General paresis or Bayle disease

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ABSTRACT

Introduction. General paresis was for several centuries considered not only a true model of mental disease due to its rapid and irreversible course towards dementia and death, but also a symbol of the incurable nature of mental diseases.

Objective. We conducted a historical analysis of the concept of dementia paralytica with particular emphasis on Bayle and the introduction of the anatomical-clinical model in psychiatry.

Development. In 1822, Antoine Laurent Jessé Bayle described six cases of general paresis after the autopsies revealed the presence of chronic meningitis. This represented the peak of the so-called mental revolution of the 18th century and the introduction of the anatomical-clinical model. It was not until 1907 that syphilis was confirmed as the aetiological agent of general paresis, a crucial discovery for developing the definitive treatment for general paresis.

Conclusions. General paresis is a historical example of how the scientific community fought and succeeded in determining the aetiology of a disease and finding a suitable treatment.

KEYWORDS
Neurosyphilis, syphilis, mental diseases, history of medicine, dementia, general paresis

Introduction

Very few cases of dementia paralytica are diagnosed these days. From the late 19th century to the early 20th century, however, this disease was responsible for 10% to 20% of all admissions to psychiatric departments at hospitals and 6.2% to 34.7% of all admissions to mental institutions. Furthermore, it was the cause of dementia in approximately 15% of cases.[1,2] Although general paresis was a very common disorder, it is also true that diagnostic criteria before the introduction of the Wassermann reaction were quite imprecise. Despite the low incidence of dementia paralytica, syphilis screening tests are even today part of the protocol for assessing dementia, possibly because of an atavistic fear, the influence of diagnostic tradition, and more importantly the fact that general paresis is a treatable cause of dementia.

For several centuries general paresis was considered a true model for mental disease due to its rapid and irreversible course towards dementia and death, as well as a symbol of the incurable nature of mental diseases.[3] Dementia paralytica has never been a stable process either in its definition or in its clinical progression. This may in part justify the disparities between diagnostic clinical criteria. It was Bayle's description which finally paved the way for the emergence of the anatomical-clinical model in psychiatry.

Development

Term

General paresis was first termed 'chronic arachnoiditis' (Bayle, 1822),[4] a descriptive name of pathological findings rather than the designation of a disease. This

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denomination was soon replaced by other terms showing a more markedly clinical approach: incomplete general paralysis (Delaye, 1824), general paralysis of the insane (Calmeil, 1826; Mickle, 1880), dementia with paralysis (Marchand, 1844), progressive general paralysis (Requin, 1846), *folie paralytique* or 'paralytic insanity' (Falret, 1853), paralytic dementia (Baillarger, 1857), syphilitic dementia (Ball, 1889), progressive paralysis (Cerletti, 1905), etc. Most of these terms reference the two main symptoms of the disease that resulted from syphilis infection: severe deterioration of mental function (meaning both madness and cognitive decline or dementia) and motor alterations (paralysis). In fact, Bayle stated that "the symptoms of chronic arachnoiditis can all be included in the condition of general incomplete paralysis and derangement of the intellectual functions".[3]

