotemporal dementia,[19] AD, and behavioral variant frontotemporal dementia.[20] Probably, the superior psychometric properties of IFS in comparison with FAB in the evaluation of MCI patients (md-aMCI subtype) results from the addition of subtest that had demonstrated a high sensitivity to detect subtle executive dysfunctions.[19]

The study had some limitations. First, the MCI group is rather small. In future studies, large samples are needed to confirm statistically significant differences between diagnostic instruments. Furthermore, future studies must delve into the effect of education on performance in FAB and IFS. It is crucial to obtain normative data on the Cuban population according to different years of education in order to prevent biased interpretations and to avoid false-positive or false-negative cases. Additionally, future research should also explore the relationship between results of cognitive screening tests and the structural and functional aspects of brain activity.

In conclusion, the present findings showed that, in comparison with FAB, the IFS presented higher sensitivity for the detection of MCI patients (md-aMCI subtype) with executive dysfunctions. We recommend the inclusion of such test in screening protocols for dementia for the early detection of executive dysfunctions in MCI patients, in all levels of the Cuban Public Health System. The use of IFS in everyday clinical practice would allow detecting frontal dysfunctions in MCI patients with greater precision, facilitating early intervention and impeding the transition to more severe cognitive dysfunctions.

ACKNOWLEDGMENTS

The authors thank Angela María Manso Gramatges for the suggestions and linguistic corrections made to the manuscript.

Authors' contributions. ZFF: conceptualization, data curation, formal analysis, methodology. EJP: conceptualization, investigation, methodology. YBP: conceptualization, data curation, formal analysis, investigation, methodology, writing — original draft. SMO: data curation, investigation, methodology, validation. LRCR: investigation, methodology, supervision.

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Original Article

https://doi.org/10.1590/1980-57642021dn15-010011

Cross-sectional associations between cognition and mobility in Parkinson's disease

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ABSTRACT. Cross-sectional studies show an association of decline in mental flexibility and inhibitory control with reduced gait speed and falls, as well as divided attention deficit and difficulty in initiating gait. **Objective:** To investigate the relationships between cognitive function and gait performance in patients with Parkinson's disease (PD) who participated in a hospital neurorehabilitation program. **Methods:** A total of 107 patients (79 males, 28 females; mean age 61.00±8.2 years; mean schooling 11.7±4.1 years) with idiopathic PD (mean disease duration 5.5±4.1 years) were recruited for this study. Among them, 78.50% were in stages I and II of the Hoehn & Yahr Scale. Cognitive functions were evaluated through the Digit Span test, Trail Making Test, and Addenbrooke's Cognitive Examination III. Motor function was assessed with the 10-Meter Walk Test, the short version of the Balance Evaluation Systems Test (Mini-BESTest), and the Timed Up and Go Test. **Results:** Balance skills were significantly correlated with global cognition and specific domains, including divided attention, verbal fluency, and visuospatial function. Functional mobility showed a significant association with all cognitive tests, except for the number of errors on TMT-A. Gait speed presented a significant correlation with global cognition scores, memory, and attention, including divided attention. **Conclusion:** These findings might help early identification of cognitive deficits or motor dysfunctions in PD patients who may benefit from rehabilitation strategies, as well as facilitate fall risk assessments and strategies to prevent falls. Future prospective studies are needed to investigate the effects of cognitive training on motor performance, since the difficulty in motor rehabilitation may be more related to cognitive loss than to motor damage.

Keywords: Parkinson's disease, gait, cognitive impairment, balance, executive functions.

ASSOCIAÇÕES TRANSVERSAIS ENTRE COGNIÇÃO E MOBILIDADE NA DOENÇA DE PARKINSON

RESUMO. Estudos transversais mostram associação entre declínio da flexibilidade mental e controle inibitório com redução da velocidade de marcha e quedas, assim como déficit de atenção dividida e dificuldade para iniciar a marcha. **Objetivo:** Investigar as relações entre a função cognitiva e o desempenho da marcha em pacientes com Doença de Parkinson (DP) que participaram de um programa de reabilitação hospitalar. **Métodos:** Um total de 107 pacientes (79 homens, 28 mulheres; idade média de 61,00±8,2 anos, média de escolaridade 11,7±4,1) apresentando DP idiopática (duração média da doença: 5,5±4,1 anos) foram recrutados para o estudo. Desses, 78,50% estavam nos estágios I e II da Hoehn e Yahr. As funções cognitivas foram avaliadas por meio do teste de Dígitos Spam, Teste de Trilhas e Exame Cognitivo de Addenbrooke (terceira versão). A função motora foi examinada por meio do teste de caminhada de 10 metros, Mini BESTest e teste *Timed Up and Go*. **Resultados:** As análises de correlação mostraram que as habilidades de equilíbrio estavam significativamente correlacionadas com a cognição global e com domínios específicos, incluindo atenção dividida, fluência verbal e função visuoespacial. Além disso, a mobilidade funcional apresentou correlação significativa com todos os testes cognitivos, exceto TMT-A (erro). A velocidade da marcha mostrou correlação significativa com escores globais de cognição, memória e atenção, incluindo atenção dividida. **Conclusão:** Esses achados podem ajudar na identificação precoce de déficits cognitivos ou disfunções motoras em pacientes com DP que podem se beneficiar de estratégias de reabilitação, facilitar avaliações de risco de queda e estratégias de prevenção de queda. Estudos prospectivos futuros são necessários para investigar os efeitos do treino cognitivo no desempenho motor, uma vez que a dificuldade na reabilitação motora pode estar mais relacionada à perda cognitiva do que aos prejuízos motores.

Palavras-chave: doença de Parkinson, marcha, comprometimento cognitivo, equilíbrio, funções executivas.

This study was conducted at the Rede SARAH de Hospitais de Reabilitação – Reabilitação Neurológica, Unidade de Salvador, Salvador, BA, Brazil.

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Disclosure: The authors report no conflicts of interest.

Funding: none.

Received on May 21, 2020. Accepted in final form on October 26, 2020.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, which has cognitive impairment as a prevalent and debilitating non-motor symptom. Non-motor symptoms, such as disturbances of the autonomic nervous system, sleep disorders, depression, and cognitive and neuropsychiatric disorders, can precede motor symptoms or appear throughout the disease, impacting the functional independence of the patient.[1,2]

Cross-sectional and longitudinal studies[3-5] have reported that gait changes may be associated with cognitive impairment, particularly executive functions. Additional investigations have also revealed that slow gait speed predicted cognitive impairment and dementia.[6] However, some studies have suggested that cognitive impairment preceded gait changes.[7,8]

Studies that correlated the performance on the Montreal Cognitive Assessment (MoCA) with motor tests have found a significant association with dexterity and mobility evaluated through the Purdue Pegboard Test and the Timed Up and Go Test (TUG). Furthermore, although no correlation was found between the tremor dominant subtype and cognitive impairment, the postural instability/gait difficulty (PIGD) subtype showed an association with lower performance on cognitive tests.[9-12]

Associations between gait and cognition in PD indicate an influence of attention and executive functions on the gait pace and variability.[13] Another study[14] argues whether the impact of cognition on gait performance can be so specific that data collected by wearable devices can contribute to differentiating dementia subtypes.

Consistent findings have shown the limited ability of this population to cope with complex tasks that require cognitive demands, namely, recognizing and avoiding obstacles, dividing attention while walking.[15] The ability to plan and monitor gait adequately while dealing with cognitive overload, as well as when performing dual-tasking (DT), is impaired in this population.[16-18] Carrying out two tasks simultaneously is difficult for these individuals.[19] Executive function deficit, mainly inhibitory control and mental flexibility, has been associated with gait impairment and freezing of gait (FOG).[11,20,21] Another study revealed that gait and balance are related to specific cognitive skills, suggesting similar cerebral cortical circuitry for mobility and cognitive function.[13]

Cognitive control is essential for gait; cognitive issues are risk factors for poor gait performance, especially falls, consequently limiting the community participation in daily activities. Balance skills were significantly correlated with the ability to divide attention and the visuospatial ability in a recent study conducted by these authors.[22] In addition, several investigations have reported that gait performance, risk of falling, freezing, and PD stage were strongly and significantly associated with DT.[23,24]

Thus, the present study aimed to examine the association between cognitive ability, including global and specific cognitive functions (i.e., executive function, visuospatial ability, attention, language, and memory), and gait performance in PD patients. In this study, the characteristics of the sample assessed, that is, a homogeneous group as to cognitive profile (patients with mild cognitive impairment), as well as the sample size, contributed to the accuracy of the analyses.

METHODS

Participants

This is a cross-sectional study of 107 patients diagnosed with PD, according to the UK Brain Bank criteria.[25] The subjects were part of an outpatient neurorehabilitation program at the SARAH Network of Rehabilitation Hospitals.

The inclusion criteria were: idiopathic PD patients aged over 50 years, more than 4 years of schooling, no psychiatric disorders before the PD diagnosis, as well as no history of substance use and abuse, absence of behavioral, motor, and/or sensory changes that may interfere with the performance of the cognitive tests (patients evaluated in the ON state, with no motor fluctuation during the assessment). Patients with moderate or severe depressive symptoms (Beck Depression Inventory — BDI≥20),[26] Hoehn and Yahr Scale (H&Y) stage IV, and dementia, according to the Movement Disorder Society guidelines,[27] were excluded.

All participants signed the informed consent form. The local ethics committee approved this study.

Cognitive evaluation

The patients were evaluated on their global and specific cognitive functions by a neuropsychologist.

- Digit Span Test (forward and backward) (Wechsler Memory Scale-revised — WMS-R):[28] evaluates the immediate memory capacity and the ability to manipulate information.
- Trail Making Test (TMT) — A and B:[29] assesses visuomotor speed, selective attention, and mental flexibility.
- Addenbrooke's Cognitive Examination-third version (ACE-III):[30] focuses on the global score and subscores (attention/orientation, memory, verbal fluency, visuospatial ability, and language). The maximum score is 100.

Motor evaluation

- 10-Meter Walk Test (10MWT): measures walking speed in meters per second while the subject walks 10 meters. The participants were asked to walk at a comfortable pace.[31]
- Short version of the Balance Evaluation System Test (Mini-BESTest): assesses balance through 14 tasks (anticipatory postural adjustments, reactive postural control, sensory orientation, gait, and dynamic balance). Each task is graded according to the performance on a 3-level ordinal scale (0–2), and the maximum score is 28 points in case of normal performance.[32]
- Timed Up and Go Test (TUG test): evaluates mobility and balance, calculating the time that a person takes to rise from an armchair, walk three meters, turn around, walk back, and sit down in the chair. In the cognitive TUG, the individual performs the same motor task plus a second motor task or cognitive task concomitantly. In this study, subjects were asked to complete the TUG associated with mathematical tasks requested by the examiner.[33] This test was scored following the same Mini-BESTest scale (0–2), according to the impact of the cognitive task on motor performance.

Data analysis

Statistical Package for the Social Sciences (SPSS) software, version 22.0, was used for data analysis. Descriptive analysis of the study participants was expressed as mean and standard deviation (SD). Pearson's correlation was applied to assess the association between gait parameters (speed, balance, and functional mobility) and cognitive scores (total and per domains). Some variables (such as age and disease duration and severity) could have skewed these results. A multivariate linear regression analysis was performed to minimize these effects. The probability level was set at 0.05 to determine significance.

RESULTS

Demographic and clinical characteristics

The study included 107 participants (79 male and 28 female). Among them, 84 had mild impairment (stages I–II of H&Y), that is, no patients had less severe disease. PD patients had an average disease duration of 5.5±4.1 years. Table 1 presents their demographic and clinical characteristics.

Cognitive and motor performance

Table 2 shows the descriptive data from cognitive and motor performance.

Associations between gait and cognition

Significant associations were found between TUG scores and ACE-III total and domain scores, in addition to other neuropsychological tests, except for TMT-A errors (r=-0.0686, p=0.4827). The Mini-BESTest also demonstrated a significant correlation with cognitive

Table 1. Demographic and clinical characteristics of participants.

n=107	Mean±SD/n (%)
Age (years)	61.00±8.2
Gender (male/female)	79 (73.83)/28 (21.4)
Schooling (years)	11.7±4.1
Disease duration (years)	5.5±4.1
Hoehn & Yahr Scale	
I–II	84 (78.50)
III–IV	23 (21.49)
BDI	6.3±4.8

SD: standard deviation; BDI: Beck Depression Inventory.

Table 2. Descriptive statistics of cognitive and motor tests.

n=107	Mean±SD/n (%)	Minimum	Maximum
ACE-III/Total score	85.07±11.30	54	99
Attention/Orientation	16.36±1.78	11	18
Memory	19.64±4.73	4	26
Fluency	9.97±2.70	2	14
Language	25.00±2.17	11	26
Visuospatial	14.09±2.60	3	16
Digit Span (forward)	5.52±4.47	3	7
Digit Span (backward)	3.62±1.02	2	5
TMT-A (s)	68.93±29.79	0	189
TMT-A (errors)	1.57±1.19	0	4
TMT-B (s)	197.40±108.68	1	654
TMT-B (errors)	1.19±1.57	0	6
TMT (A–B)	-128.5±95.0	-1	-573
10MWT	294±23.98	11	200
Mini-BESTest	22.39±4.23	6	28
TUG 0 or 1	74 (69.15)	-	-
TUG 2	33 (30.84)	-	-

SD: standard deviation; ACE-III: Addenbrooke's Cognitive Examination; TMT: Trail Making Test; 10MWT: 10-Meter Walk Test; Mini-BESTest: Mini-Balance Evaluation Systems Test; TUG: Timed Up and Go Test.

measures. Correlations were identified between 10MWT and ACE-III total and memory scores, as well completion time for TMT-A and B (Table 3).

Table 4 reveals that the ACE-III total score was associated with cognitive TUG (β=0.01918, p=0.009), disease severity (evaluated by H&Y), Mini-BESTest (β=-2.74613, p=0.000), and TUG (β=-0.25986, p=0.004).

Secondary analyses were carried out, with the formation of subgroups of aspects such as age and disease duration and severity, since these factors can interfere with the association between gait and cognition variables. The results were the same when correlated with the functional mobility test (TUG).

Table 5 indicates a significant correlation between the TUG test and several cognitive tasks, regardless of the sample stratification by the median. Regarding other motor tests (Mini-BESTest and 10MWT), the association was present in younger individuals and those whose disease diagnosis was more recent (shorter disease duration).

Table 3. Correlations between cognitive and motor variables.

Variables	Mini-BESTest	TUG	10MWT (cm/s)
Total score (ACE-III)	r=0.2231 p=0.0209*	0.4876 0.0000***	0.2152 0.0260*
Attention/ Orientation	r=0.1126 p=0.2481	0.4117 0.0000***	0.0405 0.6791
Memory	r=0.1658 p=0.0878	0.4094 0.0000***	0.2857 0.0029**
Fluency	r=0.1910 p=0.0488*	0.3906 0.0000**	0.1673 0.0849
Language	r=0.0899 p=0.3573	0.2645 0.0059**	0.1791 0.0649
Visuospatial	r=0.2642 p=0.0060**	0.3874 0.0000***	0.1835 0.0585
TMT-A (s)	r=-0.1981 p=0.0408*	-0.4420 0.0000***	-0.2044 0.0347*
TMT-A (errors)	r=0.0132 p=0.8928	-0.0686 0.4827	-0.1297 0.1832
TMT-B (s)	r=-0.3024 p=0.0015**	-0.4701 0.0000***	-0.2291 0.0176*
TMT-B (errors)	r=-0.2315 p=0.0170*	-0.3366 0.0004***	0.1117 0.2542
TMT (B-A)	r=0.2633 p=0.0061**	r=0.3689 p=0.0001***	r=0.1815 p=0.0614
Digit Span (forward)	r=0.1912 p=0.0486*	0.3811 0.0001***	0.0697 0.4758
Digit Span (backward)	r=0.1354 p=0.1645	0.3757 0.0001***	0.1660 0.0874
BDI	r=-0.1007 p=0.3021	-0.1133 0.2454	-0.0476 0.6260
H&Y	r=-0.4615 p=0.0000***	-0.3635 0.0001***	-0.1766 0.0689

ACE-III: Addenbrooke's Cognitive Examination; TMT: Trail Making Test; H&Y: Hoehn & Yahr Scale; BDI: Beck Depression Inventory; Mini-BESTest: Mini-Balance Evaluation Systems Test; TUG: Timed Up and Go Test; 10MWT: 10-Meter Walk Test; r: Pearson's correlation coefficient. *significant at p<0.05; **significant at p<0.01; ***significant at p<0.001.

DISCUSSION

The present study aimed to determine whether cognitive functions were associated with gait performance, mobility, and balance in idiopathic PD. The findings revealed that motor parameters were significantly related to cognitive skills, especially aspects connected to executive functions and global cognition, evidencing that balance ability and functional mobility were significantly correlated with the ability to divide attention between tasks performed at the same time, as found in similar research.[17,18] This interaction has been identified in cognitive tests that assess mental flexibility (TMT-B and TMT B-A), attention (Digit Span forward), working memory (Digit Span backward), and functional mobility (cognitive TUG). The correlation between the simultaneous performance of a functional mobility activity and a mental task increased with cognitive dysfunction.

Cognitive decline, especially in executive functions, has been associated with gait disorders and risk of falling.[16,20] The association between executive functions and bradykinesia has been reported in individuals with PD,[3,18] as well as the correlation between the ability to divide attention between two tasks and balance.[30]

A study that researched the relationship between cognition, emotion, and motor function found that those who presented higher freezing rates had worse performance on the Wisconsin Card Sorting Test, TMT-A, and Rey Auditory Verbal Learning Test, indicating an association with tests of executive functions and attention/processing speed.[20]

A previous investigation showed a correlation between a functional mobility motor test (TUG) and cognition. However, no correlation between cognitive variables and gait speed test was found. After increasing the sample, the 10MWT also demonstrated a significant association with some cognitive variables, suggesting that impaired cognitive function might be related to slower gait speed. TUG continued to be the motor test with the best correlation, followed by the Mini-BESTest.[22]

Table 4. Multiple linear regression analysis.

Dependent variables	ACE-Total	Digit Span (forward)	Digit Span (backward)	TMT-A (s)	TMT-B (s)	Disease duration	H&Y
TUG							
β	0.01918	0.0092051	0.0096998	-0.002354	-0.000338	0.001427	-0.25986
p	0.009**	0.463	0.896	0.349	0.562	0.915	0.004**
Mini-BESTest							
β	-0.06708	0.14169	-0.403646	0.007995	-0.034887	-0.06364	-2.74613
p	0.196	0.115	0.445	0.656	0.403	0.000***	0.000***
10MWT							
β	-0.46584	0.721661	1.53593	-0.01004	0.05360	-0.28694	-5.19196
p	0.147	0.193	0.638	0.928	0.835	0.625	0.183

ACE: Addenbrooke's Cognitive Examination; TMT: Trail Making Test; H&Y: Hoehn & Yahr Scale; TUG: Timed Up and Go Test; Mini-BESTest: Mini-Balance Evaluation Systems Test; 10MWT: 10-Meter Walk Test. *significant at p<0.05; **significant at p<0.01; ***significant at p<0.001.

Table 5. Pearson's correlation coefficient. Subgroup: Timed Up and Go Test.

	Age (y)	Age (y)	Disease (y)	Disease (y)	H&Y	H&Y
	<60	≥60	<5	≥5	I–II	III
ACE (total score)	r=0.4189	0.5544	0.5276	0.4504	0.4690	0.4472
	p=0.0000***	0.0000***	0.0000**	0.0010**	0.000***	0.0250*
Attention/Orientation	r=0.2506	0.5740	0.4319	0.4362	0.3845	0.2620
	p=0.0732	0.0000***	0.0008***	0.0015**	0.0004***	0.2058
Memory	r=0.4007	0.4242	0.3979	0.4608	0.3933	0.4255
	p=0.0032**	0.0012**	0.0022**	0.0008***	0.003**	0.0340*
Fluency	r=0.3467	0.4133	0.5049	0.2993	0.3810	0.3805
	p=0.0118*	0.0017**	0.0001***	0.034*	0.0004***	0.0606
Language	r=0.2110	0.3184	0.2493	0.2330	0.2697	0.1709
	p=0.1333	0.0178*	0.0614	0.1035	0.0143*	0.4140
Visuospatial	r=0.3232	0.4164	0.5003	0.2019	0.3533	0.4920
	p=0.0194*	0.0016**	0.0001***	0.1596	0.0111*	0.0125*
TMT-A (s)	r=-0.4446	-0.4665	-0.5077	-0.3249	-0.3800	0.4379
	p=0.0010**	0.0003***	0.0001***	0.0213*	0.0004***	0.0286*
TMT-A (errors)	r=-0.0537	-0.0530	-0.1221	-0.0241	-0.0536	0.2705
	p=0.7052	0.7006	0.3657	0.8682	0.6324	0.1909
TMT-B (s)	r=-0.4506	-0.4758	-0.5150	-0.3576	-0.4340	0.4239
	p=0.0008***	0.0002***	0.000***	0.0108*	0.0000***	0.0347*
TMT-B (errors)	r=-0.3098	-0.3518	-0.4989	-0.0754	-0.3125	0.3481
	p=0.0254*	0.0091**	0.0001***	0.6026	0.0045**	0.0882
TMT (A-B)	r=0.3561	0.3573	0.4178	0.2774	0.3769	0.2052
	p=0.0096**	0.0074**	0.0012**	0.0511	0.0005***	0.3251
Digit Span (forward)	r=0.4120	0.3811	0.3546	0.4365	0.3365	0.4129
	p=0.0024**	0.0041**	0.0068**	0.0015**	0.0020**	0.0402*
Digit Span (backward)	r=0.3754	0.3736	0.4132	0.2976	0.3031	0.4114
	p=0.0061**	0.0050**	0.0014**	0.0358*	0.0056*	0.0411*

ACE-III: Addenbrooke's Cognitive Examination; TMT: Trail Making Test; H&Y: Hoehn & Yahr Scale; *significant at p<0.05; **significant at p<0.01; ***significant at p<0.001.