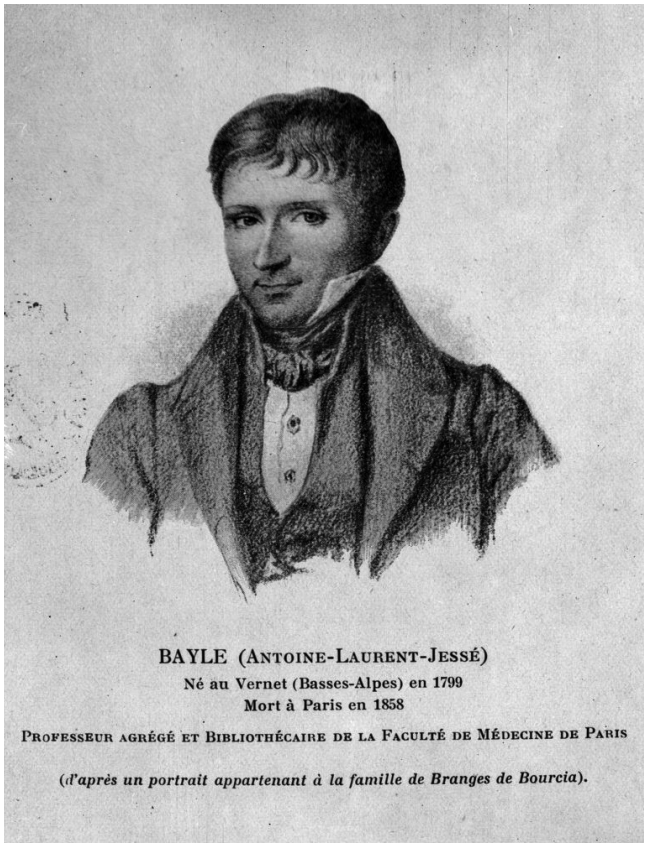

Figure 1. Antoine Laurent Jessé Bayle. ©BIU Santé (Paris)

Medical history

The first descriptions of syphilis in Europe date back to the late 15th century (Grünpeck, 1496; López de Villalobos, 1498), a period when this infectious process became epidemic with no apparent cause. Two different theories have been proposed to explain the circumstances surrounding this rapid spread of *Treponema pallidum*: the Columbian and the pre-Columbian hypotheses. The pre-Columbian hypothesis proposes that syphilis was already present in Europe some 20 000 years ago due to a mutation of yaws or bejel, two non-venereal treponematoses known since ancient times and which have been found in lesions in Egyptian mummies and skeletons dating back to the 14th century in Hull, United Kingdom. The Columbian hypothesis, on the other hand, states that syphilis was carried from America to Europe by Columbus' crew, and subsequently to Naples by both these sailors and the mercenaries of The Great Captain, Gonzalo Fernández de Córdoba. From there, syphilis spread across Europe.

Similarly, it is surprising that there are no descriptions of paralytic dementia or mental illness secondary to syphilis until well into the 17th century. The first known mention is attributed to Tomás Murillo y Velarde, author of *Aprobación de ingenios y curación de hipochondríacos con observaciones y remedios muy particulares* (Zaragoza, 1672); the 12th chapter of this book addresses 'hypochondriac melancholia' secondary to 'morbus gallicus'. However, brain lesions secondary to syphilis had already been reported by several authors: Guarinoni (1619) described cerebral syphilitic gummata; Botallo (1660) reported syphilitic lesions at the base of the brain, and Astruc wrote *De morbis venereis* (1740), a treatise in which he described cerebral syphilitic lesions that he attempted to correlate with clinical manifestations.[7] The first description of paralytic dementia has been attributed to Willis. In his book *De anima brutorum quae hominis vitalis ac sensitiva est, exercitationes duae* (Amsterdam, 1672), he described a patient presenting dementia associated with paralysis, although he also considered the possibility of vascular dementia. He stated: "I have seen many patients with mental illness who suffer mental slowness, impaired memory, and subsequently stupidity and lack of judgement, eventually leading to paralysis, as I had predicted". Hare,[8] however, accredited the first description to the pharmacist of

Bethlem, John Haslam (*Observations on insanity*, London, 1798), who stated that "the paralytic affections are a more frequent cause of insanity than is believed, and are also a very common sequela of mania (...) in the majority of patients, memory is materially weakened".[9] Chiarugi[10] has also been attributed with providing the first clinical description: among his 100 patients with mental diseases there were four (cases 3, 19, 23, and 58) who very likely had general paresis. Although Pinel[11] did not specifically address this type of dementia, he proposed exhaustion due to sexual excess as one of the main causes of dementia in general. This aetiological hypothesis was also supported by his student Esquirol. In 1819, W. Lawrence and Monro performed an autopsy on a 40-year-old patient who had died after admission to Bethlem for delirium and paralysis, and stated that "all the vessels in the dura mater and pia mater were congested. The surface of the pia mater was soaked in a serous fluid. The arachnoid was thickened and opaque in the convexities of the cerebral hemispheres".[8] Some years later, in 1821, Parent-Duchatelet and Martinet wrote *Recherches sur l'inflammation de l'arachnoïde cérébrale et spinale*, in which they described a disease called 'arachnitis' that manifested with delirium.[2]

The pivotal moment for the history of paralytic dementia, though, was 21 November 1822, the day when Bayle presented his doctoral thesis 'Recherches sur l'arachnitis chronique' in Paris. In his thesis, Bayle described six cases with general paresis whose autopsy results showed chronic meningitis. According to Bayle, mental alienation might be a symptom of chronic inflammation of the arachnoid based on the high frequency of this pathological finding in mental patients.[3] This description represents the culminating moment of the so-called mental revolution of the 18th century along with the emergence of the anatomical-clinical model.

Bayle's conceptual contributions were many. He established that mental symptoms of paralytic dementia were a consequence of a specific lesion (the concept of 'lesion specificity'), which could be observed and located in a specific place ('cerebral localisation'). He also supported the existence of an anatomical-clinical correlation and unitary psychosis (dementia-madness) as opposed to Esquirol's dualism (paralytic dementia on the one hand, paralytic insanity on the other), which meant that the disease was regarded as a sequential phenomenon (symptoms are interrelated and progress in several stages).[2] According to Bayle, the disease was a single entity and had three stages. The first stage manifested with impaired gait, decreased intellectual function, and monomaniacal delirium. The second stage presented maniac delirium, agitation, and violent behaviour. General and incomplete paresis increased in the third stage (dementia). In this third stage, patients experience difficulties in articulation, speech is sometimes unintelligible, and understanding is extremely impaired, leading to almost complete paralysis of voluntary movements and in some cases idiotism. This proved that motor neurological disorders (paralysis) and mental illnesses (dementia, delirium) in these patients were not independent, but rather pertained to the same disease and were a direct consequence of lesions or pathological changes in the brain (chronic arachnoiditis). This process constituted, especially since 1850, the model of mental disease[3] which included several symptoms (somatic –paralysis– and psychiatric –dementia, delirium, mania–) that until then were considered independent. This meant a change from a philosophical approach (mental, psychic) to an organicist approach (lesion) to the brain. The anatomical-clinical mindset was defined and reinforced with this major change in the field of mental illness (a discipline with apparently little connection to organicism) when the results of neuropathological examination demonstrated that these clinical findings were caused by the same agent (chronic arachnoiditis).

Bayle subsequently published *Nouvelle doctrine des maladies mentales* (Paris, 1825) and *Traité des maladies du cerveau et de ses membranes: maladies mentales* (Paris, 1826), in which he described 214 cases.[8] In the second of these books, Bayle restated his hypothesis that paralytic dementia was caused by chronic arachnoiditis[13] These ideas are inimical to the supposition that until then had been supported by several renowned neuropsychiatrists, especially Pinel and Esquirol and their students (Georget, Delaye, and Falret). For years, these authors advocated that progressive general paresis (PGP) was a mere epiphenomenon of insanity.[14] Pinel once even stated that Bayle's theories were premature and useless.[3] It was not until 1860, two years after his death, that the scientific community finally acknowledged Bayle's contributions. Baillarger (1859) suggested naming paralytic dementia the eponymic '*maladie de Bayle*'.

French neuropsychiatrists showed a great interest in this disease and reported similar observations from the beginning, probably due to the high incidence of general paresis among the patients admitted to their psychiatric hospitals.[2] Among them, Calmeil stands out. He was the first author to publish a monograph about the disease: *De la paralysie considérée chez les aliénés* (1826). In his work, Calmeil posited that chronic diffuse periencephalitis with perivascular infiltration was the anatomic and pathologic substrate of general paresis.[7] The idea that encephalitis (rather than arachnoiditis, as Bayle had suggested) was the substrate of the disease was supported by other authors including Lallemand (1834), Romberg (1840), Winn (1848), Verga (1849), Schützenberger (1850), and, in Spain, Giné Partagás, who talked about diffuse perimeningoencephalitis.[15] Alzheimer was one of the neuropathologists that most contributed to the knowledge of paralytic dementia. In fact, this was his most published subject as well as the topic of his habilitation thesis, or *venia legendi*.

In Spain, however, there was not much interest in general paresis until the late 19th century and, as a result, no prevalence data were available until the first Spanish Symposium on Phrenopathy, which was held in 1883. According to those data, patients with general paresis accounted for 8% to 25% of all patients admitted to neuropsychiatric institutions. In any case, Giné Partagás had already addressed this disease in his work *Ensayo teórico-práctico sobre la homología y heterología frenopáticas ó sean semejanzas y diferencias entre los procesos de la razón y de la sin-razón* (1878), and Vera, one of Esquerdo's students, had published *Estudio clínico de la parálisis general progresiva de los enajenados* (Madrid, 1880).[2]

Discovering the aetiology of the disease

Numerous aetiopathogenic hypotheses had been suggested before *Treponema pallidum* was discovered. These hypotheses proposed alcohol[9] or sexual excess, even within a marriage, as aetiological factors. In this line of reasoning, all preventive treatments required that women avoid "being loved in excess by their husbands" and "being excessively loving with their husbands", as stated in the *Journal of Mental Science* (1873). According to Austin,[16] PGP was caused by 'moral agony'.