As real-world activities usually involve the combination of motor and cognitive tasks, the performance of the TUG test with a cognitive task has been chosen as a more sensitive outcome measure to predict the risk of falling. Thus, the cognitive TUG test has been recommended as an essential outcome measure to evaluate mobility and risk of falling.[34] Moreover, a retrospective cohort study of individuals with PD investigated the impact of adding a task (manual or cognitive) to the TUG test and concluded that it increases the responsiveness of the test in detecting the risk of falling.[35] Therefore, the role played by attention skills in safety, effectiveness, and independence during the performance of motor tasks is evident, especially when multiple stimuli are competing with this activity, which is usual when it comes to community participation.

The present results are consistent with a previous cross-sectional study that also reports an association between changes in gait and cognitive decline.[14,20]

Finally, this research offers some ideas for the assessment, referral, and holistic treatment of PD patients, since the individual who seeks the medical or physical therapy service with gait and mobility deficits may be eligible for a cognitive assessment and personalized rehabilitation program that covers not only the motor aspects. This interdisciplinary and biopsychosocial approach is also acknowledged in two recent meta-analyses.[36,37]

This study has several strengths: neuropsychological evaluation with standardized cognitive measures, patients with similar cognitive characteristics (mild cognitive impairment), motor assessment through a quantitative tool. It also has some limitations, such as evaluating only gait speed, without other measures like cadence and single or double support time.

In conclusion, the present findings suggest the critical role played by divided attention, visuospatial ability, and mental flexibility in the gait of PD patients. Thus, individuals with impaired mobility should not only be evaluated by a neuropsychologist but also have a personalized rehabilitation plan involving motor and cognitive training, when possible.

Authors' contributions. NMFS: conceptualization, investigation, data curation, formal analysis, writing — original draft, writing — review & editing. RCM: conceptualization, investigation, writing — original draft. SMDB: conceptualization, writing — review & editing.

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Dement Neuropsychol 2021 March;15(1):112-120

Original Article

https://doi.org/10.1590/1980-57642021dn15-010012

Extramural gerontology management devising an integrating record for a geriatric care service, an experience report

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ABSTRACT. The Gerontological Care Plan is idealized through case management that includes in its aspect engaging the elderly, self-care and the acquisition and maintenance of health-promoting behaviors. **Objective:** To evaluate the importance of a gerontological care plan, in a geriatric service of a referral hospital in the city of São Paulo. **Methods:** Fifteen older adult patients were interviewed and the Gerontological Care Plan (PAGe) was applied. **Results:** Most respondents were classified as independent for instrumental activities of daily living, 42% of whom lived alone. Data from 277 yellow sheets were analyzed, that is, referral forms, in which it was found that the most affected areas were: social work and psychology. For the social worker, the most recurring requests were: verification of the social support network, namely lack of companion and caregiver, with 53%; family problems, with 20%; lack of adherence to treatment, 12%, and problems related to medication, 10%. In the area of psychology, 82% of referrals were due to the need for psychological support, psychotherapy, and help with family problems, depression and grief. **Conclusions:** A gerontological management proposal was developed within the Geriatric Services of Hospital das Clínicas. The management plan was intended to integrate the actions carried out by the interprofessional team, through the creation of an Integrating Form that allowed the gerontologist to propose, execute and implement a plan of care, follow-up, and monitoring of cases, including the extra context-hospital.

Keywords: aging; older adults; comprehensive health care for the elderly; health services management; gerontology.

GESTÃO GERONTOLÓGICA EXTRAMUROS: A PROPOSTA DE CRIAÇÃO DE UM PROTOCOLO INTEGRADOR PARA UMA UNIDADE DE INTERNAÇÃO HOSPITALAR

RESUMO. O Plano de Atenção Gerontológica é idealizado por meio da gestão de casos que engloba em sua vertente, engajamento da pessoa idosa, autocuidado e aquisição e manutenção de comportamentos de promoção de saúde. **Objetivo:** Avaliar a importância de um plano de atenção gerontológica em um serviço de geriatria de um hospital de referência na cidade de São Paulo. **Métodos:** Foram entrevistados 15 pacientes idosos, sendo aplicado o Plano de Atenção Gerontológica (PAGe). **Resultados:** Em sua maioria, os entrevistados foram classificados como independentes para as atividades instrumentais de vida diária, sendo que 42% deles residem sozinhos. Dados de 277 folhas amarelas foram analisados, ou seja, Fichas de Encaminhamento, nos quais foi possível verificar que as áreas mais acionadas foram o serviço social e a psicologia. Para assistência social, as solicitações mais recorrentes foram a verificação da rede de suporte social, falta de acompanhante e de cuidador, com 53%, problemas familiares, com 20%, falta de adesão ao tratamento, 12%, e problemas relacionados a medicamentos, 10%. Na área da psicologia, 82% dos encaminhamentos foram feitos por necessidade de acompanhamento psicológico/psicoterapia, problemas com família, depressão e luto. **Conclusões:** Elaborou-se uma proposta de Gestão Gerontológica dentro dos Serviços de Geriatria do Hospital das Clínicas. O plano de gestão teve o intuito de integrar as ações realizadas pela equipe interprofissional, por meio da criação de uma Ficha Integradora que permitiu ao profissional gerontólogo propor, executar e implementar um plano de atenção, acompanhamento e monitoramento dos casos, incluindo o contexto extra-hospitalar.

Palavras-chave: envelhecimento; pessoa idosa; atenção integral à saúde do idoso; gestão dos serviços de saúde; gerontologia.

INTRODUCTION

In the past 20 years, Brazil´s ranking among countries with the largest elderly populations rose from 16th to 10th in the world. By 2025, the proportion of the nation's elderly population is set to reach 15.1%, making Brazil a country of elderly as opposed to younger individuals.[1]

This study was conducted at the Escola de Artes, Ciências e Humanidades, Universidade de São Paulo, São Paulo, SP, Brazil.

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Disclosure: The authors report no conflicts of interest.

Funding: none.

Received on May 25, 2020. Accepted in final form on October 02, 2020.

This rise in the number of elderly, from a health perspective, translates to an increase in long-term chronic conditions and diseases, which often require high-cost interventions involving complex technology for adequate treatment. Consequently, the aging population poses a socioeconomic challenge for the government and society.[2] Thus, short-, medium- and long-term planning is vital to establish a social well-being and healthcare policy for Brazil's elderly population, involving a multidisciplinary team and professionals specialized in gerontology.

The elderly should be evaluated globally, and parameters such as functional capacity and cognitive, social, psychological and cultural aspects should never be left to the background, when thinking about doing case management with the performance of the interdisciplinary team in health institutions.[3,4]

Protocols do not always allow the fulfillment of these requirements; however, currently, knowledge and studies demonstrate the effectiveness of using a Comprehensive Gerontological Assessment. In this sense, one of the instruments of knowledge of the gerontologist, such as the Gerontological Assessment (PAGe) that proposes integrated and shared actions, seeks to meet the aforementioned requirements.[1,2]

As well as being fundamental tools for medium- and long-term therapeutic planning, it is an essential part of the inter- and multidisciplinary approach to the management of care for the elderly. It should be noted that the multidimensional assessment instruments for the older adults, as previously reported, are essential in the management of the individual's routine and care.[2]

Accordingly, it is not possible to dissociate case management from broad gerontological assessment, as this assessment, which is one of the gerontologist's screening tools, is also associated with the concept of promoting healthy aging, by tracking physical, cognitive, functional changes, having as goals the stimulation, rehabilitation and/or functional preservation, through a performance with an interdisciplinary team. Thus, contributing to the promotion of longevity, and increase in life expectancy with health, autonomy and independence, thus reducing risks of institutionalization, hospitalizations and recurrent hospitalizations.[3,4]

On the basis of this context, our objective was to evaluate the importance of a gerontological care plan, in a geriatric service of a referral hospital in the city of São Paulo. Also, we aimed to carry out a documentary analysis of medical records, through retrospective analysis, and to fill out an integrating form of practices performed by geriatric services of the same institution, to optimize the communication between the institution's services and the management plan carried out. by the interdisciplinary team that was caring for elderly users, to have humanized and integrated referrals.

METHODS

Study type

A descriptive exploratory study of quantitative data based on information collected at each of the different areas of medical residency was conducted. The study was performed in 3 sectors of the Geriatrics Service of Hospital das Clinicas: the Infirmary, Outpatient Clinic and Day-Hospital. Patients and health professionals from the 3 sectors took part in the study.

Participants and protocol

The following instruments were used: the Gerontology Care Plan (PAGe) encompassing a battery of instruments for biopsychosocial assessment of elderly, an analysis of patient referrals to professionals at Hospital das Clínicas (via Yellow Sheets), and an interview with professionals heading each area of residency. The PAGe instrument was developed by the instructors in the gerontology degree program of the Universidade São Paulo, on the basis of the gerontology assessment instruments recommended in the Handbook on Primary Health for the Elderly of the Ministry of Health[5]. The objective of PAGe is to collect information on biopsychosocial aspects of older adults for integrated assessment. These results then provide a basis for devising a management plan. The instrument contains questions on habits, nutrition (outside hospital), functional autonomy, sleep, spirituality, falls, depression, risk screening, disease besides physical, and psychological, socioeconomic and family status.[6]

PAGe also has a field for the gerontologist's assessment and for suggested intervention to resolve problems identified, i.e., to devise a management plan together with the elderly patient/caregiver. Lastly, there is a section for a management plan that recruits other professionals on the team.

To obtain a broader picture of the life of the elderly and to better cater to their needs, PAGe can be used in conjunction with other instruments, such as: scales assessing Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs), Geriatric Depression Scale (GDS), Functionality Scale, Cognitive Screening Scale, Measures of Subjective and Psychological Well-being, Beliefs and Attitudes about Aging and others.

A total of 15 elderly patients were interviewed using the PAGe, applied between March and May 2010 at the different areas of residency within Hospital das Clinicas. Elderly individuals who agreed to take part by signing the Free and Informed Consent Form were included.

Besides the PAGes, from which some questions pertinent to the study objectives were selected, an analysis of 277 referral records involving other professionals of Hospital das Clinicas and respective reasons for these referrals was performed.

Lastly, interviews with sector heads were conducted using a questionnaire containing closed-ended questions. The questionnaire collected relevant data and information for subsequent use by residents as indicators of the main reasons for unplanned readmissions, repeat consultations and recurrences at the infirmary, outpatient clinic and day-hospital, respectively. These instruments and techniques were pivotal in the development of a Gerontology Care Plan for the services.

Study investigation sites and criteria for using the service

Under the Brazilian National Health System (SUS), healthcare is structured into different levels of care, namely: primary care, medium complexity and high complexity. University teaching hospitals, such as Hospital das Clínicas of the Faculdade de Medicina of the Universidade de São Paulo (HC-FMUSP) of São Paulo State, are SUS-affiliated tertiary hospitals. These facilities engage in numerous activities such as primary health care promotion and prevention programs, secondary rehabilitation and prevention, primary care, social support, and homecare programs, among other specific care policies aimed at reducing hospital admissions.

Hospital das Clinicas is a leading healthcare, teaching and research institution and recognized center of excellence in the development of health technology. The hospital predominantly serves SUS users, but also delivers care to private patients holding health plans, given its extensive operating capacity, constant renewal of facilities and high-quality care staff.[7]

The Geriatrics Service of the HC-FMUSP boasts a multidisciplinary team specialized in treating elderly patients and is renowned for its educational training of geriatricians and gerontologists, as well as research studies conducted in the area of aging. The Geriatrics Service currently encompasses an Outpatient Clinic, Infirmary Ward and Day-care Hospital, as outlined below.

The Geriatrics Outpatient Clinic provides, on average, 11,900 consultations per year. The service operates on Wednesdays and Thursdays and deploys a team of 8 medical residents on each of these days. Users are referred to the Geriatrics Outpatient Clinic from the SG-HC Infirmary Ward, Day-care Hospital and other services, such as Interconsulta and the Hospital Auxiliar de Cotoxó.[7,8]

Information is recorded to guide diagnosis and treatment. These data can be collected using a variety of instruments, including: anthropometric measures, the Mini-Mental State Exam (MMSE), Geriatric Depression Scale (GDS), Tinetti Scale (POMA-Brasil), Katz Scale and Functional Independence Measure (FIM). Different members of the care team investigate aspects such as psychiatric disorders, gait disturbances and brief social issues.[7,8]

The Geriatric Infirmary of the HC-FMUSP is equipped with 17 beds and admits elderly patients aged ≥60 who present with different diseases not requiring surgical interventions or admission to an intensive care unit (ICU) at the time of hospitalization. In addition, patients whose therapeutic condition does not indicate palliative care are referred to this infirmary.[8]

Patients arrive at the Geriatric Infirmary from the Emergency Room, ICU, Geriatric Outpatient Clinic, or from other units in the hospital, such as homecare units. The multidisciplinary care team is made up of professionals trained in gerontology, including geriatricians and residents, nurses, speech-hearing and language therapists, psychologists, physiotherapists, nutritionists and social workers.

In 2007, the Geriatric Day Hospital (GDH) commenced operation with several objectives, including: to lower hospital admission/readmission rates of elderly; promote early discharge of elderly admitted to the infirmary; provide rapid resolution of problems diagnosed; establish a comprehensive diagnosis of patient health; carry out minor surgical procedures, offer guidance after hospital discharge and reduce costs related to patient management.[9]

The GDH boasts 18 beds and a team of geriatric physicians, a nurse, nursing assistants, a nutritionist and speech-language therapist.[9]

The criteria for referral to the GDH are: being aged >60; enrolled at the HC Complex or referred by the Paula Souza Health Center; presenting with acute decompensated refractory disease, infections, delirium or behavioral syndrome; requiring urgent diagnostic investigation, parenteral or intravenous drug infusion, treatment adherence control, certain procedures (tubes, tests, biopsies), blood transfusions or oral anticoagulation and functional rehabilitation.

At time of discharge, guidance is given by the team, and the patient is referred for the appropriate follow-up according to their needs.[9] The aging process

is accompanied by biopsychosocial aspects, calling for multidisciplinary care team qualified in catering to the wide variety of profiles inherent to the elderly population.[10] A multidisciplinary team is therefore essential to enable implementation of actions that support the patient, caregiver and family.

Gerontology care should embrace components involving the assessment of psychosocial aspects and patient health status; care planning; solution coordination and implementation; treatment plan monitoring; and outcome assessment.[11] Further, treatment non-adherence, as well as the culture, beliefs, values, economic conditions and family structure of patients should be taken into account.

Case management encompasses continuous patient-centered integral care which may be carried out by a professional or health team. Also, management is a cooperative process that diagnoses, plans, implements, coordinates, monitors and assesses options and services according to the patient´s health needs, through the available resources and communication.[12]

To this end, gerontology specialists, who hold multidisciplinary knowledge on the aging process, draw on their abilities and competencies to integrate and coordinate teams working with the elderly, performing case management to improve self-care, reduce care fragmentation, increase satisfaction of patient and of committed professionals, and make optimal use of the resources available.

According to Filho,[9] on the abstract level, a gerontologist knows less about medicine and healthcare than a physician or nurse, less about psychology than a psychologist, and less about sociology than a sociologist or social worker. Nevertheless, again on the abstract level, this practitioner is more skilled than any of the specialists cited at developing and implementing activities involving the elderly and aging, from a holistic perspective of the life cyle.[10-12]

Lastly, gerontologists can help integrate professionals involved in patient care, establishing a focused consultation that is more cost-effective for patients, family and the institution.[13] In this context, the study aim was to devise a gerontology management plan for both intramural and extramural use to determine the causes of readmission to the Infirmary, recurrence at the Day-Hospital and repeat consultation at the Outpatient Clinic. The study also sought to analyze the reasons for clinical referrals to other professionals in the hospital, to determine social and family profiles and screen risks and to analyze the functional capacity of patients interviewed.

RESULTS AND DISCUSSION

Data collected using PAGe revealed that 50% of subjects were 71–80 years old and 33% >80 years, typifying the 21st century pattern of a rapidly growing contingent of older elderly (aged >80 years), a group more prone to frailty and more likely to depend on a support network for assistance in everyday activities;[14] 42% were married and 42% widowed. The vast majority of the sample (67%) were women, confirming the phenomenon of feminization in old age, whereby females far outnumber males in the elderly population.[15] With regard to education, 100% of the individuals reported incomplete primary education.

Results for the PAGe question on Autonomy and Functioning showed that 90% of elderly were independent for basic activities and 72% for instrumental activities, indicating that most were able to perform basic and instrumental activities of daily living without assistance, such as: domestic chores, feeding, dressing, etc.

With regard to Social and Family Conditions, 42% lived alone and 33% lived with others or spouse, while 25% lived with their son/daughter.

For self-perceived health, 25% of the elderly rated their health as very good, 33% as good, 29% as regular, and 12% as poor. None of the elderly classified their health as excellent. Overall, 67% of the sample reported having sought a physician more than twice in the past 12 months.

Another point investigated by the team of residents was an analysis of referrals made to other professionals following a medical consultation. The referral sheets (used by physicians from the outpatient clinic to request an assessment by other professionals on the team) are known internally as "Yellow Sheets" and contain requests normally filled out by the attending physician. A total of 277 Yellow Sheets were analyzed, predominantly involving referrals to social services (53%) and the psychology areas. The various professionals receiving the remaining 9% of referrals were: Physiotherapy, Urology, Occupational Therapy, Nutritionist, Physical Education specialist and Long-stay hospital.

The reasons underlying the most common referrals to the social service area were: social support network (lack of companion or caregiver), 53%; family problems, 20%; non-adherence to treatment, 12%; and medication-related problems, 10%. There were many reasons underlying treatment non-adherence or medication-related problems, including biological, psychological or social factors, such as fear of the disease, financial problems, educational and cultural level, forgetfulness, and self-medication.[14,16,17] Other less frequent reasons included search for 3rd age group, social benefits and equipment, among others.

The most important exponents of the elderly´s relationship network are family, friends and community. However, forms of family support have shifted with a major decline in birthrate (currently averaging 2.1 children born per woman), migration of young adults to more promising regions leaving their parents with no family support, and a growing number of women joining the workforce, factors that have reduced or eliminated female figures in the role of sole caregiver of dependent family members.[14,16] In the area of psychology, 82% of referrals were due to the need for psychological support (psychotherapy, family problems, depression and grieving).

None of these yellow forms hold information on the outcome of the intra- or extramural referrals.

The most common reasons for referral to the Day-Hospital were uncompensated chronic diseases (47.6%) and infections (37.9%). Elderly often present with a number of chronic health problems such as arterial hypertension, arthropathies, diabetes and dementia, which can limit their everyday life.[18,19] Similarly, infections are among the leading causes of hospitalization and death in the elderly. One of the main issues surrounding infections in this group is late diagnosis and consequent delay in treatment.[20]

Data collected from the interviews of sector heads revealed the absence of any formal recording of recurrences, return visits and readmissions or of missed routine outpatient consultations. Collecting this information would require individually searching all medical records.

The findings to date highlight the importance of integrating multidisciplinary information from medical charts and on treatment plans adopted to enable more effective management within the scope and situation of each patient, thereby promoting improved quality of life.

An integrated care approach can reduce the bureaucracy inherent to the service, rendering it more dynamic and less repetitive, while optimizing the use of human and material resources.

This effort is justified because it can deliver more comprehensive gerontology care, besides integrating the actions prescribed in multidisciplinary consultations via an integrating record. The approach also allows extramural management of cases with monitoring of self-care and resources needed, such as social, financial and psychological support. This management ensures prescriptions are followed, thereby preventing unplanned readmissions, consultations or recurrences. All instruments outlined below, when used in conjunction, provide integral complete gerontology management for patients and their relatives (micromanagement).

Integrating record for case management

The first part of the proposal developed consists of an instrument that integrates measures taken by the multidisciplinary team, called the Integrating Record. The instrument comprises the following fields: service area (medicine, psychology, nursing and others), patient clinical status, care plan, objective, observations and attending physician. All these fields are completed by the gerontologist using information drawn from the patient´s medical record and are updated if and when the case requires.

The Integrating Record (depicted in Figure 1 and in Appendix A) is kept by the gerontologist, but any professional can access it or request information. Upon patient discharge, the Integrating Record is attached to the patient´s medical chart. The aim of the Record is to provide the gerontologist with sufficient information to devise a Gerontology Care Plan integrating the actions recommended by the other professionals, making these as pertinent as possible to the patient.

The Gerontology Care Plan is made up of four fundamental elements: a) planning and assessment of care; b) coordination and implementation of solutions; c) monitoring of care plan; and d) assessment of results. The plan also incorporates active ongoing reassessment allowing goals to be adjusted. Akin to the Integrating Record, the care plan should also be attached to the patient´s medical record.

To consolidate referrals and recommendations for gerontology care plans, gerontologists shall hold meetings with the team involved in treatment, providing them with the latest information on the patient´s compliance with actions, guidance, and prescriptions given. On the basis of this integrated data, the team can devise new strategies. Subsequently, these strategies will, after group consensus, be proposed to the patient and monitored by the gerontologist, consolidating the interface of the extramural and intrahospital care which are pillars of this management, as outlined below.

Extramural care plan, based on the integrating instrument

Based on the Integrating Record and Gerontology Care Plan, the gerontology resident provides cases with extramural care, follow-up and monitoring of self-care and the necessary resources, such as social, financial and psychological support (Figures 1 and 2).

The monitoring is carried out by the gerontologist responsible for the case by means of regular telephone contact with patients and/or caregivers. Home visits can also be arranged according to the needs observed during follow-up. The purpose of this extramural care is to intensify monitoring of the plan, ensure prescriptions are

followed, identify potential risks and provide guidance on the risks identified, thereby preventing unplanned readmissions, repeat consultations and recurrences.

Case management to optimize the interventions provided by the multidisciplinary care team in older adult patients is a care model that when employed as part of the healthcare action plan, transforms single-faceted care into multi-faceted care; that is, it encompasses biological, psychological, social and environmental needs, beyond the remit of traditional medical services.[21,22]

The role of the case manager (CM)[23] includes identifying current and future needs of his/her client/patient, bringing together and coordinating the services available, advising patients and relatives, besides guiding and assisting them as service users. The CM scrutinizes the case, seeking all information necessary to devise a treatment plan. Subsequently, the CM implements and closely monitors this plan for effectiveness, adapting it to meet new needs, if and when they arise.

The term case manager is a derivative of case management, defined as a global, multidisciplinary effort centered on the individual and drawing on different areas of knowledge that address the needs detected. Heber[24] points out that many professionals involved in case management tend to seek and explore only those needs related to their own area of expertise and background. The author states that there are at least four main case management models: Nursing, entailing managing health/disease, dysfunction and rehabilitation; Social Work, encompassing a range of social activities and variables; and Health Care, addressing health-related needs.

Another important aspect for case management is that care interventions of a generalist targeting health status can be run, constituting a key tool for promoting treatment adherence through education of the patient on their health condition and drugs treatment. Indeed, the literature indicates, as corroborated by the present study, there is great value associated with the knowledge held by the elderly on concepts such as health.[25]

Holding knowledge on how to cope and live daily with a chronic disease, such as hypertension, constitutes a valuable tool for implementing strategies that render treatment more effective and thus better manage the patient´s clinical condition.

In the context of the structural shift in contemporary society, i.e., a growing elderly population, it is clear that, besides the importance of specialized training of professionals qualified to cater to the health needs of this group, the available resources in the tertiary health service must be optimized to deliver this care effectively.

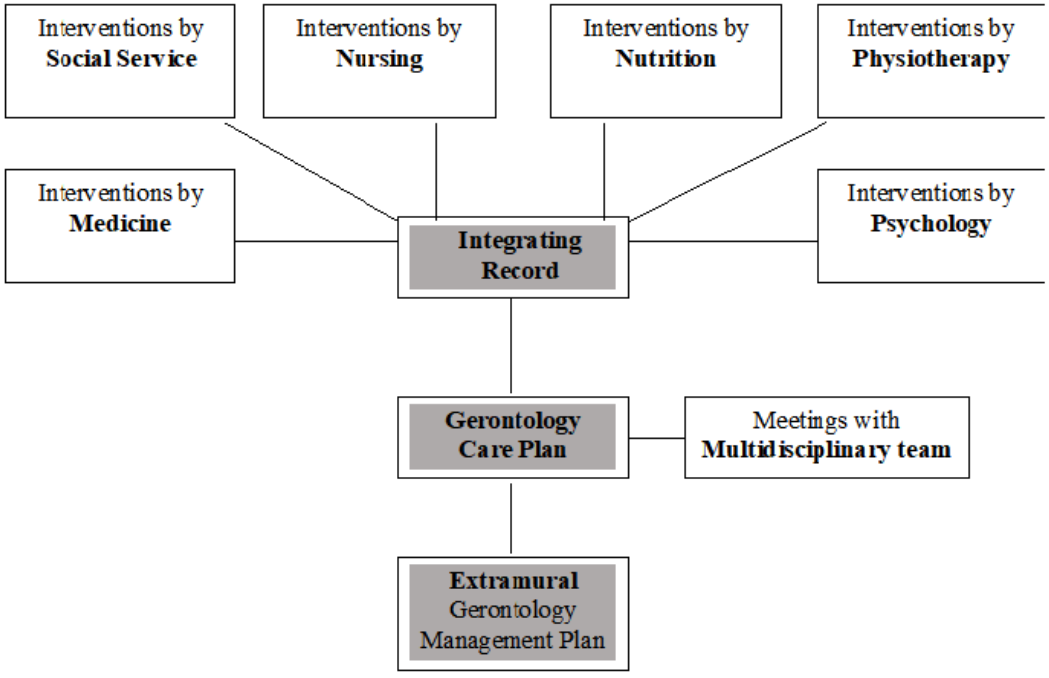


Figure 1. Integrating Record of Care interventions and referrals to Care Management for Elderly within Geriatric Services of a Tertiary Hospital, São Paulo, 2020.

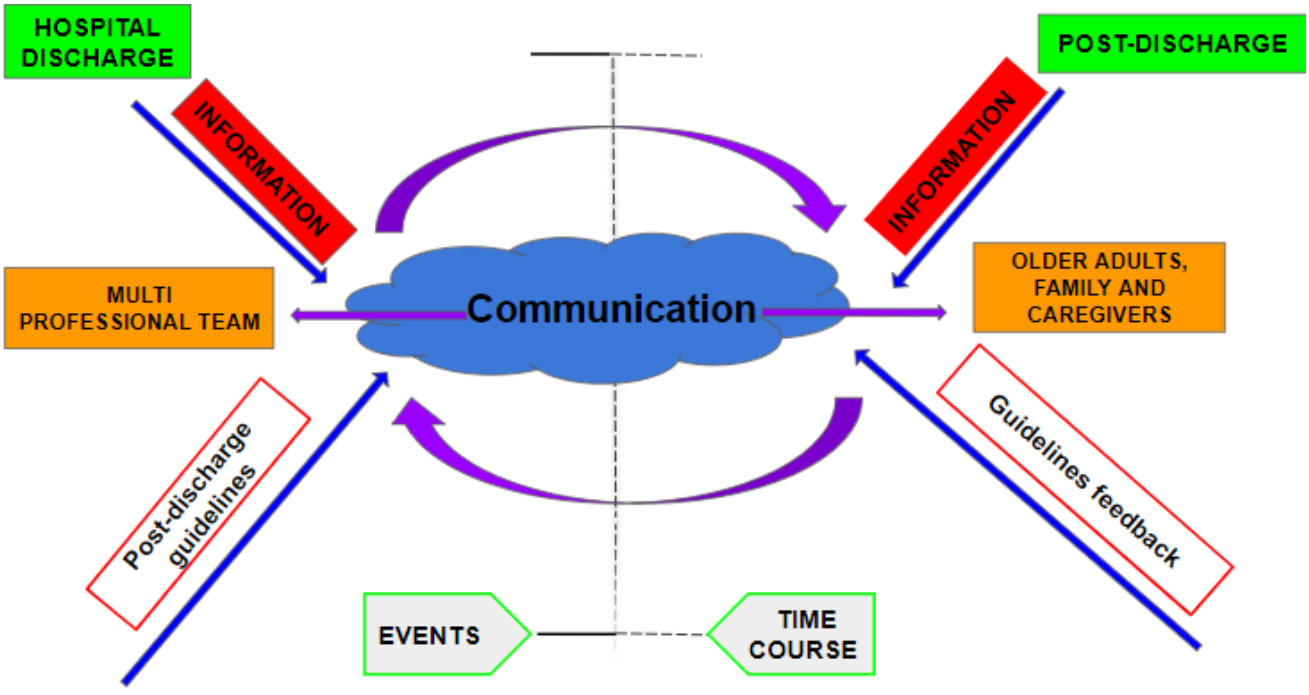
In the present study, there was an evident need for a gerontology management plan within the Geriatric Services of Hospital das Clinicas. The purpose of the management plan is to integrate actions performed by the multidisciplinary team through use of the Integrating Record. This instrument enables gerontologists to follow, propose a care plan and monitor cases, also extramurally, assessing the quality of social support networks and resources the elderly patient and family have at their disposal. It is noteworthy that this model of integrating record could potentially be applied to other medical areas and sectors besides geriatrics.

Case management can be applied in interventions to promote health in the elderly, prevent the collateral effects of comorbidities which may arise, assign new meaning to the ageing process and old age, expand the social support network, and provide guidance thereby increasing uptake of the use of services and promoting quality of life.

However, it is important to emphasize that case management, to be well planned and effective, requires a thorough multidimensional assessment of the elderly patient. Currently, several types of multidimensional assessment are typically used by all members of the multidisciplinary team, also referred to as comprehensive geriatric assessment (CGA).

The Gerontology Management Plan is broad and designed to prevent unplanned readmissions, consultations and recurrences as a result of poor adherence to interventions prescribed by professionals or of exposure to risk factors. As outlined earlier, the interviews conducted with heads of the sectors failed to elucidate the reasons for recurrences, repeat consultations or readmissions. Hence, given the absence of formal statistical records, this information would need to be gathered from all patient medical charts, requiring an extensive period of time.

Future studies should be conducted that enable ongoing assessment and refinement of the management plan goals proposed by the gerontology specialist at all stages of care: Integrating Record, Gerontology Care Plan and Extramural Gerontology Management Plan.



Original flowchart (in Portuguese) of the proposal for extramural management made by the Gerontology team at the same university, for the geriatric services of Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo.

Figure 2. Flow diagram of extramural management, São Paulo, 2020.

ACKNOWLEDGEMENTS

The authors extend their thanks to the management team of the Geriatrics Service of Hospital das Clínicas of the Faculdade de Medicina of the Universidade de São Paulo for their collaboration, without which this study would not have been possible, namely: gerontologists Ana Teresa Baruffi Franco, Carlos Eduardo Veronese, Gessyca Selmara Harumy Suenaga, Heloisa Almeida Rodrigues, Karen Elise Campos, Mariana Sandrin, Mayra Guesso, Milena Yoshino, Samila Franco, Thais Freitas, Thaissa Bessa, Thamires Rocha, Patrícia Furlan Innocencio, Paula Giovanna Mesquita Bissoli and Young Shim Mori.

Authors' contributions. TBLS contributed to conception and design, and acquisition, analysis and interpretation of data, participated in drafting the article and gave final approval of the version to be submitted; EBA contributed to conception and design, and acquisition, analysis and interpretation of data, participated in drafting the article and gave final approval of the version to be submitted; FB contributed to conception and design, and acquisition, analysis and interpretation of data, participated in drafting the article and gave final approval of the version to be submitted; TNO contributed to conception and design, and acquisition, analysis and interpretation of data, participated in drafting the article and gave final approval of the version to be submitted; MARD contributed to conception and design, and acquisition, analysis and interpretation of data, participated in drafting the article and gave final approval of the version to be submitted.

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Appendix A. Integrating record of interventions by multidisciplinary team.

Date				
Professional/Name				
Action				
Strategy				
Results				
Facilitators				
Barriers				
Referrals				

Dement Neuropsychol 2021 March;15(1):121-127

Original Article

https://doi.org/10.1590/1980-57642021dn15-010013

Cognitive performance of older adults with a low level of education with and without depression

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ABSTRACT. Major depression can develop in individuals aged 60 years or older and is commonly associated with cognitive decline in this population, especially the domains of working memory, attention, executive functions, and processing speed. Schooling is a protective factor with regard to cognitive decline. **Objective:** To compare the cognitive performance of community-dwelling older adults with a low level of schooling with and without major depression. **Methods:** A descriptive, analytical, cross-sectional study was conducted with 22 community-dwelling older adults with depression and 187 without depression. The following assessment tools were employed: Mini Mental Health Examination, Brief Cognitive Screening Battery, Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Digit Span Test (forward and backward), and an object similarity test. **Results:** No statistically significant differences were found between the groups with and without depression on any of the tests. **Conclusions:** This study demonstrated that there are no differences in the cognitive performance of older people with and without depression on neurocognitive tests commonly used in clinical practice. Future studies with different designs and methods as well as specific tests for older people with a low level of schooling could assist in the understanding of these relations and the mechanisms involved.

Keywords: aging, depression, cognition, mental health, educational status.

DESEMPENHO COGNITIVO DE IDOSOS COM BAIXA ESCOLARIDADE COM E SEM DEPRESSÃO

RESUMO. A depressão maior pode se manifestar em indivíduos com 60 anos ou mais e, comumente, está associada ao declínio cognitivo, especialmente nos domínios memória de trabalho, atenção, função executiva e velocidade de processamento. Nesse contexto, a escolaridade é um fator de proteção em relação ao declínio cognitivo. **Objetivo:** Comparar o desempenho cognitivo entre idosos de baixa escolaridade da comunidade com e sem depressão maior. **Métodos:** Trata-se de um estudo transversal, descritivo e analítico. Foram selecionados 22 idosos da comunidade com depressão e 187 idosos sem depressão, que foram avaliados por meio dos seguintes instrumentos: Mini-Exame do Estado Mental (MEEM), Bateria Breve de Rastreio Cognitivo (BBRC), *Consortium to Establish a Registry for Alzheimer's Disease* (CERAD), teste de extensão de dígitos de ordem direta e inversa, e um teste de semelhança de objetos. **Resultados:** Não foram encontradas diferenças estatisticamente significativas entre os grupos com depressão e sem depressão em nenhum dos testes aplicados. **Conclusões:** O presente estudo demonstrou que não existem diferenças no desempenho cognitivo de idosos com e sem depressão em testes neurocognitivos comumente utilizados na prática clínica. Estudos futuros com métodos e delineamentos diferentes, com testes específicos para idosos com baixa escolaridade, podem auxiliar na compreensão dessas relações e dos mecanismos envolvidos.

Palavras-chave: envelhecimento, depressão, cognição, saúde mental, escolaridade.

This study was conducted at the Universidade Federal de São Carlos, São Carlos, SP, Brazil.

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Funding: This study received funding from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP [State of São Paulo Research Assistance Foundation]; process 2015/16412-1). Ana Julia de Lima Bomfim received a master's grant from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES [Coordination for the Advancement of Higher Education Personnel]) – Financing code: 001).

Disclosure: The authors report no conflicts of interest.

Received on September 02, 2020. Accepted in final form on December 29, 2020.

INTRODUCTION

Major depression can develop in individuals aged 60 years or older, among whom the prognosis is worse, the course of the disease is more persistent, and the relapse rate is higher in comparison to younger individuals; moreover, concomitant cognitive decline is also often found in this population.[1,2] Approximately 30% of older adults with depression exhibit cognitive decline, especially in the domains of working memory, attention, executive functions, and processing speed.[2,3]

Concomitant depression and cognitive decline exert a negative impact on quality of life and functional capacity, along with an increase in the relapse rate of depression, a delayed response to treatment, and greater use of specialized services.[4] Moreover, cognitive impairment can persist after effective treatment for depression.[5,6] Approximately 45% of patients with previous depression continue to exhibit significant cognitive impairment even after the treatment and remission of depressive symptoms.[7]

Evidence indicates that a current or past history of depression is a risk factor for the decline in cognitive function, which, in turn, is a predictor of future depressive symptoms.[8] Moreover, social isolation, a low level of schooling, a poor socioeconomic status, and the occurrence of cardiovascular disease, such as hypertension, are risk factors shared by both depression and cognitive decline.[9,10]

The prevalence of cognitive impairment is higher among individuals with a low level of schooling.[11] In Brazil, the prevalence is 18.7% among older adults and both age group and a low level of schooling are directly associated with the increase in cognitive impairment in this population.[11] Moreover, even with no evidence of cognitive decline based on clinical history and examinations, individuals with a low level of schooling can perform poorly on cognitive tests.[12]

Although diverse cognitive assessment tools have been developed to screen for the decline in cognitive functions, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), educational level has implications with regards to the skills that are assessed using these instruments.[13] Therefore, the prevalence of cognitive decline may be overestimated, especially in low- and middle-income countries, such as Brazil, as a good performance on cognitive screening tests is influenced by schooling.[12]

Evidence points to a deficit in the communication of brain regions underlying the performance on cognitive tasks among older adults with a low educational level.[14,15] Thus, older people with a higher level of schooling have a compensatory network and can employ different strategies when performing a cognitive task, indicating that a higher level of education can contribute to greater cognitive reserve.[16]

Like cognitive impairment, a low level of schooling can be considered a risk factor for depression and the interaction between the two exerts an influence on the performance of neuropsychological tests.[17] Therefore, the aim of the present study was to compare the cognitive performance of community-dwelling older adults with low schooling with and without major depression using a cognitive assessment protocol that encompasses memory, language, executive functioning, abstraction, and attention.

METHODS

Setting and participants

This study was conducted in the city of São Carlos, located in the state of São Paulo, Brazil. The participants were selected from a study for the screening of psychiatric disorders in the coverage area of a family health unit (Brazilian primary care modality). All homes were visited and a total of 289 older adults were invited to participate. Five declined, two were bedridden, and 15 did not undergo the psychiatric interview. Thus, 267 older adults were submitted to a diagnostic psychiatric assessment.

The exclusion criteria were severe vision or hearing impairment that could affect the understanding of the questions and tests and a diagnosis of a major neurocognitive disorder, psychotic disorder, intellectual deficiency, bipolar affective disorder, schizophrenia, or epilepsy. Fourteen individuals with more than eight years of schooling (two from the group with depression and 12 from the group without depression) were also excluded. The final sample was composed of 209 older adults, who were divided into two groups: 1) those with major depression (n=22) and 2) those without major depression (n=187).

The group with depression had eight individuals with comorbid anxiety disorder [general anxiety (n=6), specific phobia (n=4), and social anxiety disorder (n=1)]. Only two individuals in the group used a therapeutic dose of antidepressant medication (fluoxetine 40 mg/day and escitalopram 10 mg/day)]. In the group without major depression, 68 individuals had anxiety disorder [general anxiety (n=37), specific phobia (n=25), and social anxiety disorder (n=6)]. Five individuals in this group took a therapeutic dose of

antidepressant medications (escitalopram 10 mg/day, sertraline 50 mg/day, fluoxetine 20 mg/day, and nortriptyline 50 mg/day.

Procedures

For the diagnosis of psychiatric disorder, the participants were evaluated during a detailed clinical interview performed by three psychiatrists (NMSC, RMPP, and LRL) on the basis of the guidelines of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published by the American Psychiatric Association,[18] which has a structure for diagnostic investigations and offers screening questions for the disorders listed in the DSM-5.[19]

The participants were also evaluated using an assessment protocol that encompassed sociodemographic characteristics and a battery of cognitive tests, which was performed by five trained gerontologists. The evaluations were conducted in the homes of the participants with a maximum interval of 30 days between evaluations. The data were collected between March 2016 and February 2017. There was no specific order for these steps of the study.

All volunteers agreed to participate by signing a statement of informed consent, which had received approval from the Human Research Ethics Committee of the Federal University of São Carlos (certificate number: 48602515.5.0000.5504).

The cognitive assessment consisted of the following tools.