Although Bayle had already suggested a potential connection between syphilis and mental disorders, the first clear reference to this pathology as the aetiology of PGP came in 1857, when Esmarch and Jessen observed the high number of PGP patients with a history of syphilis.[17] This hypothesis was later corroborated by Hildebrandt (1859), Kjellberg (1863), who stated that individuals without syphilis could not develop PGP,[2] and especially Fournier, who contributed numerous statistical data in *Leçons sur la syphilis tertiaire* (Paris, 1875) and stated that syphilis was usually, if not entirely, the cause of PGP. Fournier would later confirm his hypothesis in *La syphilis du cerveau* (1879).[3] In the following years, the number of publications presenting syphilis as the cause of paralytic dementia grew by leaps and bounds. Highlights include works by Redlich (1892, 1897), Binswanger (1894), Berkley (1900), and especially Kraepelin, who stated that syphilis infection was requisite for developing general paresis at a later stage (*Psychiatrie*, 1904). However, several authors still questioned the role syphilis played in the pathogenesis of PGP. Krafft-Ebing (1894) suggested that excessive tobacco use may at times cause general paresis, and Nonne (1902) and Osler (1903) denied any connection between syphilis and paralytic dementia.

Syphilis was successfully transmitted to rabbits by Haensell in 1881, and to chimpanzees by Metchnikoff and Roux in 1903. These two studies established the infectious nature of the disease, but its causative agent still remained to be discovered. Finally, on 3 March 1905, German zoologist Schaudinn, along with Hoffmann, detected the presence of a spiral-shaped microorganism in fluid from genital lesions and in inguinal lymph nodes in a patient with primary syphilis (chancres). First named *Spirochaeta pallida*, this microorganism was later called *Treponema pallidum*. In 1909, Coles described the use of dark-field microscopy to envision the spirochaetes, and in 1907 Plaut published his results using the Wassermann reaction on CSF, which confirmed the connection between syphilis and PGP.[18] In 1909, Ranke confirmed the presence of *Spirochaeta pallida* in the pia mater and the vascular layer of several brains from patients with congenital syphilis. That same year, Williamson mentioned the so-called *Bacillus paralyticans*.[19] Finally, in February 1913, Noguchi and Moore[20] published *A demonstration of Treponema pallidum in the brain in*

cases of general paralysis, where they gave evidence that *Treponema pallidum* was the infectious agent responsible for paralytic dementia after finding the microorganism in the brains of twelve of their study patients. Interestingly, Noguchi and Moore used Cajal's silver nitrate method to demonstrate the presence of treponemes. Therefore, before publishing their findings, these authors sent several preparations to Cajal so he could corroborate that the undulating images in the cerebral cortex corresponded to spirochaetes and not to neuroglial fibres or neurofibrils. Cajal sent the preparations to Gayarre, Achúcarro, and Lafora before giving his opinion.[21]

Regarding the role of spirochaetes in paralytic dementia, Hare suggested that this type of dementia was a new disease caused by a highly neurotropic mutant strain which produced severe impairment of the central nervous system.[8] According to his theory, this strain appeared in the north of France between the late 17th century and the early 18th century, and spread across the world following the main trade routes, especially maritime routes. The change in incidence of paralytic dementia was very significant in that period and had no apparent triggering factor. It may have been due to diagnostic errors: general paresis might have been mistaken for other diseases with similar clinical manifestations, such as arteriosclerotic dementia, alcoholic dementia, and senile dementia. In fact, doctors wondered why there were no or very few previous cases of paralytic dementia when the disease was very common and had been reported in a large number of patients. It was also hypothesised that paralytic dementia had emerged in the early 19th century and until then had been inhibited by smallpox in Europe (before Jenner developed a vaccine) and malaria in other regions, which may have acted as fever therapy.[3] Bayle himself admitted in his *Traité des maladies du cerveau et de ses membranes: maladies mentales* that the lesions he reported had not been described before. At that time, doctors and naturalists held the idea that diseases were fixed and immutable; they rejected the possibility of *de novo* diseases as they were of the opinion that all illnesses had existed since the beginning of time. Another possibility is that PGP had existed previously but had not been diagnosed because it was mistaken for senile dementia or vascular dementia, or that a significant percentage of patients had died before developing PGP due to vascular alterations associated with syphilis.