Mini Mental State Examination

The MMSE is commonly used to screen for cognitive decline. It was created by Folstein et al.[20] and translated into Brazilian Portuguese by Bertolucci et al.[21] The MMSE is composed of domains that enable an objective assessment of spatial and temporal orientation, registration, registration recall, attention, calculation, and language. The cutoff point for cognitive impairment differs depending on the degree of schooling. The total score ranges from 0 to 30 points, with lower scores denoting greater cognitive decline.[20]

Cognitive Screening Battery

The BCSB is used to identify individuals with dementia in epidemiological studies[22] and employs figures for the assessment of memory. The battery consists of naming, incidental memory, immediate recall, learning, delayed recall, and recognition as well as a verbal fluency test and clock-drawing test. The BCSB has good accuracy in populations with high illiteracy rates or low levels of schooling.[23]

Similarity Subtest of the Cambridge Examination for Mental Disorders (CAMDEX)

The similarity subtest of the CAMDEX consists of four questions for assessing the capacity for abstraction.[24] The evaluator states the name of two objects and the participant must say how the objects are similar. For example: "In what way are a shirt and dress similar?". The score on this subtest ranges from 0 to 8 points, with a higher score denoting a better performance. This instrument has been translated and adapted to Portuguese.[25]

Digit span test (forward and backward) from the Wechsler Memory Scale revised

The digit span test is comprised of seven pairs of numeric sequences.[26,27] The test is administered in forward and backward sequences. The sequences have three to nine numbers in the forward test and two to eight numbers in the backward test. The examiner reads the sequence of numbers and the respondent repeats them. The examiner reads the sequence with a one-second interval between numbers and the sequence must be repeated after immediately after the reading. The test ends after mistakes occur on two consecutive sequences.

Consortium to Establish a Registry for Alzheimer's Disease

The CERAD is a battery of neuropsychological tests developed by Morris et al.[28] to establish an assessment standard for Alzheimer's disease. The battery is composed of the following cognitive tests: verbal fluency (animals), 15-item Boston naming test, word list memory test, constructive praxis, recognition list, and praxis recall.[29]

Data analysis

Descriptive analysis was performed to characterize the sociodemographic profile of the groups. The Kolmogorov-Smirnov test was used to determine the normality of the data. The Student's t-test and Mann-Whitney test were used to evaluate differences between groups according to the distribution of the variables, and the chi-square test was used for the comparison of categorical variables. Statistical analysis was performed with the aid of the SPSS 23.0 program, with the level of significance set at 5% ($p<0.05$).

RESULTS

The clinical-demographic data of the sample are displayed in Table 1. No significant differences between

Table 1. Clinical and demographic characteristics of the groups with and without depression.

	Major depression (n=22)	Without major depression (n=187)	p-value
	Mean (SD)		
Age (years)	71.40 (±9.63)	70.05 (±7.23)	0.739
Schooling (years)	2.22 (±2.06)	2.85 (±2.27)	0.266
Family income (minimum wage)	2.55 (±1.38)	2.64 (±1.23)	0.635
	n (%)		
Sex			
Female	15 (68%)	109 (58%)	0.256
Male	7 (32%)	78 (43%)	
Polypharmacy			
Yes	12 (55%)	51 (27%)	0.010*
No	10 (45%)	136 (73%)	
Diabetes			
Yes	7 (32%)	49 (26%)	0.348
No	15 (68%)	138 (74%)	
Arterial hypertension			
Yes	16 (73%)	114 (61%)	0.162
No	6 (27%)	73 (39%)	
Heart disease			
Yes	5 (23%)	35 (19%)	0.363
No	17 (77%)	152 (81%)	
Smoker/ex-smoker			
Yes	7 (32%)	76 (41%)	0.309
No	15 (68%)	111 (59%)	

SD: standard deviation; *statistically significant result.

Table 2. Mean and standard deviation (±) values according to the cognitive domains evaluated between groups with and without depression.

	Major depression (n=22)	Without major depression (n=187)	p-value
	Mean (SD)		
Global cognition			
MMSE	23.31 (±3.88)	22.88 (±3.82)	0.489
Memory			
BCSB – incidental memory, immediate recall and learning	21.89 (±5.50)	21.00 (±5.23)	0.560
BCSB – delayed recall	7.42 (±1.95)	6.94 (±2.34)	0.817
BCSB – recognition	8.26 (±2.80)	8.82 (±2.08)	0.200
CERAD – word list	14.15 (±5.75)	12.64 (±5.46)	0.516
CERAD – delayed recall	3.84 (±2.43)	3.15 (±2.42)	0.303
CERAD – recognition list	7.31 (±2.88)	7.64 (±2.54)	0.541
Language			
Boston naming test	11.00 (±3.41)	11.44 (±2.49)	0.442
Verbal fluency test	10.84 (±2.75)	10.76 (±3.63)	0.778
Executive functions			
Clock-drawing test	5.10 (±2.75)	4.96 (±3.52)	0.867
CERAD – constructive praxis	5.26 (±3.21)	5.53 (±3.092)	0.812
CAMDEX similarity subtest	3.15 (±2.56)	2.69 (±2.10)	0.319
Attention			
Digit span test (forward)	4.42 (±1.21)	4.57 (±1.20)	0.606
Digit span test (backward)	2.10 (±1.44)	2.37 (±1.16)	0.574

SD: standard deviation; MMSE: Mini Mental State Examination; BCSB: Brief Cognitive Screening Battery; CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

groups were found regarding age (p=0.739), sex (p=0.256), family income (p=0.635), or schooling (p=0.266). Mean schooling was low in both groups. A statistically significant difference was found for polypharmacy, as the use of five or more medications was more frequent in the group with depression (p=0.010). No significant differences between groups were found regarding self-reported heart disease, hypertension, diabetes, or being a smoker or ex-smoker.

Table 2 displays the mean and standard deviation values according to the cognitive domains. No significant differences between groups were found for any of the cognitive domains evaluated.

DISCUSSION

In the present study, no significant differences were found between the groups with and without depression with regard to cognitive domains. This finding differs from data described in the majority of studies in the literature, as an association between depressive symptoms and cognitive impairment has been reported in both cross-sectional[4,5,30,31,32] and longitudinal[33,34] studies.

A cross-sectional study conducted by Giri et al.[30] evaluated the association between cognitive decline and

depressive symptoms in a sample of 538 older people using the MMSE and 30-item Geriatric Depression Scale (GDS-30). Approximately 51% of the sample had 11 or more years of schooling. On the basis of the findings, depression was considered a predictive factor for cognitive decline, and cognitive impairment was associated with an increased risk of depression.

Likewise, Bunce et al.[33] evaluated the temporal association between depressive symptoms and cognitive function in 896 community-dwelling older people between 70 and 97 years of age for a period of four years. The participants were divided into two groups: those with up to two depressive symptoms and those with more than two depressive symptoms. Mean schooling was 11.39±2.64 and 11.28±2.45 years, respectively. The results indicated that the presence of depressive symptoms exerts an influence on processing speed and reaction time, suggesting that depression may occasionally precede cognitive decline. The studies cited above used the presence of depressive symptoms to evaluate the association with cognition, which can facilitate the findings. Moreover, it is not always possible to clinically differentiate depressive and cognitive symptoms, as concentration problems and difficulties making decisions are commonly found in depressive conditions.

Regarding studies conducted in Brazil, Novaretti and Nitrini[31] evaluated the performance of older adults with depression using the BCSB and CERAD. The sample was composed of 25 individuals with late-onset depression (mean age: 73.6±6.6 years; mean schooling: 9.1±5.7 years) and 30 healthy individuals (mean age: 73.8±5.8 years; mean schooling: 9.1±5.4 years). The group with depression had a poorer performance on the CERAD in the domains of verbal fluency (animal category) and word list recall and on the BCSB in the domains of learning and verbal fluency (fruit category). However, the groups were not matched for sex and the schooling of the sample was higher than that in the present sample, which may explain the divergent results.

A cross-sectional study conducted in the city of São Paulo, Brazil, evaluated the association between cognitive performance and both sociodemographic and health-related variables in a sample of 384 older adults (65 years of age or older), among whom 79.6% had less than four years of schooling. Cognition was assessed using the MMSE and BCSB. The results showed that age, sex, schooling, and depressive symptoms exerted significant influences on the cognitive performance of the individuals evaluated.[32] However, the coefficient of partial determination (partial R^2) in this study was 0.018, indicating that, despite being statistically significant, the presence of depressive symptoms only explained 1.8% of the variation in the MMSE scores.

The descriptions offered above reveal divergences in the findings reported in the literature. In the present investigation, no significant differences were found between the two groups regarding any cognitive domain. A possible hypothesis for this finding regards the level of schooling in the sample, as most studies that found differences between older groups with and without depression were conducted in high-income countries with samples that had higher levels of schooling.[4,5,30,33,34] Thus, the low level of schooling in both groups of the present study may have influenced the results, as most of the test scores were low. Therefore, the determination of differences between the groups may have been hindered due to the floor effect. which can hinder the detection of differences in comparative analysis, facilitating the occurrence of type II errors.

As educational level exerts a direct influence on the performance of cognitive assessment tools, the choice of the cognitive battery to be used should always take this aspect into consideration. Moreover, the interpretation of the results of cognitive tests administered to older adults with a low level of schooling is questionable, as it is not possible to differentiate (especially in studies with a cross-sectional design) whether the poor performance is due to the low level of schooling or cognitive decline. Bento-Torres et al.[35] found a poorer cognitive performance among older adults with low schooling (1 to 7 years) compared to those with eight or more years of schooling. The older adults in this study did not have any previous or current history of traumatic brain/head trauma, stroke, language impairment, chronic alcoholism, neurological diseases, memory problems or depressive symptoms, and had normal scores on the MMSE.

Another important aspect is that most epidemiological studies use scales to evaluate the presence of depression or depressive symptoms. The gold standard for the diagnostic evaluation would be the use of a semi-structured clinical interview, as this strategy would diminish the possibility of diagnostic errors. For instance, the GDS, which is widely used, can have different cutoff points depending on clinical comorbidities,[36,37] and the presence of a symptom does not necessarily indicate that it can be attributed to depression. The GDS itself has an item directly related to memory impairment.[38]

The present study had limitations that should be considered, such as the absence of a measure for quantifying depression and the non-use of cognitive tests specific for respondents with low levels of schooling and for the evaluation of other domains, such as executive functions, attention, and processing speed.

Moreover, the occurrence of anxiety disorders in some of the participants may have exerted an influence on the results and should also be considered a limitation of this study.

On the basis of the present findings, the identification of cognitive impairment in older adults with depression and a low level of schooling may be more complex and it is essential for the assessment to be as thorough as possible, considering the characteristics of the population, the cognitive battery used and the instrument employed for the diagnosis of depression. Cognitive instruments that are able to detect subtle differences and that can be adjusted for low levels of schooling are preferable. In the evaluation of depression, the use of a structured or semi-structured clinical interview is ideal, preferably based on the criteria of the DSM. Moreover, the scarcity of studies addressing the impact of depression on the cognitive performance of older adults with low schooling underscores the need for further investigations with different methods.

In the present study, older adults with low schooling and with depression did not have a poorer performance in comparison to those without depression on cognitive tests evaluating general cognition, memory, language, executive functions, and attention. Future studies with different designs and methods as well as specific tests for older people with a low level of schooling could assist in the understanding of these relations and the mechanisms involved.

ACKNOWLEDGEMENTS

We thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP [State of São Paulo Research Assistance Foundation] for the financial support. We also thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES [Coordination for the Advancement of Higher Education Personnel]) for the master's grant to Ana Julia de Lima Bomfim.

Authors' contributions. AJLB: data curation, formal analysis, project administration and original draft. NMSC: data curation, formal analysis and original draft. LRL: data curation, formal analysis and original draft. RMPP: data curation, formal analysis and original draft. BLCF: formal analysis and original draft. MHNC: conceptualization, formal analysis, Methodology, supervision and original draft.

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Dement Neuropsychol 2021 March;15(1):128-135

Original Article

https://doi.org/10.1590/1980-57642021dn15-010014

Neuropsychiatric symptoms associated with family caregiver burden and depression

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ABSTRACT. Alzheimer's disease (AD) is a progressive and degenerative condition affecting several cognitive areas, with a decline in functional abilities and behavioral changes. **Objective:** To investigate the association between neuropsychiatric symptoms in older adults with AD and caregiver burden and depression. **Methods:** A total of 134 family caregivers of older people diagnosed with AD answered a questionnaire with sociodemographic data and questions concerning the care context, neuropsychiatric symptoms, caregiver burden, and depressive symptoms. **Results:** Results revealed that 95% of older adults had at least one neuropsychiatric symptom, with the most common being: apathy, anxiety, and depression. Among the 12 neuropsychiatric symptoms investigated, 10 were significantly associated with caregiver burden, while 8 showed significant correlations with depressive symptoms. **Conclusions:** Neuropsychiatric symptoms were related to caregiver burden and depressive symptoms. In addition to the older adult with AD, the caregiver should receive care and guidance from the health team to continue performing quality work.

Keywords: behavioral symptoms, Alzheimer's disease, depression, caregivers.

SINTOMAS NEUROPSIQUIÁTRICOS ASSOCIADOS À SOBRECARGA E DEPRESSÃO DO CUIDADOR FAMILIAR

RESUMO. A doença de Alzheimer (DA) é progressiva e degenerativa, afetando diversas áreas cognitivas com declínio nas habilidades funcionais e alterações comportamentais. **Objetivo:** Investigar a associação entre presença de sintomas neuropsiquiátricos apresentados por idosos com doença de Alzheimer e sobrecarga, e depressão dos cuidadores. **Métodos:** Um total de 134 cuidadores familiares de idosos com diagnóstico da doença de Alzheimer responderam a um questionário com dados sociodemográficos e questões referentes ao contexto de cuidado, sintomas neuropsiquiátricos, sobrecarga e depressão do cuidador. **Resultados:** Os resultados revelaram que 95% dos idosos apresentaram pelo menos um sintoma neuropsiquiátrico. A apatia, a ansiedade e a depressão foram os sintomas neuropsiquiátricos mais frequentes nos idosos. Dos 12 sintomas neuropsiquiátricos investigados, 10 associaram-se significativamente à sobrecarga do cuidador (exceto ansiedade e alteração alimentar), e oito sintomas neuropsiquiátricos apresentaram correlações significativas com os sintomas de depressão. **Conclusão:** A presença de determinados sintomas neuropsiquiátricos está relacionada com a sobrecarga e com sintomas de depressão apresentados pelos cuidadores. Além do idoso com doença de Alzheimer, o cuidador deve receber cuidados e orientação da equipe de saúde para que possa continuar desempenhando sua função com qualidade.

Palavras-chave: sintomas comportamentais, doença de Alzheimer, depressão, cuidadores.

INTRODUCTION

Alzheimer's disease (AD) is a progressive and degenerative brain condition that affects multiple cognitive areas and results in a decline in functional abilities and behavioral changes.[1] The literature widely recognizes that AD clinical manifestations are not limited to cognitive changes but also include neuropsychiatric symptoms (NPSs),[2] that is, a heterogeneous group of perceptual,

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Disclosure: The authors report no conflicts of interest.

Funding: Lais Lopes Delfino received financial support from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) — Process 02P-4588/2018.

Received on September 10, 2020. Accepted in final form on December 29, 2020.

thought, mood, personality, and behavioral disturbances.[3,4] The terms "neuropsychiatric symptoms" and "behavioral and psychological symptoms of dementia" are used interchangeably in the literature. According to population studies, more than 80% of AD patients develop behavioral and psychological symptoms at some point during the course of the disease.[3,5]

NPSs in patients with dementia are associated with worse prognosis, higher health care costs, greater impairment in daily functioning and quality of life, faster cognitive decline, early institutionalization, as well as increased mortality and caregiver burden.[6-8] Multiple factors contribute to the manifestation of NPSs, including aspects related to the person with dementia, the pathophysiological process of the disease, acute conditions, unmet needs, and pre-existing personality factors. Environmental conditions, caregiver-related factors, neglected needs, patient and caregiver personality, among other variables, can also lead to the manifestation of NPSs.[9] Stress and depression increase when a caregiver manages NPSs, and these symptoms can be triggered or exacerbated when a caregiver is stressed or depressed.[10]

The burden experienced by caregivers has many causes, such as the constant and increasing need to supervise the patient, the older adult's physical and cognitive dependence, the lack of support from other family members, family conflicts, financial difficulties, and social deprivation.[11,12] Researchers have shown that NPSs of an older adult affected by AD are some of the main determinants of caregiver burden.[11,13] NPSs are reported as more stressful for caregivers than cognitive and functional problems, perhaps due to the unstable nature of these symptoms. While the functional and cognitive trajectories of the patient with dementia follow a constant and expected decline, behavioral problems may fluctuate, which may leave the caregiver less prepared to deal with them properly. In addition, NPSs alter the patient's personality and may be more dramatic reminders of the major changes undergone by the patient and the loss experienced by the caregiver.[13,14]

The results of a Brazilian population study involving a sample of 10,853 individuals, including 205 caregivers, showed that caregivers of people with AD presented a substantially higher risk of depressive symptoms, major depressive disorder, anxiety, insomnia, hypertension, pain, and diabetes (all with $p<0.015$).[15] These negative outcomes require the development of new strategies for prevention, early detection, and interventions to deal with dementia caregiver burden.

Many studies that provided evidence of the association between NPSs and caregiver burden and depression investigated the variables globally; thus, the effect of each symptom on caregiver burden and depression needs to be further explored in the literature.[13,16] Our research hypothesized that NPSs are associated with caregiver burden and/or depressive symptoms. Knowledge of the impact that each NPS has on the caregiver's life contributes to identifying those at high risk of stress so that health services can be tailored to the needs of these patients, and admission to long-term care facilities can be delayed. This study aimed to investigate the relationship between each NPS presented by people with AD and the caregiver burden and depressive symptoms.

METHODS

Participants

The study protocol was approved by the Ethics Committee of the Universidade Estadual de Campinas (UNICAMP) (CAAE 47901615.5.0000.5404). The sample comprised 134 caregivers of patients with AD recruited from a geriatric clinic in Marília, São Paulo, Brazil, using a non-probabilistic convenience sample. All subjects provided written informed consent for participation in accordance with the study protocol.

The inclusion criteria were: being a primary caregiver, that is, providing daily care in routine activities for at least 4 hours a day, being the caregiver of an older adult diagnosed with AD, according to the criteria recommended by the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[17]

After the screening, all participants were assessed for the following exclusion criteria:

- caregivers of people with other diagnoses, such as cancer and psychiatric disorders (schizophrenia, bipolar disorder, obsessive-compulsive disorder, and others);
- caregivers of individuals with a score above the cut-off point on the Mini-Mental State Examination, based on the score suggested by Brucki et al.[18] (1 to 4 years of schooling: 22; 5 to 8 years: 24; over 9 years: 26);
- taking care of people living in nursing homes or those who are in a terminal stage according to medical evaluation.

Interview procedures

First, medical records of the individuals diagnosed with AD were checked to collect information about the caregivers and the results of the Mini-Mental State

Examination. Caregivers who met the criteria established in this study were contacted by telephone to schedule the interview. The interviews were conducted by a researcher trained to administer the selected instruments. The caregiver could not be accompanied by the patient during the interview, so the patient stayed in a waiting room, where they were monitored by the clinic staff. The duration of each interview ranged from 35 to 80 minutes. The mean interview length was 46 minutes.

Measures

A questionnaire with items about sociodemographic aspects (age, education, income, occupation) and the relationship between caregiver and dementia care recipients (family care, co-residence, care time) was administered to the caregivers.

The participants answered the Neuropsychiatric Inventory (NPI).[19] This questionnaire independently evaluates 12 behavioral domains (delusions, hallucinations, dysphoria/depression, anxiety, agitation/aggression, euphoria, disinhibition, irritability/emotional lability, apathy, aberrant motor activity, sleep and nighttime behavior change, and appetite and eating change). The caregiver initially responds to a screening question, and, in case of a positive result, the frequency and intensity of each item are evaluated. The total score for each domain is calculated by the equation frequency × severity. The total NPI score ranged from 0 to 144.

Furthermore, an additional scale, NPI Caregiver Distress (NPI-D), was developed and validated to provide a quantitative measure of the distress experienced by caregivers for each NPI symptom presented by the patient. Caregivers were asked to rate their emotional or psychological distress on a 6-point scale: 0 (not at all distressed), 1 (minimally distressed), 2 (mildly distressed), 3 (moderately distressed), 4 (severely distressed), and 5 (very severely or extremely distressed). The Brazilian versions of the NPI and NPI-D subscale were validated in 2008.[20]

Caregivers responded to Zarit Burden Interview (ZBI) to investigate burden.[21] This scale consists of 22 questions with answers ranging from zero (never) to four (nearly always), reflecting the perception of the caregiver as to health, personal and social life, financial situation, personal well-being, and interpersonal relationships. Its score ranges from 0 to 88 and reveals the level of caregiver burden — the higher the score, the greater the perceived burden. ZBI was validated in Brazil with a sample of caregivers of people with psychiatric illnesses by Scazufca.[21] In this study, the participants' total scores were divided into: 0–23 (low burden), 24–26 (moderate burden), and ≥27 (high burden).

Caregivers also answered the Beck Depression Inventory.[22] The original scale consists of 21 items, including symptoms and attitudes. The items refer to mood, pessimism, sense of failure, lack of satisfaction, guilt feelings, sense of punishment, self-dislike, self-accusation, suicidal wishes, crying, irritability, social withdrawal, indecisiveness, distortion of body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido. The score for each category ranges from zero to three, with zero meaning the absence of depressive symptoms and three representing the most intense ones. Thus, the minimum score is 0, the maximum is 63, and the sum of the scores of individual items provides a total score, which corresponds to the intensity of depression, classified as minimal, mild, moderate, or severe. The cut-off points adopted were those suggested by Kendall et al.:[23] scores up to 15 for the subgroup "without depression"; 16 to 20 for the subgroup "dysphoria or mild depression"; 21 to 29 for the subgroup "moderate depression"; and 30 or more for "severe depression".

Data analysis

The sample profile was described through frequency tables of categorical variables, with absolute (n) and percentage (%) values, and descriptive statistics of numerical variables, expressed as mean and standard deviation. Chi-square and Fisher's exact tests were used to compare the categorical variables. The Mann-Whitney test was adopted to compare the groups with and without NPSs, and the Spearman's rank correlation test was used to investigate the correlations between variables. The significance level set for the statistical tests was 5%, that is, $p<0.05$. The analyses were performed in Statistical Social for the Social Sciences (SPSS), version 22 (IBM SPSS Statistics).

RESULTS

Table 1 shows sociodemographic data, the frequency of caregiver burden and depressive symptoms, and the characteristics of people with AD. The results revealed a predominance of female caregivers, who co-reside with the family member, are the patient's adult children, present high burden, and do not have depressive symptoms. Most patients are women, use psychotropic medications, and have at least one NPS.

Figure 1 illustrates the frequency of patients with each NPS. Apathy, followed by anxiety, depression, and delusions were the most common symptoms among dementia care recipients and the more distressing, according to the caregiver (Table 2).

Table 1. Characterization of the sample of caregivers and people with Alzheimer's disease according to the variables investigated.

	Mean (SD) or frequency (%)
Caregiver	
Age	58.24 (12.6)
Gender (female)	107 (80)
Schooling (years)	14 (3.9)
Hours spent caring	
5 to 10 hours	64 (47)
11 to 15 hours	7 (5)
>16 hours	63 (47)
Lives with patient	
Yes	78 (58)
No	56 (42)
Work in the profession	
Yes	86 (64)
No	48 (36)
Income	
1 to 5 MW	16 (12)
3.5 to 5 MW	37 (28)
>5 MW	81 (60)
Relationship	
Son/daughter	86 (64)
Husband/wife	34 (25)
Brother/sister	5 (4)
Other relatives	9 (7)
Burden (ZBI total)	31.46 (10.3)
Burden (ZBI scores)	
≤23	36 (27)
24 to 26	17 (13)
≥27	81 (60)
Distress (NPI-D)	13 (9.07)
Depressive symptoms (BDI)	6.26 (5.98)
Depressive symptoms (BDI scores)	
0 to 15	122 (91)
16 to 20	7 (5)
21 to 29	5 (4)
Patient	
Age	80 (7.9)
Gender (female)	82 (61)
Schooling (years)	8 (5.7)
MMSE	18 (5.9)
Use of psychotropic medication	
Yes	120 (90)
No	14 (10)
Diagnosis time (years)	3.3 (3.7)
Neuropsychiatric symptoms (NPI)	
Yes	127 (95)
No	7 (5)

SD: standard deviation; MW: minimum wage; ZBI: Zarit Burden Interview; NPI-D: Neuropsychiatric Inventory Caregiver Distress Scale; BDI: Beck Depression Inventory; MMSE: Mini-Mental State Examination.

Significant differences were found between groups that presented or not each NPS (except anxiety and eating disorders) when compared to the burden scale scores. Regarding the Depression Inventory scores, the same group comparison demonstrated that only the mean scores of symptoms of anxiety, disinhibition, irritability, and eating change did not present statistically significant differences (Table 3). The results showed a greater burden and more depressive symptoms among caregivers in all NPSs investigated.

When analyzing the correlations between each NPS and the total burden and depression scores, the findings indicated that the studied variables are positively associated. Namely, the greater the presence of NPSs, the greater the burden and depression scores. Table 4 presents the statistically significant correlations.

DISCUSSION

This study investigated the relationship between each NPS in people with AD and caregiver burden and depression. The results showed a high prevalence of patients diagnosed with AD who had at least one NPS (95%). Apathy (53%), anxiety (49%), and depression (42%) were the most frequent symptoms and also the ones that caused greater distress for the caregiver, according to the NPI-D score.

Our findings on the frequency of people with dementia who presented NPSs are in agreement with studies elaborated in Brazil and other countries. Tiel et al.[24] investigated NPSs in a sample of older Brazilians diagnosed with AD and found that 90.8% of the sample had one or more symptoms, among which psychomotor agitation, aberrant motor behavior, and apathy were the most prevalent. In the population study conducted by Siafarikas et al.,[4] 91% of people with dementia presented at least one NPS, with the most frequent being agitation, apathy, and nocturnal behavior. A meta-analysis of studies on the prevalence of NPSs in AD patients, dating from 1964 to 2014, revealed that the most

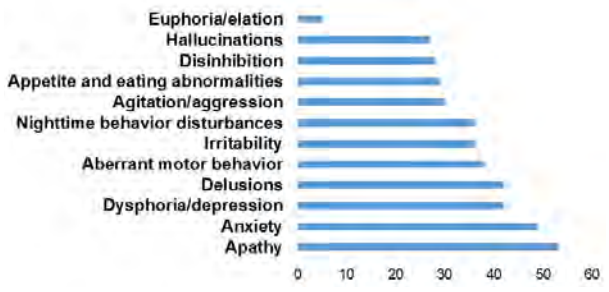

Figure 1. Frequency of patients with neuropsychiatric symptoms (%).

Table 2. Frequency of patients with neuropsychiatric manifestation and mean Neuropsychiatric Inventory score and distress reported by caregivers for each symptom.

	n (%)	Mean NPI (SD)	Mean distress (SD)
Apathy	71 (53)	3.40 (3.89)	1.61 (1.63)
Anxiety	65 (49)	2.76 (3.44)	1.40 (1.55)
Dysphoria/depression	57 (42)	2.12 (3.26)	1.21 (1.54)
Delusions	55 (42)	2.10 (3.26)	1.19 (1.56)
Aberrant motor behavior	51 (38)	2.87 (4.40)	1.13 (1.60)
Irritability	49 (36)	2.16 (3.38)	1.18 (1.66)
Nighttime behavior disturbances	49 (36)	2.64 (4.08)	1.12 (1.62)
Agitation/aggression	40 (30)	1.96 (3.64)	0.91 (1.53)
Appetite and eating change	39 (29)	2.20 (3.90)	0.93 (1.52)
Disinhibition	38 (28)	2.10 (3.79)	0.90 (1.49)
Hallucinations	37 (27)	1.37 (2.94)	0.79 (1.41)
Euphoria/elation	6 (5)	0.13 (0.88)	0.04 (0.36)

NPI: Neuropsychiatric Inventory; SD: standard deviation.

Table 3. Mean values and standard deviation of burden and depression for each neuropsychiatric symptom of the Neuropsychiatric Inventory.

		Burden (ZBI)			Depression (BDI)		
		Mean	SD	p-value	Mean	SD	p-value
Delusions	No	29.14	10.12	0.001	4.77	4.73	0.001
	Yes	34.78	9.9		8.4	6.91	
Hallucinations	No	29.63	9.91	<0.001	5.32	5.36	0.004
	Yes	36.24	10.16		8.73	6.84	
Agitation/aggression	No	29.04	9.27	<0.001	5.33	5.5	0.003
	Yes	37.13	10.73		8.45	6.53	
Dysphoria/depression	No	28.74	9.36	<0.001	4.96	5.05	0.004
	Yes	35.12	10.62		8.02	6.69	
Anxiety	No	30.74	9.42	0.558	6.12	6.26	0.496
	Yes	32.22	11.32		6.42	5.71	
Euphoria/elation	No	30.93	10.04	0.003	5.99	5.76	0.016
	Yes	48.5	5.97		15	7.07	
Apathy	No	28.89	10.66	0.004	4.98	5.88	0.004
	Yes	33.73	9.62		7.39	5.88	
Disinhibition	No	30.06	9.97	0.043	6.07	5.93	0.422
	Yes	34.97	10.67		6.74	6.16	
Irritability/lability	No	28.81	9.02	<0.001	5.74	5.76	0.174
	Yes	36.04	11.04		7.16	6.3	
Aberrant motor behavior	No	30.12	10.65	0.041	5.41	5.4	0.031
	Yes	33.63	9.62		7.65	6.64	
Nighttime behavior disturbances	No	29.4	9.79	0.003	5.48	5.84	0.01
	Yes	35.02	10.48		7.61	6.02	
Appetite and eating change	No	30.68	9.49	0.203	6.05	6.02	0.434
	Yes	33.33	12.19		6.77	5.91	

p-value for the Mann-Whitney test to compare values between the two groups (those who presented and did not present each NPS). ZBI: Zarit Burden Interview; BDI: Beck Depression Inventory; SD: standard deviation; NPS: neuropsychiatric symptom.

Table 4. Correlations between neuropsychiatric symptoms of people with Alzheimer's disease and caregiver burden and depression.

	Burden (ZBI)		Depression (BDI)	
	r	p-value	r	p-value
Delusions	0.32	0.000	0.28	0.001
Hallucinations	0.31	0.000	0.23	0.008
Agitation/aggression	0.37	<0.0001	0.25	0.003
Dysphoria/depression	0.35	<0.0001	0.22	0.010
Anxiety	0.12	0.231	0.05	0.593
Euphoria/elation	0.26	0.003	0.21	0.016
Apathy	0.23	0.008	0.18	0.04
Disinhibition	0.21	0.016	0.09	0.304
Irritability	0.33	0.000	0.12	0.167
Aberrant motor behavior	0.17	0.048	0.17	0.054
Nighttime behavior disturbances	0.24	0.005	0.23	0.008
Appetite and eating change	0.11	0.211	0.06	0.459
NPSs (total)	0.44	<0.0001	0.32	0.000

ZBI: Zarit Burden Interview; BDI: Beck Depression Inventory; r: Spearman's rank correlation coefficient; NPSs: neuropsychiatric symptoms.

frequent NPS was apathy, with an overall prevalence of 49%, followed by depression, aggression, anxiety, and sleep disorder. The least common NPS was euphoria, with a total prevalence of 7%.[25] Data from studies on the most common NPS manifestation in AD present discrepancies. However, apathy appears to be one of the most frequent NPSs in people with AD.[5]

Apathy comprises a spectrum of symptoms that includes lack of initiative, interest, motivation, energy, and enthusiasm to start some activity compared to the previous level of functioning of the patient and that is in disagreement with their age or culture.[26] According to Sherman et al.,[27] apathetic patients require more support, management, and resource utilization, therefore, generating high levels of attrition for caregivers. The distress of the caregiver of a patient with apathy can also be explained by the greater disability that this NPS imposes on the patients and by the feeling of frustration in the caregivers. The lack of motivation and interest in performing activities compromise the rehabilitation of these patients.[28] Anxiety and depression were also the NPSs that increased distress, as reported by caregivers. In the study by Liu et al.,[26] patient depression was highly associated with caregiver burden.

Our data revealed that most caregivers of dementia care recipients (60%) participating in this study presented high burden. The mean ZBI score was 31.47, similar to that found in other studies.[6,29] This result has been discussed in the national and international literature. Caregivers of AD patients suffer more than those of physically frail older people, given the specific symptoms experienced by dementia patients, such as behavioral problems, disorientation, personality change, need for continuous supervision, as well as the caregiver isolation due to the patient's behavioral problems and the progressive deterioration of the patient's condition, which reduces or eliminates a long-term prospect of improvement, contributing to increased caregiver burden.[30]

Caregivers also feel more burdened when they have to deal with NPSs. This fact was confirmed by the data correlations between mean burden scores and NPSs, which revealed that the higher the caregiver burden, the greater the number of NPSs in dementia care recipients. These results corroborate other studies that identified a positive association between burden and NPSs.[6,30]

Only anxiety and appetite change were not significantly associated with burden. Although anxiety was one of the symptoms considered to be more stressful by the caregiver, the comparison test between groups with and without NPSs and the correlation test showed that anxiety was not significantly related to burden. This finding indicates that caregiver burden does not necessarily depend on the frequency or severity of the NPS presented. Similar results were reported by Huang et al.[31]

Concerning appetite change, a systematic review conducted by Terum et al.[23] showed that this symptom

had the weakest statistical association with caregiver burden. In this review, irritability, followed by agitation/aggression, delusions, and apathy were the symptoms that contributed to a greater caregiver burden.

A study of 881 caregivers aiming to investigate the factors associated with caregiver burden according to different degrees of cognitive impairment in AD patients revealed that aggressiveness, agitation, aberrant motor behavior, apathy, and sleep disorders were strongly associated with caregiver burden in the early and moderate stages of AD.[8]

Aggression can be the sole determinant of greater caregiver burden and early institutionalization.[32] Aberrant motor behavior and nighttime change can increase the burden because patients need attention and constant supervision, which, in turn, can cause a more stressful situation for caregivers. Patients who experience changes in the sleep-wake cycle may have more NPSs, such as agitation, irritability, and apathy, resulting in high levels of caregiver burden.[8]

In this study, caregivers presented a low score of depressive symptoms evaluated by the Beck Depression Inventory. This result contrasts with data from other surveys, in which symptoms of depression are common in caregivers of patients with AD.[26] One possible explanation is that most caregivers in this study are the patient's adult children (64%). According to a meta-analysis performed by Pinquart and Sorensen,[33] adult children caregivers have lower levels of depressive symptoms than spouse caregivers. Adult children caregivers report fewer health problems and spend less time on care tasks compared to spouse caregivers. Although caregivers did not present high scores of depressive symptoms, when investigating depression in the presence of each NPS, the mean depression score increased for all NPSs investigated.-

A systematic review of articles published between 1980 and 2015 investigated the role of individual NPSs as to their impact on different measures of the family caregiver well-being, revealing that depressive behaviors were the most distressing for them, followed by agitation/aggression and apathy.[16] In another systematic review, patient depression was the symptom most often associated with caregiver depression. The three most commonly reported impactful symptoms were: patient depression affecting caregivers in 40% of studies, aggression in 50%, and sleep disturbances in 43%.[34]

Offering support to caregivers in coping and managing NPSs of older adults with AD is crucial. In Brazil, the great difficulty in recognizing symptoms as part of a dementia process is well known. Many still consider NPSs a result of the aging process and lack information on how to deal with the patient's dysfunctional behavior. Therefore, before providing information to those involved, the relationship between the caregiver and the older person with dementia must be understood from the caregiver's behavioral and emotional point of view. Certainly, it is possible to offer tools for the caregiver, with resources that impact the quality of life of both those who receive and provide care.

Many AD patients (95%) had at least one NPS. The caregivers of this sample had high levels of burden and low depression scores. Due to the high rate of caregiver burden and the strong association with NPSs, health professionals, especially physicians and gerontologists, should pay close attention to the burden of caregivers of people with AD. The results of this study represent an important reference material for clinicians to manage NPSs hierarchically. Agitation, depression, and delusions were the three main symptoms significantly associated with depression and caregiver burden. Therefore, the successful management of these symptoms is clinically important, especially to reduce caregiver depression and burden.

This study contributes to understanding some caregivers' characteristics associated with AD patients, such as knowledge, and can be useful in individualizing educational objectives for caregivers. These caregivers' behavioral and emotional characteristics should be considered primary endpoints in the overall care of AD patients.

Authors' contributions. LLD: conceptualization, investigation, data curation, formal analysis, writing — original draft, writing — review & editing. RSK: conceptualization, writing — review & editing. CK: investigation. ALN: conceptualization, writing — review & editing. MC: conceptualization, writing — review & editing.

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Dement Neuropsychol 2021 March;15(1):136-144

Original Article

https://doi.org/10.1590/1980-57642021dn15-010015

Effects of language stimulation on cognition of institutionalized aged people

A preliminary case series study

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ABSTRACT. Cognitive stimulation programs for institutionalized elderly people show positive results, however few studies have investigated the effectiveness of language stimulation programs for the health of this population. **Objectives:** To characterize the cognitive-linguistic profile of institutionalized elderly and to compare their performance before and after a language stimulation program (LSP). **Methods:** An exploratory case series study was conducted with nine residents of a Home for the Aged. Elderly people aged 60 or over, of both sexes, without neurological or neuropsychiatric diseases, communication disorders, intellectual impairment or severe visual or hearing impairment were included. The participants were submitted to an initial assessment through the Montreal Cognitive Assessment (MoCA) and Montreal Toulouse Battery Language Assessment – Brazil to characterize the cognitive-linguistic profile of the studied group. Five elderly were selected to participate in the LSP, of wich only two participated effectively in the program, but all were reassessed after the program was completed. **Results:** on the initial assessment, of the nine participants, only one had adequate cognitive performance and all presented changes in macro and/or microlinguistics aspects of oral discourse, with oral comprehension preserved. On the reassessment carried out with five participants, only two participants who adhered effectively to the program obtained improvements in MoCa scores. In regarding language, three participants performed better in the oral emission measures. The performance of the participants in oral comprehension remained or declined. **Conclusion:** The speech-language therapy intervention through a LSP contributes to improving the cognitive-linguistic performance of institutionalized elderly.

Keywords: language, cognition, homes for the aged, language therapy, treatment outcome.

EFEITOS DA ESTIMULAÇÃO DA LINGUAGEM NA COGNIÇÃO DE IDOSOS INSTITUCIONALIZADOS: ESTUDO DE SÉRIE DE CASOS PRELIMINAR

RESUMO. Programas de estimulação cognitiva voltados para idosos institucionalizados mostram resultados positivos, contudo poucos estudos investigaram a eficácia de programas de estimulação da linguagem para a saúde dessa população. **Objetivos:** Caracterizar o perfil cognitivo-linguístico de idosos institucionalizados e comparar o desempenho antes e após um programa de estimulação de linguagem (PEL). **Métodos:** Foi realizado um estudo exploratório do tipo série de casos, com nove residentes de instituição de longa permanência para idosos (ILPI). Incluíram-se idosos com 60 anos ou mais, de ambos os sexos, sem doenças neurológicas ou neuropsiquiátricas, distúrbios da comunicação, deficiência intelectual, ou deficiência visual ou auditiva grave. Os participantes foram submetidos a uma avaliação inicial, com a Montreal Cognitive Assessment (MoCa) e a Bateria Montreal Toulouse de Avaliação da Linguagem – Brasil, para caracterizar o perfil linguístico-cognitivo do grupo estudado. Foram selecionados cinco idosos para participar do PEL, dentre os quais apenas dois participaram efetivamente do programa, porém todos foram reavaliados imediatamente após a finalização do programa. **Resultados:** Na avaliação inicial, dos nove participantes, apenas um participante apresentou desempenho cognitivo adequado, e todos apresentam alteração de aspectos macro e/ou microlinguísticos do discurso oral, com compreensão preservada. Na reavaliação realizada com cinco participantes, apenas os dois que aderiram efetivamente ao programa obtiveram melhoras no escores do MoCa. Em relação à linguagem, três participantes apresentaram melhor desempenho em emissão oral. O desempenho dos participantes em compreensão oral manteve-se ou declinou. **Conclusão:** A intervenção fonoaudiológica por meio de um PEL contribui para a melhora do desempenho cognitivo de idosos institucionalizados.

Palavras-chave: linguagem, cognição, instituição de longa permanência para idosos, terapia da linguagem, resultado do tratamento.

This study was conducted at the Universidade Federal Fluminense, Instituto de Saúde de Nova Friburgo, Departamento de Formação Específica em Fonoaudiologia, Nova Friburgo, RJ, Brazil.

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Funding: Programa Institucional de Bolsas de Iniciação Científica (PIBIC), Process n. IC190495.

Disclosure: The authors report no conflict of interests.

Received on April 25, 2020. Accepted in its final form on December 02, 2020

INTRODUCTION

In the year 2050, the aged population in Brazil will be some 3.7 times greater than in 2000, standing at around 49 million.[1] This rise is due, among other factors, to the increased survival of the older population, as a result of improvements in health care for this group.[2] Thus, the need for greater vigilance among this age group is clear, given the many challenges in providing this rapidly growing population with the chance of a healthy active old age.[3] One of these challenges is the burden families face in caring for older people in their own homes,[4] leading to an increased demand for homes for the aged.

Institutionalization can lead to limitations in the social functioning of elderly residents who, in most cases, cease to perform their usual daily tasks due to the dynamics of the facility, causing loss of autonomy and independence.[5] Preserving cognition in institutionalized aged individuals is paramount to ensure that residents can carry out their activities and maintain the ability to perform self-care.[6] Another factor which should be taken into account is communication, since this function can be impaired due to cognitive decline,[7] with repercussions on social participation and individual behavior.[8] Therefore, communication must not be overlooked during assessment and follow-up of institutionalized elderly.

Acquired language disorders, such as aphasias and linguistic-cognitive disorders, are common in this population, resulting from strokes and dementia. Language skills in these cases may be more compromised when aged people are institutionalized.[9] Therefore, the early stimulation of these skills is indicated for the maintenance of social interactions and the quality of life of these elderly.[8]

The benefits promoted by cognitive stimulation programs for elderly residents of homes for the aged has already been described in a national study.[9] In this study, the cognitive stimulation promoted benefits among institutionalized elderly, despite the low educational level of the group and the limitations in intervention accessibility and performance.[10]

Regarding language abilities, few studies have investigated the effectiveness of language stimulation programs for the health of this population.[11-13] Favorable results for greater social interaction were pointed in a qualitative study with 10 neurologically healthy aged people, exposed to linguistic-discursive activities in 16 group meetings held at a home for the aged.[11] Positive effects of interventions implemented were also observed in two single-case studies of aged people with dementia residing at a home for the aged.[12,13] However, the associations between language and cognitive skills were not investigated in these studies.

The present study sought to contribute with new evidence by investigating the effects of language stimulation on the cognition of institutionalized aged people. Therefore, this study aimed to characterize the cognitive-linguistic profile of the institutionalized aged and to compare performance before and after a Language Stimulation Program (LSP).

METHODS

An exploratory case series study approved by the Research Ethics Committee of the lead institution (permit No. 3.281.461) was conducted. The study involved aged residents of a home for the aged housing 66 individuals, located in a city of Rio de Janeiro State. All participants and/or their legal guardians consented and/or agreed to take part in the study, conducted in 2019.

From this population, a sample of 11 participants was recruited, aged 60 years old or older, of both genders, with no history of neurological or neuropsychiatric disease and/or no current or previous diagnosis of communication disorders. The remaining residents were excluded for presenting neuropsychiatric conditions, including moderate or severe dementia, or intellectual disability, blindness, or non-corrected poor vision and/or deafness, which precluded standard assessment of cognition and/or language. Of the 11 residents who met the inclusion criteria, 9 agreed to take part in the study and underwent the initial assessment to characterize cognitive-linguistic profile.

The second stage involved the selection of participants for inclusion in the LSP. They were selected from the 9 participants in the first stage of the research, in which the linguistic-cognitive profile of the group was investigated. For eligibility, participants' performance had to lie within the normal range in one of the language subtests applied. After appliying the initial assessment, a sample of 6 individuals was included based on performance, although 1 resident subsequently died. None of the participants met the diagnostic criteria for neurogenic language disorders. Thus, a total of 5 aged individuals completed the final assessment, entailing application of the same instruments used in the first assessment. However, only 2 participants actually joined the program, often with sessions above 90%. Data on the other participants who did not join, that is, who participated in some sessions or none of them, were analyzed for comparison purposes.

Participants were assessed pre and post-LSP by applying two instruments, validated and standardized for use in aged Brazilian Portuguese speakers, namely: the Montreal Cognitive Assessment (MoCa), a screening test to differentiate patients with mild cognitive impairment (MCI) from aged people with normal cognitive aging,[14] and the Montreal Toulouse Language Assessment Battery – Brazil (MTL-BR), used for screening for language disorders.[15] In the present study, the MTL-BR subtests Oral narrative discourse and Oral text comprehension were used to analyze participants' expressive and receptive language aspects, respectively.

Each brief evaluation (assessment or reassessment) was performed through one or two weekly sessions lasting up to 60 minutes each, conducted at the home for the aged. At each assessment, the MoCa was applied followed by the subtests of the MTL-BR Battery, as per standardized instructions, and answers were scored using criteria based on normative data for each test.[14,15]

The LSP is designed to promote the communication of institutionalized aged people, thereby improving their cognitive status and helping them maintain cognitive and linguistic abilities. The program was implemented in groups for 11 weeks, entailing 13 intervention sessions of 50 minutes each, whose therapeutic goals were: to optimize communicative practices among residents; and optimize both expressive and receptive aspects of spoken language. An overview of the program is presented in Chart 1, including specific goals and therapeutic strategies covered in each session.

Performance of the participants in the LSP was recorded at each session by making individualized notes and audio and/or video recordings, when applicable, to observe aspects related to auditory comprehension and oral expression of each participant during the group sessions. In addition, clinical evolution of participants from initial assessment to reassessment was tracked by collecting data from medical records. The following data were collected: medications administered, exams performed, behavior, health status and family assistance, encompassing aspects which might influence the results of this study.

Statistical analysis:

In view of the exploratory nature of the present study and the sample size, the data obtained were analyzed using descriptive statistics, including analysis of the distribution of relative frequency for categorical variables, and median, minimum, and maximum values for continuous variables. The independent variable analyzed was the adherence to the program. Dependent variables were: the total score on the MoCA test and the measures in the language subtests (number os words, number of information units (IU), number of scenes and score on the oral comprehension test). Pre- and post-LSP results were compared by calculating the difference between the scores attained at the two assessments, with results plotted in line graphics and bar charts.

RESULTS

At the time of recruiting participants for the study, only 16.7% of the aged residents of homes for the aged had no diagnosed neuropsychiatric diseases or visual and/or hearing loss in their medical charts. Of the sample of 9 participants who agreed to take part in the study, most were male (66.6%) and age ranged from 64 to 93 years (median=1 years). Regarding educational level, 88.9% had ≤8 years of formal schooling. Time institutionalized ranged from 7 to 144 months.

On the initial assessment, MoCA scores ranged from 10 to 27 (median=16). Only one participant had a score within the normal expected range (≥26). Regarding linguistic performance, in the oral expression subtest of the MTL-BR Battery (Oral narrative discourse), participants produced discourse of 7 to 144 words (median=53) and only one participant a score below normal for this measure.[15] Median scores in the other measures of this subtest were: 2 points for IU, range 0–8 points, and 0 points for scene elements (minimum: 0; maximum: 3), suggesting impairment of micro/macrolinguistic aspects of oral discourse.[15] Only 33.3% of the group produced coherent and cohesive narratives. In the auditory comprehension subtest of the MTL-BR Battery (oral text comprehension), participants scored 2–8 points, median of 5 points and, thus, performance was within normal parameters.[15] However, the performance of 3 participants was below normal. Results of these assessments by participants in each MoCa task or MTL-BR subtest item are given in Table 1.

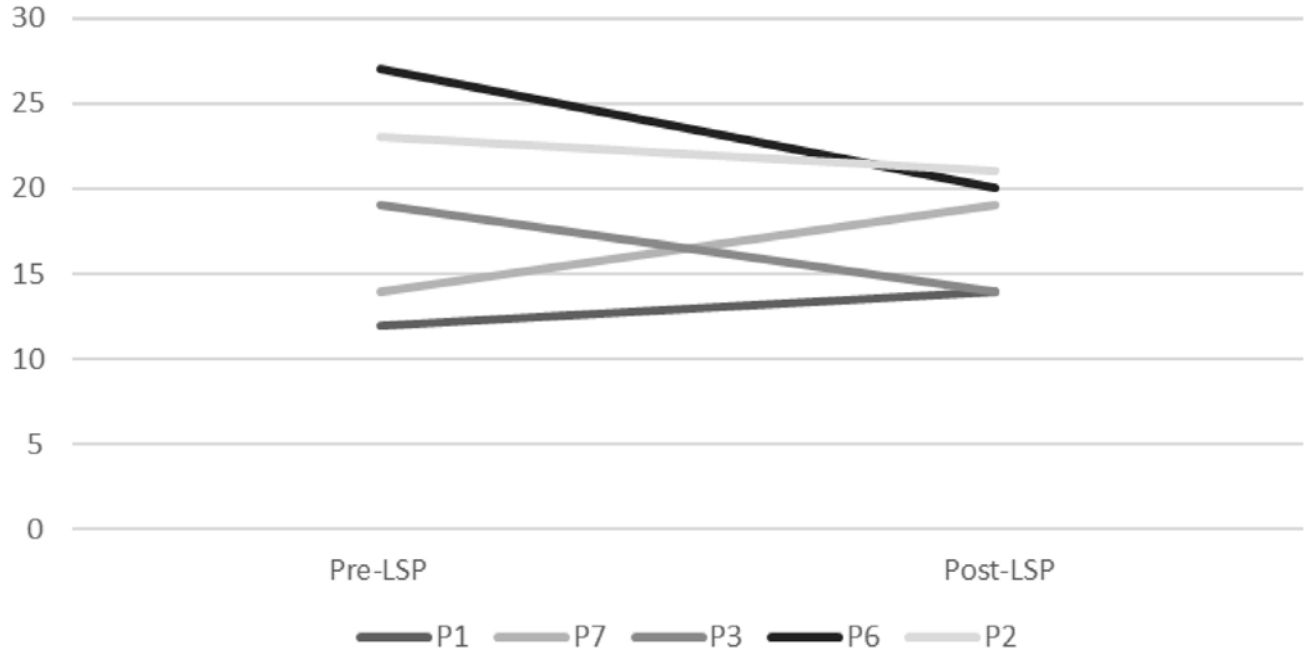
Sociodemographic data of the 5 participants who participated in the LSP and completed the final assessment are presented in Chart 2. They had different levels of intervention adherence, from 92 to 0% of attendance to the LSP sessions (Chart 2). Thus, they were grouped into: subgroup 1 (P1 and P7), which effectively joined the program; subgroup 2 (P3 and P6), which participated in less than 1/3 of the sessions; and subgroup 3, composed only of P2, who did not participate in the program.

Total MoCa scores for each participant in the initial assessment and reassessment are depicted in Figure 1. Results show that the scores of participants in subgroup 1 improved in the reassessment. Participants' performance in the MoCa test for each task, together with the

Table 1. Cognitive and linguistic performance of institutionalized elderly.

Tests	Scores of participant								
	P1	P2	P3+	P4+	P5	P6§	P7	P8	P9
MoCa									
Executive functions (1/5)	0	0	0	0	0	4	0	0	0
Naming (4/3)	3	4	3	4	2	3	3	2	4
Memory/ delayed recall (5/5)	1	0	0	0	0	3	2	1	0
Attention (3/3)	0	3	1	0	0	3	1	1	0
Language/ fluency (2/3)	0	1	1	1	1	2	1	0	1
Abstraction (3/2)	2	2	1	1	1	2	1	2	1
Orientation (6/6)	4	6	6	6	4	6	5	4	4
Calculation (3/3)	1	3	3	2	1	3	0	0	3
Visual perception (3/0)	0	3	3	1	0	---	0	0	2
Extra point (schooling)	1	1	1	1	1	1	1	1	1
Total score (30)	12	23	19	16	10	27*	14	11	16
MTL-Oral narrative									
Number of words	17*	93*	100*	37*	53*	144*	21*	7	55*
Information units (10)	1	6*	4*	1	1	8*	2	0	2
Scenes (3)	0	2*	2*	0	0	3*	0	0	0
Cohesion (1)	1	1	1	1	0	1	0	0	0
Coherence (1)	0	1	1	0	0	1	1	0	0
MTL-Oral text comprehension									
Total (9)	7*	5*	7*	6*	2	8*	5*	3	2

MoCa: Montreal Cognitive Assessment; MTL: Montreal Toulouse Language Battery; *Performance above the cut-off score; +elderly people aged 80 years or older; §scores vary due to applied version.



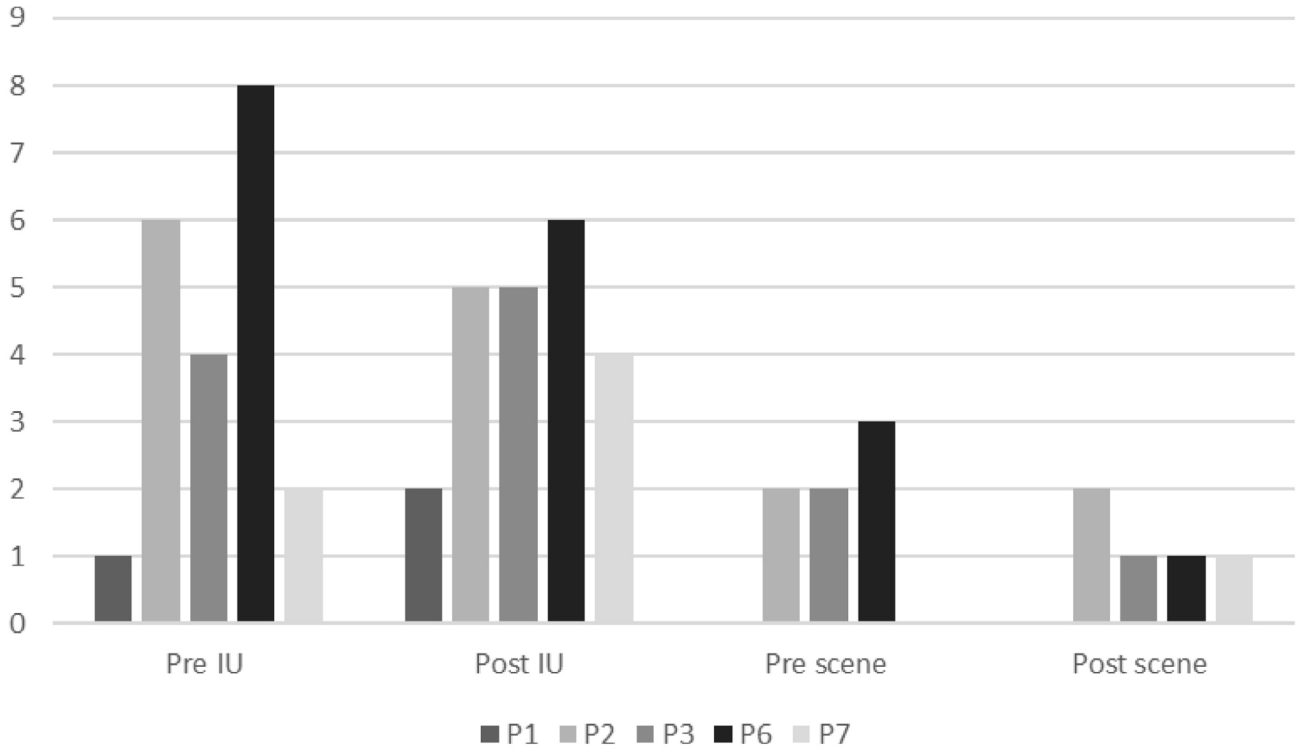
LSP: Pre Language Stimulation Program.

Figure 1. Performance in the Montreal Cognitive Assessment test on assessment and reassessment.

difference between assessment and reassessment, are given in Table 2.

Participants' performance for the measures of oral expression (IU and scenes) of the MTL-BR Battery in the two assessments is depicted in Figure 2. Results show that 3 participants improved IU scores (subgroups 1 and 2), whereas only 1 improved scores in the MTL scenes (subgroup 1).

The total scores for the oral text comprehension test at assessment and reassessment were compared (Figure 3). Performance in oral text comprehension



IU: information units.

Figure 2. Performance in the Oral narrative subtest of the Montreal Toulouse Language Battery on assessment and reassessment.

Table 2. Performance in the Montreal Cognitive Assessment test tasks for assessment and reassessment.

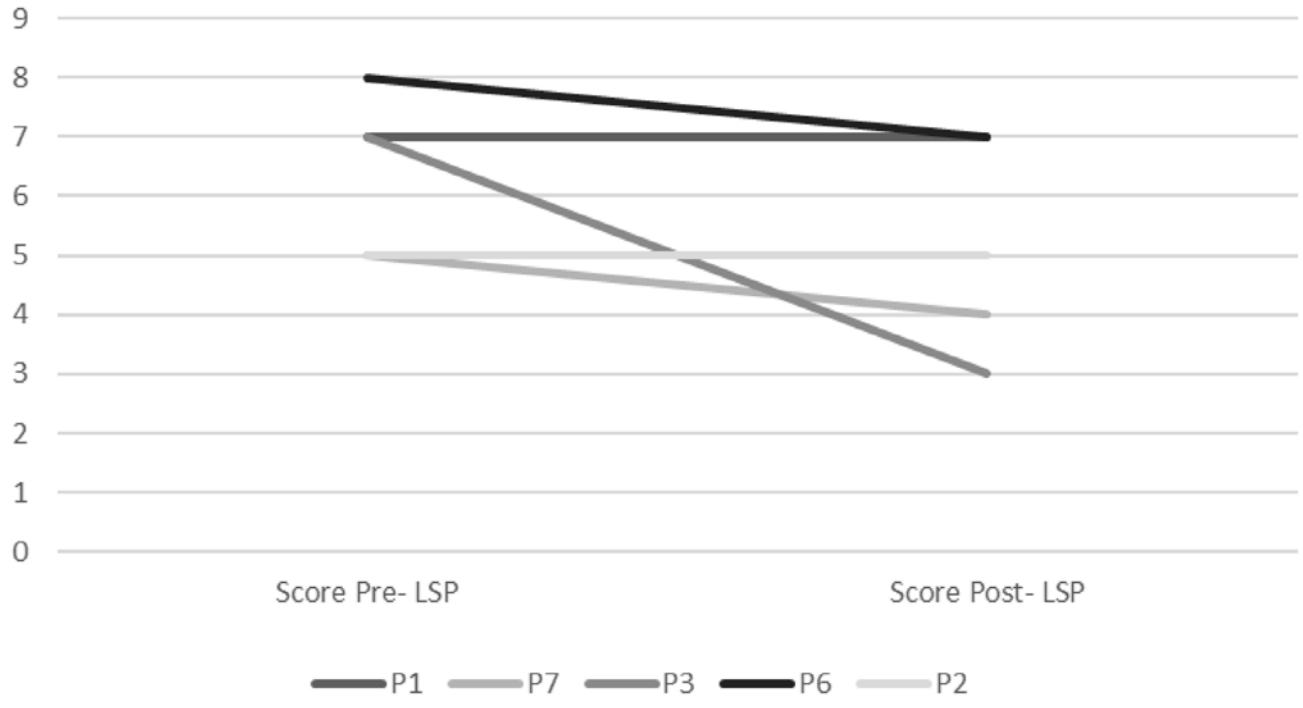
MoCa tasks	Performance														
	P1			P7			P3+			P6§			P2		
	Asǁ	Re¶	Dif**	As	Re	Dif	As	Re	Dif	As	Re	Dif	As	Re	Dif
Executive functions (1/5)	0	0	0	0	0	0	0	0	0	4	4	0	0	0	0
Naming (4/3)	3	4	-1	3	3	0	3	4	-1	3	3	0	4	4	0
Memory/delayed recall (5/5)	1	0	1	2	2	0	0	0	0	3	2	1	0	1	-1
Attention (3/3)	0	0	0	1	3	-2	1	0	1	3	3	0	3	2	1
Language/fluency (2/3)	0	0	0	1	1	0	1	0	1	2	1	1	1	1	0
Abstraction (3/2)	2	2	0	1	2	-1	1	1	0	2	0	2	2	1	1
Orientation (6/6)	4	5	-1	5	4	1	6	4	2	6	5	1	6	6	0
Calculation (3/3)	1	2	-1	0	1	-1	3	3	0	3	1	2	3	3	0
Visual perception (3/0)	0	0	0	0	2	-2	3	2	1	---	---	0	3	3	0
Total	12	14	-2	14	19	-5	19	15	4	27*	20	7	23	22	1

MoCa: Montreal Cognitive Assessment; *Performance above the cut-off score; +elderly people aged 80 years; §sores vary due to applied version; ǁassessment; ¶reassessment, **difference.

either declined (subgroups 1 and 2) or remained stable (subgroups 1 and 3) for all participants.

The scores of the participants in the oral narrative discourse and in oral text comprehension for the MTL-BR Battery subtests at assessment and reassessment, along with the difference between them for each measure, are given in Table 3.

A summary of the most relevant findings for participants' clinical progression between assessment and reassessment by subgroup is given in Chart 3.



LSP: language stimulation program.

Figure 3. Performance of the participants in the Oral text comprehension of the Montreal Toulouse Language Battery on the assessment and reassessment.

Table 3. Performance on the Montreal Toulouse Language Assessment-Brazil Battery subtests for assessment and reassessment.

MTL-Brazil subtests	Performance														
	P1			P7			P3			P6			P2		
	As+	Re§	Difll	As	Re	Dif	As	Re	Dif	As	Re	Dif	As	Re	Dif
Oral narrative															
Number of words	17*	45*	-28	21*	37*	-16	100*	102*	-2	144*	47*	-97	93*	99*	-6
Information units	1	2	-1	2	4*	-2	4*	5*	-1	8*	6*	2	6*	5*	1
Scenes	0	0	0	0	1*	-1	2*	1*	1	3*	1*	1	2*	2*	0
Cohesion	1	1	0	0	0	0	1	1	0	1	1	0	1	1	0
Coherence	0	0	0	1	1	0	1	1	0	1	1	0	1	1	0
Oral text comprehension															
Total	7*	7*	0	5*	4*	1	7*	3	4	8*	7*	1	5*	5*	0

MTL: Montreal Toulouse Language Battery; *Performance above the cut-off score; +assessment; §reassessment; ||difference.

DISCUSSION

Most of the participants who underwent the initial assessment through MoCa performed less than expected (88.9%), despite having no neuropsychiatric diagnosis recorded in their medical charts. The results of a previous Brazilian study assessing the performance of community-dwelling older adults revealed conditions related to probable cognitive decline/dementia in 26% of the studied sample (n=99),[16] suggesting that the number of aged individuals with these impairments in homes for the aged could be considerable. According to Mello et al.,[17] institutionalization is a factor that can contribute to a decline in cognitive performance of aged residents. In their study, 39.3% of participants presented cognitive impairment.[17]

The current analysis of individual performance of each participant (Table 1) revealed that everyone committed errors involving more than one cognitive ability. Performance in tasks involving executive functions, delayed recall/memory, attention, and visuoperceptual ability was affected in a greater number of residents (4–8 participants), all of whom scored zero. Regarding the language/fluency and abstraction tasks, over 50% of participants scored half the total or less, indicating a higher rate of impairment of these abilities.

For the group's language performance, this ability was more preserved than cognitive performance. Of the language measures used, the group's performance was within the expected range in the oral text comprehension subtest, but lower for the oral expression of the discourse. In cases of MCI, there is a pattern of linguistic impairment involving more specifically the semantic level and emissive tasks, such as naming, verbal fluency and processing at the discursive level.[18] A total of 33.3% of participants had normal performance in the oral expression and comprehension measures (Table 1).

Comparison of scores on the MoCa for the initial assessment and the reassessment (Figure 1), showed that the LSP promoted improvement in overall cognitive performance, as measured by the total test score. Only participants of subgroup 1 (P1 and P7) who fully adhered to the program had higher scores in the reassessment. As shown in Table 2, P1 improved in naming, orientation, and calculation tasks, but worsened in memory ones; whereas P7 improved performance in attention, abstraction, calculation, and visuospatial tasks, but declined in the orientation task. Tasks whose performance varied between assessments were not common in these two cases, except for the improvement in the calculation task, whose relationship with language skills is quite specific.[19] Considering that a cognitive screening test was used, it is not possible to analyze the possible impact of linguistic stimulation on specific cognitive skills. Future research using cognitive assessment batteries may contribute to a better understanding of these possible associations.

Participants of subgroups 2 (P3 and P6) and 3 (P2) showed no improvement in the total score on reassessment. Participant P6, whose performance was normal in the initial assessment, had below average performance in reassessment. With regard to subgroup 2, clinical deterioration occurred during the course of the study, which may have contributed to the performance decline seen in these participants during reassessment, such as behavioral disorders and medication use (Chart 3).[20] The performance of participant P2 in the MoCa also worsened, albeit to a lesser extent. Although this individual had no relevant clinical complications in the period, the subject displayed social engagement constraints, with limited social interaction practices, refusing to take part in activities at the home. Social isolation and institutionalization are risk factors for the development of cognitive dysfunctions and, therefore, the lower scores might be partially explained by these aspects. Thus, it is vital that professionals working in these environments devise strategies to enable communication and help users to better adapt to the changes brought about by institutionalization.[11,21]

The results of this preliminary study suggest that group language stimulation may help improve cognitive abilities in institutionalized aged people with impaired cognition and oral expression, exemplified by the cases analyzed. In the neurolinguistics field, human interactions and language are regarded by many scholars as a fundamental factor for the development of cognition.[8,11,22]

With regard to the possible effects of LSP on the linguistic performance of the participants, for oral expression abilities (Figure 2), IU scores increased in the two members of subgroup 1 (P1 and P7) and also in P3 from subgroup 2, but decreased in the other cases. Resident P7 attained the cut-off score for this measure, indicating no impairment in this aspect of the discourse after intervention. The declines seen in the other cases did not translate into impairment of this ability, *i.e.*, their scores remained within normal limits on reassessment. Participant P3, whose involvement in the program was greater than that of P6, showed improvement in this task, indicating that a minimum number of sessions is required to yield positive results for oral discourse under the program. Case studies with institutionalized aged people with dementia indicated an improvement in lexical skills in the oral discourse after individualized LSP.[12,13]

The performance of users in terms of number of scenes revealed that the only participant who improved in the macrolinguistic aspect was part of subgroup 1, *i.e.*, who adhered to the treatment (P7), whereas participant P1 did not improve in this parameter. Although the other participants failed to show performance improvements, their scores remained within normal limits, with no clinically relevant impairments detected. Additionally, no qualitative differences in discourse cohesion or coherence between the two assessments were observed. In the study by Marquete, with an institutionalized elderly woman with dementia, there was no change in this measure after the proposed LSP using the same test. However, when the evaluation took place through oral narrative discourse, based on a sequence of scenes, an improvement was observed in the production of macropropositions.[12] Such evaluation strategies seem to be more sensitive according to the review carried out on language changes in MCI and dementia.[18]

For oral discourse comprehension, none of the participants exhibited improvements. However, performance remained within parameters of normality for this measure in reassessment, confirming no clinical decline in this ability among participants, except for P3 from subgroup 2, whose overall clinical status declined over the study period (Chart 3). In LSP applied to an institutionalized aged person with dementia mentioned above,[12] who showed impaired oral comprehension, an improved performance was observed.

In terms of the LSP implementation, although designed as a group intervention, strategies were adapted to the specificities of each participant, such as pre-intervention cognitive profile, where this may have influenced the results of the subgroup which fully adhered to the program. Mapping the cognitive profile of the aged allows targeted treatment plans for personalized care, promoting strategies that produce greater satisfaction for residents of homes for the aged.[23] Speech and language therapists, given their focus on communication, are best placed to implement therapeutic strategies that stimulate oral discourse abilities and communication exchange of residents with team members, relatives, and friends, creating a care environment that favors the cognitive health of these elderly. Such health promotion pratices contribute to the engagement of the aged in richer communicative interactions with their interlocutors and can contribute to the reduction of linguistic isolation and its consequences, including the cognition of this group.[24] Additionally, this professional can contribute to the identification of changes in language skills in individuals at risk for MCI.[7]

The present study has several limitations. A limitation was the small sample size, due to the high level of morbidity found in the home for the aged, precluding the inclusion of many potential participants. Therefore, the therapeutic treatment plans of this study should be adapted to the situation of residents of each institution, determining which care practices meet their health needs, including end-of-life care. Another limitation involved the study type, preventing conclusions about the effectiveness of the program. The inclusion of more outcome measures related to language and cognition would also be necessary to assess the effects of the program. Further studies with an emphasis on clinical effectiveness should be conducted in the form of randomized clinical trials encompassing other previously investigated group therapy approaches.

The present study revealed that, in the initial assessment, all participants had evidence of impairment in more than one cognitive ability. In the group studied, language proved more preserved than other cognitive functions, particularly oral comprehension of discourse. The LSP promoted an improvement in cognitive performance, assessed by the total MoCa score, and oral language expression of those residents who adhered effectively to the group intervention. However, no positive effects on the participants' oral comprehension abilities were evident. This finding highlights the need to adapt the program, particularly its oral comprehension strategies, so it can be used in future studies. Further studies will be necessary considering the preliminary nature of this study.

ACKNOWLEDGMENTS

The authors would like to thank the Institutional Program of Scientific Initiation Scholarships (*Programa Institucional de Bolsas de Iniciação Científica* — PIBIC) for the funding granted for this study.

Authors' contributions. RDBC: conceptualization, data curation, formal analysis, investigation, metholology, resources, writing original draft. TFP: conceptualization, investigation, supervision, writing – review & editing. SSB: conceptualization, data curation, funding acquisition, methodology, project administration, supervision, writing – review & editing.

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Dement Neuropsychol 2021 March;15(1):145-152

Original Article

https://doi.org/10.1590/1980-57642021dn15-010016

Comparison of screening tests in the evaluation of cognitive status of patients with epilepsy

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ABSTRACT. Epilepsy, a chronic neurological condition which is associated with neurobiological and psychosocial changes, affects 0.5 to 1% of the world's population, presenting in most cases a deficit in reasoning, memory and attention. **Objective:** To contribute to the implementation of screening strategies for cognitive decline and memory deficits in patients with epilepsy. **Methods:** Two questionnaires, MMSE and MoCA, were used in this cross-sectional and observational study. Fifty-four patients diagnosed with different types of epilepsy (55% refractory) were assessed; they were all over 18 years old, of both genders, with autonomy to answer the questionnaire. They were followed exclusively at an outpatient clinic of the Neurology Service Department, specialized in epilepsy, which is part of the tertiary healthcare level of the Brazilian Unified Health System (SUS). **Results:** The final sample consisted of 54 patients. There was a significant correlation ($p<0.001$) between the scores of both tests, indicating that low values in the MMSE score also corresponded to low values in the MoCA score. Sensitivity was 90% (ROC curve adjusted) and 87.5% of the patients with a normal score in the MMSE test obtained alterations in the MoCA scores. None of them showed a low MMSE score with a normal MOCA score. The Spearman correlation coefficient was 0.80. Also, there was a significant relationship between both immediate memory and delayed recall memory and the type of seizure ($p<0.03$) and level of schooling ($p<0.001$), respectively. **Conclusion:** The MoCA is a well-suited test to be performed in epilepsy patients to evaluate their cognition as it seems more extensive and complete compared to MMSE.

Keywords: epilepsy, cognition, memory disorders.

COMPARAÇÃO DE TESTES RASTREIO NA AVALIAÇÃO DO ESTADO COGNITIVO EM PACIENTES COM EPILEPSIA

RESUMO. A epilepsia, condição neurológica crônica associada a alterações neurobiológicas e psicossociais, afeta de 0,5 a 1% da população mundial. Na maior parte dos casos, há redução de raciocínio, memória e atenção. **Objetivos:** Contribuir para a implementação de estratégias de rastreio de declínio cognitivo e distúrbios na memória nos pacientes com epilepsia. **Métodos:** Estudo transversal observacional de 54 pacientes diagnosticados com epilepsia de diversos tipos (55% refratários) e com idade superior a 18 anos, de ambos os sexos, com autonomia para responder o questionário e em acompanhamento exclusivamente pelo Sistema Único de Saúde (SUS) em um ambulatório especializado em epilepsia, do serviço de neurologia, que faz parte do nível terciário de atenção à saúde. Foram aplicados dois questionários: o MEEM e o MoCA. **Resultados:** Amostra final de 54 pacientes. Encontrou-se uma correlação significativa ($p<0,001$) entre os escores dos dois testes, o que significa que valores baixos do escore MEEM correspondem a valores baixos do escore MoCA. Sensibilidade de 90% (curva ROC ajustada). Verificou-se que dentre os pacientes considerados normais no MEEM, 87,5% deles obtiveram escore com alterações por meio do teste de rastreio MoCA. Não se obteve nenhum caso de escore no MEEM baixo com pontuação no MoCA normal. O coeficiente de correlação Spearman foi 0,80. Há relação significativa da memória imediata e evocação tardia com o tipo de crise ($p<0,03$) e escolaridade ($p<0,001$), respectivamente. **Conclusão:** Torna-se pertinente a adição do teste MoCA para rastreio cognitivo em pacientes com epilepsia por ser um instrumento mais extenso e preciso, minimizando as chances de "falsos-negativos" quando comparado ao MEEM.

Palavras-chave: epilepsia, cognição, transtornos da memória.

This study was conducted at the Pontifícia Universidade Católica do Paraná, Curitiba, PR, Brazil.

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Disclosure: The authors report no conflicts of interest.

Funding: none.

Received on September 04, 2020. Accepted in final form on December 16, 2020

INTRODUCTION

Epilepsy is a chronic, electrical brain disorder with neurobiological, social, cognitive and psychological consequences.[1,2] Epilepsy patients not only tend to have lower social interaction and less employment opportunities, but they also tend to have emotional distress in comparison to other chronic diseases.[3,4] In addition, the majority of epileptic patients are more prone to have a lower cognitive performance than a control group without the disease.[4,5]

Both focal and generalized epilepsy can cause deficits in memory, language and motor functions. Patients with temporal lobe epilepsy or focal onset showed more memory deficits in comparison to those with extratemporal epilepsy.[6] Also, deficits in attention and memory were detected in 30% of newly diagnosed patients with cryptogenic epilepsy.[5] Additionally, in a study with a series of neuropsychological tests with the aim of assessing both memory and psychomotor skills, about 53% of newly diagnosed and untreated epileptic patients had at least abnormal test scores in comparison to the mean of the control group.[7]

Neuropsychological evaluation is mandatory in the follow-up of patients with this condition, due to their cognition declines,[8] which, in most cases, cause a deficit in reasoning, memory and attention. It also occurs due to functional and morphological changes caused by the seizures,[9] in association with injuries, aging and progressive brain damage.[10,11] Therefore, deficits in cognition and memory are among the main concerns regarding epileptic patients, and overall, physicians tend to underestimate the importance of these conditions.[12,13]

It is known that some anticonvulsant medications, such as phenytoin, affect the quality of life of the epileptic patients by causing cognitive impairment.[14-17] Furthermore, another study conducted with a series of neuropsychological tests to assess memory and psychomotor skills, showed that about 53% of newly diagnosed and untreated epileptic patients had at least abnormal scores in comparison to the mean of the control group.[15-17]

The purpose of this study was to demonstrate a non-inferiority test of MoCA in relation to the Mini Mental State Examination (MMSE) pursuant to improve screening strategies for the assessment of cognitive decline and memory disorders in patients with epilepsy. The evaluation was subdivided according to the etiology, lobe affected, type of seizures, and duration and use of medications, thus enabling to us to determine whether they promote effective assessments, contributing to the early recognition of cognitive deficits in epilepsy patients.

METHODS

This study was observational and cross-sectional, whose participants were patients followed exclusively at an outpatient clinic of the Neurology Service Department, specialized in epilepsy, which is part of the tertiary healthcare level of the Brazilian Unified Health System.

The patients included were over 18 years old, of both genders, previously diagnosed with different types of epilepsy, and they also showed autonomy to answer the questionnaires, regardless of their socioeconomic and cultural differences. All patients gave consent to be included in the research.

The exclusion criteria consisted of: patients who, at the time of the appointment, refused to participate in this study; patients with hearing loss; patients with thyroid and/or liver disease; and patients previously diagnosed with mental retardation, depression, dementia or any other medical disorder that explains their cognitive deficits.

Two questionnaires, the MMSE and the Montreal Cognitive Assessment (MoCA), were answered by the patients, between June 2018 and March 2020. Also, during the interview, their personal information was obtained. The scales were applied by one investigator always on the same day (Monday) and order.

MMSE is a screening test already validated in the Portuguese language and used for previous studies in Brazil, which evaluates the cognitive functions in a simple and fast way. The cut-off point considered in our study was the same as proposed by Brucki et al.

MoCA is also a cognitive screening test, which is easy to perform. It evaluates cognitive domains such as memory, attention, concentration, executive functions, language, visuospatial abilities, capacity of abstraction, calculation and orientation. In this study, the addition of 1 point was maintained for those patients with less than 12 years of schooling.[7,11]

The results of quantitative variables were described by means, standard deviations, medians, and minimum and maximum values, while the categorical variables were described by frequencies and percentages. The non-parametric Mann-Whitney test was performed to compare two groups regarding the discrete quantitative variables. More than two groups were compared using the non-parametric Kruskal-Wallis test. A non-parametric approach was considered because of the type of variables (scores). Regarding the categorical variables, the comparisons were performed through either the Fisher exact test or chi-square test. The analysis of the correlation between two quantitative variables was then performed by estimating the

Spearman correlation coefficient, and the normality of continuous quantitative variables was assessed by the Kolmogorov-Smirnov test. Receiver Operating Characteristic (ROC) curve analysis was performed, and the results obtained considered a % for specificity and a % for sensitivity [area under ROC curve p and 95% confidence interval (95%CI)]. Values of $p<0.05$ showed statistical significance.

The first part of this research was submitted in May 2018 to the Ethics Committee of the Plataforma Brasil and approved by the Associação Paranaense de Cultura from the Pontifícia Universidade Católica do Paraná (PUC-PR) and the second part was submitted in September 2019 and approved.

RESULTS

Demographic variables

The mean current age was 44.7 years and the mean diagnosis age was 30.8. Fifty percent of the individual were male. Regarding level of schooling, the majority went to elementary school (55.6%). All demographic variables are shown in Table 1.

Table 1. Demographic variables of the participants of the study (n=54).

Current age and age at the diagnosis						
	n	Mean	Median	Minimum	Maximum	Standard deviation
Current age (years)	54	44.7	44.5	19	78	14.6
Diagnosis age (years)	54	30.8	31	3	73	17.9

Sex and level of schooling			
	Classification	n	%
Biological sex	Male	27	50.0
	Female	27	50.0
Level of schooling	Preschool education[a]	2	3.7
	Elementary School[b]	30	55.6
	High School[c]	20	37.0
	Higher Education[d]	2	3.7
Level of schooling (Group)	Preschool/Elementary School	32	59.3
	High School/Higher Education	22	40.7

[a]Less than 9 years of study; [b]9 years of study; [c]12 years of study; [d]a minimum period of 16 years.

Clinical variables

The principal epilepsy etiology was structural lesions (51.9%). The types of seizures were approximately evenly distributed among generalized onset (29.6%), focal onset (37%) and focal to bilateral tonic-clonic (33.3%). Thirty individuals (55%) were characterized as refractory epilepsy. Each specific type of seizure and antiepileptic medication are shown in Table 2.

Questionnaires

In this study, the MMSE cut-off point was the same as the one proposed by Brucki et al. The mean of the MMSE score (max. 30) was 23.2±4.7 (10–30); immediate memory (0 to 3) was divided into 0 to 2 correct answers (16.7%, n=9) and 3 correct answers (83.3%, n=45), while the delayed recall memory (0 to 3) was divided into 0 or 1

Table 2. Clinical variables of the participants of the study (n=54).

	Classification	n	%
Etiology	Structural	28	51.9
	Infectious	9	16.7
	Unknown	14	25.9
	Immune	1	1.9
	Metabolic	2	3.7
Type of seizures	Generalized onset	16	29.6
	Focal to bilateral tonic-clonic	18	33.3
	Focal onset	20	37.0
Non-motor autonomic	Yes	2	3.7
Non-motor sensory	Yes	3	5.6
Non-motor behavior arrest	Yes	9	16.7
Non-motor absence	Yes	2	3.7
Motor myoclonic	Yes	1	1.9
Motor tonic	Yes	2	3.7
Motor atonic	Yes	1	1.9
Motor clonic	Yes	0	0.0
Motor tonic-clonic	Yes	16	29.6
Antiepileptic medication	None	1	1.9
	Monotherapy	28	51.9
	Two or more	25	46.3
Antiepileptic medication (group)	None/monotherapy	29	53.7
	Two or more	25	46.3

correct answer (31.5%, n=17), 2 correct answers (35.2% n=19) and 3 correct answers (33.3% n=18).

The mean of the MoCA score (max. 30) was 17.2±5.4 (6–29); immediate memory (0 to 5) was divided into 0 to 3 correct answers (27.8%, n=15), 4 correct answers (35.2%, n=19) and 5 correct answers (37%, n=20), while delayed recall memory was divided into 0 correct answer (35.2%, n=19), 1 or 2 correct answers (37%, n=20) and 3 to 5 correct answers (27.8%, n=15).

Mini Mental State Examination and Montreal Cognitive Assessment

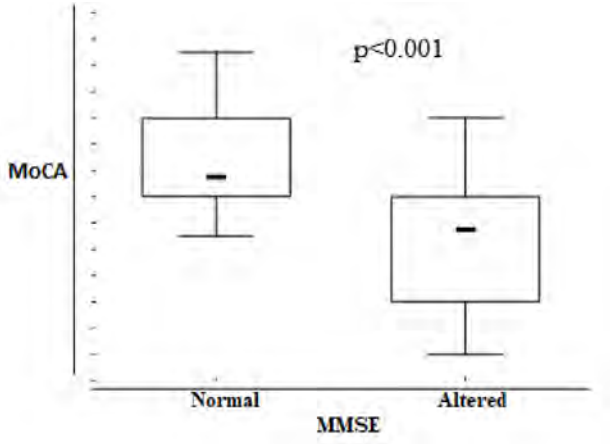
We tested the null hypothesis, in which the correlation coefficient between the scores of MMSE and MoCA was equal to zero (no correlation), *versus* the alternative hypothesis, in which the correlation coefficient was different from zero (correlation). The estimated Spearman correlation coefficient was 0.80, with statistical significance ($p<0.001$). Thus, there was a significant correlation between the scores of both screening tests and there was no random error (Figure 1).

We tested the null hypothesis, in which the results of MoCA were the same for patients with normal MMSE scores as well as for patients with alterations in the MMSE scores, *versus* the alternative hypothesis of different results from Mann-Whitney non-parametric test. All 38 cases with low MMSE scores (according to the cut-off points and schooling) also showed low scores in the MoCA. In addition, among the 16 cases with normal MMSE, 14 (88%) had low scores in MoCA. During this analysis, a $p<0.001$ was observed, indicating the absence of random error and the presence of statistical significance (Figure 2).

We also determined a cut-off point for the MoCA score that was associated with the MMSE result (normal or altered). For this analysis, a ROC curve for the MoCA scores was adjusted considering the results of the MMSE. The area under the curve was 0.82 with statistical significance ($p=0.001$). This indicates that the adjustment was good and that the MoCA score discriminated well between having normal or altered MMSE. The cut-off point for the MoCA score indicated by the adjustment is equal to 18. Therefore, scores above 18 are associated with normal MMSE and scores up to 18 were associated with altered MMSE. The sensitivity of this cut-off point was estimated to be 90% (Figure 3).

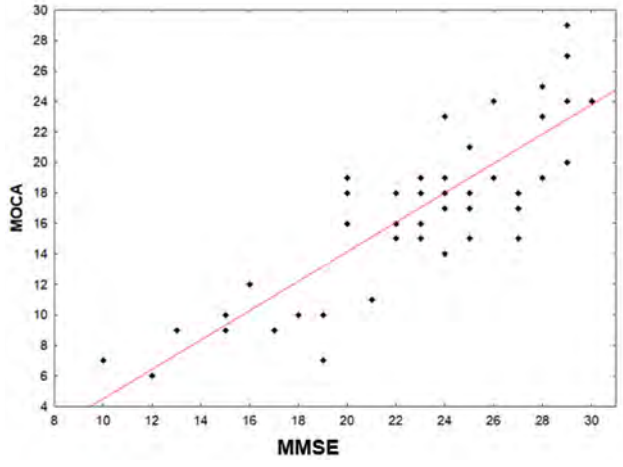
Age

We tested the null hypothesis, in which the Spearman correlation coefficient between age and score was equal to zero (no correlation), for each of the MMSE and



MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment.

Figure 2. Mann-Whitney non-parametric test.



MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment.

Figure 1. Spearman correlation coefficient=0.8.

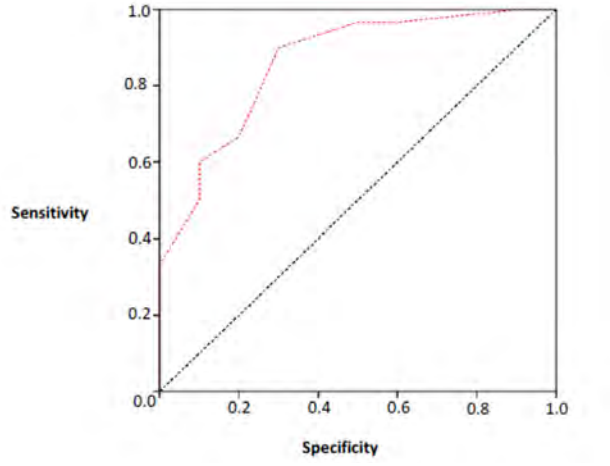


Figure 3. ROC Curve adjusted (area 0.82).

MoCA scores, as well as for both the current age (at the time that the questionnaire was answered) and the age at diagnosis; also, we tested the alternative hypothesis that the Spearman correlation coefficient was different from zero (correlation). The current age and the MMSE and MoCA scores were significantly correlated, with p=0.002 and p=0.005, respectively, indicating the absence of random error.

The Spearman correlation coefficient was used during this same statistical analysis. Current age and MMSE score gave the coefficient -0.41, while current age and MoCA score yielded the coefficient -0.38. The negative sign of this correlation coefficient indicates that low values for current age correspond to high scores in both MMSE and MoCA. The age at the epilepsy diagnosis was not significantly correlated (p>0.05).

Schooling

We tested the null hypothesis, in which the results were equal for all the classifications regarding schooling, *versus* the alternative hypothesis of different scores (Table 3).

Schooling × memory

We also tested the null hypothesis, in which there was no association between the factor and the variable, *versus* the alternative hypothesis, in which there was an association (Table 4).

Type of seizures × memory

We also tested the null hypothesis, in which there is no association between the factor and the variable, *versus* the alternative hypothesis, in which there is an association (Table 5).

Table 3. Schooling × Mini Mental State Examination and Montreal Cognitive Assessment scores (n=54).

Score	Level of schooling	n	Mean	Median	Minimum	Maximum	Standard deviation	p-value*
MMSE	Preschool/elementary school	32	21.4	22.5	10	29	4.9	
	High school/higher education	22	25.9	26	20	30	2.7	**<0.001**
MoCA	Preschool/elementary school	32	14.6	15	6	25	4.7	
	High school/higher education	22	21.1	20	15	29	3.5	**<0.001**

MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; *Mann-Whitney non-parametric test, p<0.05.

Table 4. Schooling × immediate delayed recall memory (n=54).

	Classification	Level of schooling		p-value*
		Preschool/elementary school	High school/higher education	
MMSE immediate memory	0 to 2	6 (18.8)	3 (13.6)	
	3	26 (81.3)	19 (86.4)	0.723
MMSE delayed recall memory	0 to 1	13 (40.6)	4 (18.2)	
	2	11 (34.4)	8 (36.4)	
	3	8 (25)	10 (45.5)	0.154
MoCA immediate memory	0 to 3	11 (34.4)	4 (18.2)	
	4	12 (37.5)	7 (31.8)	
	5	9 (28.1)	11 (50)	0.219
MoCA delayed recall memory	0	17 (53.1)	2 (9.1)	
	1 to 2	11 (34.4)	9 (40.9)	
	3 to 5	4 (12.5)	11 (50)	**0.001**

MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; *Fisher's exact test or chi-square test, p<0.05.

Table 5. Type of epileptic seizure × immediate memory and delayed recall memory (n=54).

	Classification	Type of seizures			p-value*
		Generalized onset	Focal to bilateral tonic-clonic	Focal start	
MMSE immediate memory	0 to 2	1 (6.3)	3 (16.7)	5 (25)	
	3	15 (93.8)	15 (83.3)	15 (75)	0.325
MMSE delayed recall memory	0 to 1	2 (12.5)	6 (33.3)	9 (45)	
	2	6 (37.5)	9 (50)	4 (20)	
	3	8 (50)	3 (16.7)	7 (35)	0.081
MoCA immediate memory	0 to 3	1 (6.3)	7 (38.9)	7 (35)	
	4	4 (25)	7 (38.9)	8 (40)	
	5	11 (68.8)	4 (22.2)	5 (25)	0.030
MoCA delayed recall memory	0	3 (18.8)	7 (38.9)	9 (45)	
	1 to 2	7 (43.8)	9 (50)	4 (20)	
	3 to 5	6 (37.5)	2 (11.1)	7 (35)	0.128

MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; *chi-square test, p<0.05

DISCUSSION

Memory is a set of brain systems that allow the processing of information for later use after a time interval consciously or not. Two types of memory: (1) hippocampal memory (declarative or episodic) is explicit or conscious evocation; (2) non-hippocampal memory (non-declarative or procedural) is implicit or unconscious evocation. Short-term memory is working memory (frontoparietal working memory) plus processing, storage, evocation for memory consolidation (hippocampal). Long-term memory is episodic or autobiographical (hippocampal), knowledge or semantic (mesial temporal lobe) and procedural (basal ganglia).

Several studies correlate the deficits of memory and cognition in epilepsy, mainly, to the temporal lobe epileptogenic focus. More specifically, memory issues are due to a lesion in the dominant medial temporal lobe, but there are reports regarding the extratemporal and frontal lobe epilepsy.[9] All these types of epilepsy result in more serious comorbidities in comparison to the generalized seizures.[18]

The main objective of this study was to compare the screening tests for decline in cognition and memory through the MMSE and MoCA questionnaires. The MoCA was, in fact, created to be more sensitive to abnormal performance of cognitive domains, such as visuospatial, executive function, naming, attention, language, abstraction, delayed recall memory and orientation.[19] Regarding memory, MoCA involves more words for the training of immediate and delayed recall memory, as well as more learning tasks; also, it has a longer time interval for recall in comparison to MMSE.

In our study, 38 patients scored below the cut-off points established by their level of schooling in the MMSE questionnaire, also obtaining low scores in MoCA. The results of the MMSE showed a difference of 14 patients, who had alteration only in MoCA scores, which categorized 52 patients with scores below expectations. Similar results were found in one study, regarding abnormal scores in epileptic patients (53.5%) from a series of neuropsychological tests.[20] However, no patient who had a low score in MMSE was categorized as normal in MoCA in our study, which did occur in the aforementioned study.

There are several factors that directly or indirectly interfere with the cognitive performance of epilepsy patients, such as the frequency of seizures, the antiepileptic medication in use, age, and location of the epileptogenic focus.[21-23] In this sense, a screening for cognitive impairment is very important. It remains unknown if the cause is the early onset of epilepsy, the accumulation of brain damage due to seizures or the interaction of an initial precipitating lesion with physiological or senile processes.[23,24]

In our study, 19 patients underwent monotherapy treatment, while 21 patients underwent treatment with a combination of several different drugs. Several reports have shown that antiepileptic drugs (AED) might be associated with adverse cognitive effects.[25] Some authors

claim that the control of seizures with monotherapy using first-line drugs is beneficial for cognitive functions, because of the reduction of the accumulated brain damage.[26,27] Otherwise, limiting the number of AEDs should also be prioritized by clinicians.[23]

In this study, immediate memory evaluates the quality of the memory immediately after the presentation of the stimulus. The words used in the MMSE test were different from those used in the MoCA test. The delayed recall analyzed by the MOCA test showed a significant relationship with the patients' level of schooling, which did not occur in the MMSE evaluation. This outcome can be explained by the two additional words for recall in MoCA totaling 5 new words to be memorized.

In our study, patients with focal-onset seizures had worse performance in immediate memory of MoCA ($p<0.05$). Similar results occurred in other studies that analyzed patients with complex focal seizures and used different tests that evaluated the same type of memory, such as that by Stella.[28] The author studied mnemonic activity in epileptic patients with complex partial seizures through the Wechsler Memory Test. In the three subtests, the patients showed cognitive performance significantly lower than the controls ($p<0.05$).

We know that epilepsy patients can experience specific effects on memory, depending on the cause of the seizures and on their location. Memory deficits are associated with the extent and location of the damage in the brain structure, as well as with the degree of physiological dysfunction, the frequency and severity of seizures, the neurotoxicity of antiepileptic drugs and the degree of cognitive development at the onset of diagnosis.[29]

Cognitive deterioration varies with the laterality affected by the epileptogenic focus, since the involvement of the left lobe causes deficiencies in verbal memory, while that of the right lobe causes deficiencies in non-verbal memory.[24] The duration of the seizures was considered another impact factor in the cognition of these individuals, exemplified by prolonged epileptic seizures of 30 minutes or more.[30-32]

There are similar items in both questionnaires; however, these same questions were not repeated a second time. The entire methodology was well designed and executed. The questions that appeared in the MMSE and had an equivalent answer in the MoCA were only asked once, during the first application (MMSE). In conclusion, all items in the topic "Orientation" in MoCA are contained in the topic "Orientation" in MMSE, and thus, the patient was not asked these items again. Same as subtraction contained in "Attention". Hence, we believe that there was no response bias or information bias in our study. However, this study had some limitations, such as its design, which is cross-sectional and allows the evaluation of the cognitive domains at only one moment. Another point is the fact that tertiary center patients may have a worse epilepsy condition in comparison with the general population.

The present study was able to identify alterations in patients with an MMSE considered normal, through the performance of the MoCA screening test. None of the patients showed a low MMSE score with a normal MoCA score. Therefore, we found MoCA to have a superior accuracy as a screening test, so we encourage the use of MoCA because it has greater specificity (less false-negatives). Furthermore, we emphasize the importance of memory screening tests in epileptic patients to differentiate cognitive complaints from normal aging. The utilization of such tools regularly in large studies or primary care, could identify the need for a more complete cognitive analysis.

Regarding the division into subgroups, we observed a significant relationship between immediate and delayed recall memory and the type of seizures and schooling, respectively. Thus, it becomes relevant to add this screening test in the evaluation of cognition and memory in epilepsy patients.

But what can we do with this information? Neuroplasticity is very important in this context. "Neurons that fire together wire together" is understood as the capacity of the brain (neurons and neural networks) to reorganize and change itself to compensate injury or dysfunction.[33]

Hippocampal neurogenesis (in the dentate gyrus) is changed by brain injury (such as in epilepsy), but hippocampal neurogenesis is also changed (and this time for good) by aerobic physical exercise, slow-wave sleep, chronic treatment with antidepressants plus cognitive training.[34]

If there is one major takeaway from this research, it is that the use of original articles, guidelines and consensus to aid decision-making improves clinical management, contributes to a change in the organizational culture of the medical class and strengthens evidence-based medicine. Whether or not the results hold up to scrutiny, we think that however small this study is and with its limitations, it may contribute to the implementation of effective strategies for screening for cognitive decline and memory in patients with epilepsy.

Authors' contributions. MCS: data curation, investigation, writing — review & editing. COP: conceptualization, methodology, project administration, writing — review & editing. LM: formal analysis, resources, visualization. CAT: conceptualization, data curation, investigation, methodology, project administration, supervision, validation, visualization, writing — review & editing.

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Erratum

https://doi.org/10.1590/1980-57642018dn13-020013erratum

In the manuscript "Neurocognitive study of school performance among Moroccan high school students: The role of working memory", DOI: 10.1590/1980-57642018dn13-020013, published in the Dement Neuropsychol. 2019;13(2):232-237, on page 232.

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Publicação prévia ou submissão duplicada. Manuscritos são recebidos entendendo-se que não estejam sob outra consideração para publicação. Esta informação deve ser inserida na carta de apresentação. Dementia & Neuropsychologia usa ferramentas para detectar semelhança de texto para verificar plágio. Quando é detectado plágio, a revista segue o Código de Conduta e as Diretrizes de Boas Práticas para Editores de Revistas do Comitê de Ética em Publicações - COPE (http://publicationethics.org/).

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Consentimento informado. Para investigações experimentais em seres humanos ou animais, coloque na sessão de "Métodos" do manuscrito que um comitê institucional aprovou o projeto. Uma cópia da aprovação do Comitê de Ética deve ser enviado com o manuscrito. Para aqueles investigadores que não possuam um comitê de ética em pesquisa formal (institucional ou regional) os princípios exibidos na Declaração de Helsinki devem ser seguidos. Uma carta de consentimento deve acompanhar todas as fotografias de pacientes na qual uma possível identificação possa ocorrer. Não é suficiente cobrir olhos para mascarar a identidade. Refira-se ao paciente por número (ou, em relatos anedóticos, por nomes fictícios). Nomes reais ou iniciais não devem ser usados no texto, tabelas ou ilustrações.

Uso não autorizado. Manuscritos aceitos tornam-se propriedade permanente de Dementia & Neuropsychologia e não podem ser publicados em outro local sem a permissão do editor.

SUBMISSÕES DE MANUSCRITOS

As submissões devem ser online: https://mc04.manuscriptcentral.com/dn-scielo. O número ORCID de todos os autores é obrigatório.

Devem ser anexados: a carta de apresentação, declarações de responsabilidade de autoria, declaração financeira e transferência de direitos autorais. Estudos que utilizem seres vivos devem submeter uma cópia da autorização pelo Comitê de ética da instituição envolvida. Ensaios clínicos serão aceitos para publicação, mediante apresentação do registro de ensaio clínico.

1. Todos os manuscritos submetidos são revistos inicialmente por um editor. Manuscritos com insuficiente prioridade para publicação serão prontamente rejeitados.
2. Os manuscritos são enviados para a revisão por pares (veja abaixo).
3. Os autores são informados pelo Editores Chefe da provável data de publicação após sua decisão final.
4. Os autores podem ser solicitados a fornecer informações adicionais sobre a apresentação prévia em encontros científicos. Esta informação pode ser dada na carta de apresentação, enviada na ocasião da submissão do manuscrito.

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1. Após aprovação dos aspectos formais, o manuscrito é submetido para revisão por pares e consultores ad-hoc, especialistas nacionais e internacionais. Cada manuscrito é avaliado por pelo menos dois revisores. As identidades dos revisores são mantidas confidenciais e a identidade dos autores não é informada aos revisores.
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6. O processo inteiro é supervisionado pelo Editor Chefe que determina o número apropriado de re-submissões, sempre focando na qualidade do trabalho a ser publicado.

Preparação do Manuscrito

Informações aos autores estão disponíveis *on line* (www.demneuropsy.com.br; e www.scielo.br). Por favor, siga as seguintes instruções:

Carta de apresentação. Declare um autor para correspondência, responsabilidade de autoria, contribuições, suporte financeiro e conflito de interesses. Forneça também, endereço para correspondência, números de telefone e fax e endereço eletrônico do autor correspondente e endereço eletrônico dos demais autores..

Página de título. Inclui o título do manuscrito e os nomes dos autores. O título deve ser conciso e descritivo, com informação essencial sobre o conteúdo do manuscrito com até 100 caracteres incluindo espaços. O nome dos autores deve incluir o primeiro nome. Ao final da página de título informe: o nome do departamento e instituição, cidade e país no qual o estudo foi conduzido, título acadêmico de cada autor e sua afiliação institucional, suporte financeiro, agradecimentos, nome e endereço (postal e eletrônico) para correspondência.

Resumo. Os resumos de artigos originais, ou comunicações breves devem ser estruturados e conter os seguintes itens: embasamento, objetivo(s), métodos, resultados e conclusões. Os resumos podem conter até 250 palavras. Resumos de relatos de caso, revisões e nota histórica não necessitam ser estruturados e podem conter até 150 palavras.

Palavras-chaves. Adicione 4 a 6 palavras-chave ou frases curtas após o resumo, seguindo os descritores em ciências da saúde (HTTP://decs.bvs.br/).

- Título, resumo e palavras-chaves devem ser fornecidos também em português. Título e resumo em português devem ser traduções do título e resumo em inglês. Aqueles que não escrevem na língua portuguesa, contarão com a tradução dos editores.

Texto. Os manuscritos originais deverão apresentar até 3000 palavras, contendo: introdução e objetivos; métodos (material e/ou casuística; método estatístico; menção à aprovação do Comitê de Ética e seu nome e o consentimento informado); resultados; discussão (que deve incluir as conclusões); e agradecimentos. Os dados apresentados nas tabelas e ilustrações não devem ser repetidos no texto. Observações: O limite para comunicações breves, nota histórica e relato de caso é até 2000 palavras e para revisões até 5000 palavras; Neuroimagem através de casos clínicos até 750 palavras.

Referências. Até 50 para manuscritos originais, numeradas consecutivamente em ordem de aparecimento. Para relatos de caso, nota histórica ou comunicações breves até 30, para "Neuroimagem através de casos clínicos" até 10 e nas revisões, até 150. As referências devem seguir a norma Vancouver e abreviado conforme o modelo do *Index Medicus* ou PubMed. Liste todos os autores quando houver seis ou menos; quando houver sete ou mais, liste os seis primeiros e depois siga com "et al".

- Artigos: autor(es). Título. Jornal ano; volume: páginas inicial-final.
- Livros: autor(es) ou editor(es). Título. Edição, se não for a primeira. Cidade de publicação: editora; ano: número de páginas.
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- Resumos: autor(es). Título, seguido por (abstr). Jornal ano; volume (suplemento e seu número, se necessário): página(s) ou, no caso de resumos não publicados em jornais: Título da publicação. Cidade de publicação: editora, ano: página(s).

Tabelas. Até cinco tabelas em manuscritos originais (até três em comunicações breves, nota histórica ou relatos de caso), cada uma apresentada em página separada, com seu título, legenda e sequência numérica. As tabelas devem conter toda a informação requerida para compreensão do leitor. Não devem ser utilizadas linhas verticais para separar os dados dentro da tabela. Não submeta tabelas como fotografias. Numere a tabela consecutivamente em ordem de sua primeira citação no texto e forneça um breve título para cada uma. Dê a cada coluna um cabeçalho curto ou abreviado. Coloque notas informativas no rodapé, não no cabeçalho. Explicite no rodapé todas as abreviações usadas em cada tabela. Para o rodapé use os seguintes símbolos, nesta sequência: *, +, +, §, ||, ¶, **, ++, etc. O Editor ao aceitar um manuscrito, pode recomendar que tabelas adicionais contendo dados importantes de suporte, muito extensos para publicação, possam ser deixadas num arquivo, tal como no sítio da revista **(www.demneuropsy.com.br)**, ou que possa ser disponibilizado pelos autores. Neste caso, uma declaração apropriada será adicionada ao texto. Submeta todas as tabelas junto com o manuscrito.

Ilustrações. Até quatro figuras, gráficos ou fotos, com seu título e legenda em páginas separadas (até três ilustrações em comunicações breves, nota histórica ou relatos de caso).

Atenção. Antes de submeter seu manuscrito, por favor, complete o check list e as declarações de autoria, conflitos financeiros e não financeiros, disponíveis na página eletrônica do jornal (www.demneuropsy.com.br) ou www.scielo.br