After *Treponema pallidum* was found in fluid from genital chancres and in inguinal lymph nodes, German bacteriologist Wassermann, director of the department of experimental therapy and serum research at the Kaiser-Wilhelm Institute (Berlin), developed a diagnostic test for syphilis in 1906, known as the Wassermann test, in cooperation with Bruck and dermatologist Neisser.[22,23] Thanks to the development of lumbar puncture, neurosyphilis could be diagnosed by analysing CSF with several diagnostic techniques, including the complement fixation test (Wassermann, 1906), the colloidal gold test (Lange, 1913), the Pandy's test,[9] or the Venereal Disease Research Laboratory test (VDRL; Kolmer, 1953). These techniques revealed findings such as low white blood cell levels (Nidal, 1901; Alzheimer, 1907)[3] or increased albumin levels (Schaeffer, 1902) in patients with the disease.

Treatment of paralytic dementia

In an attempt to escape therapeutic nihilism, a great number and variety of treatments were developed for paralytic dementia. As early as 1498, Francisco López de Villalobos suggested using plants (dodder, black hellebore, *Cassia fistula*, and agaric), bleeding, and purging to treat general paresis in his work *Sumario de la medicina, con un tratado sobre las pestíferas buvas*, the first Spanish-language treatise on syphilis. In as much as treatments achieved poor results, patients with this disease were usually abandoned to their fate or institutionalised in asylums for chronic patients.

Paracelsus treated syphilis patients with mercury (ointments or fumigations) since guaiacum bark, the traditional treatment for these patients, was shown to be ineffective. However, in the end mercury was responsible for more deaths than syphilis itself. During the 17th and 18th centuries, syphilis was treated with iodine (mostly potassium iodide since 1835), arsenic, quinine hydrochloride, and especially balneotherapy and mercurial treatment using metallic mercury, mercuric chloride, mercury iodide, and mercurial ointment (lard and mercury). Balneotherapy was based on sulphur and sodium springs, as in the French spas in Luchon, Cauterets, Bagnères-de-Bigorre, and Plombières-les-Bains, and sulfur, sodium, and chloride springs, as in Uriage and Challes-les-Eaux. These thermal waters, and those from the Spanish spas in Trillo and Ledesma, were famous as an adjuvant

therapy to mercurial treatment. In 1839, Parker proposed combining both treatments and introduced mercurial vapour baths. In Spain, Esquerdo used phosphorus to treat PGP.[2]

After analysing hundreds of arsenic mixtures, on 31 August 1909, Ehrlich and Hata finally developed one that was effective for syphilis treatment: dioxy-diamino-arsenobenzol-dihydrochloride or 'compound 606' (it was the 606th compound tested by these researchers), which was later called 'salvarsan' (i. e., 'arsenic that cures').[22,23] Some time later, in 1914, a new treatment was created by binding arsphenamine to an aldehyde of sodium bisulfite, to make 'compound 914' or neosalvarsan, which showed similar effectiveness but was less toxic. However, despite arsenic compounds effectively treated patients with primary syphilis, they failed to halt the progression to paralytic dementia.[3] In 1921, Sazerac and Levaditi introduced bismuth as a remedy for syphilis, and other treatments including radio-diathermy, light therapy, and electropyrexia were developed soon afterwards.[24]

The year 1917 was a turning point in the history of PGP: Jauregg introduced malariotherapy as a treatment for paralytic dementia after observing how mental function in patients with the disease improved when they contracted an infectious illness producing high fever.[25] Notwithstanding, in the 18th century, patients with PGP had also been prescribed hot water baths or other treatments aimed at causing fever, such as tuberculin (Battistessa, 1912).[26] On 14 June 1917, Wagner-Jauregg got a blood sample from a soldier wounded on the Balkan warfront who was suffering from tertian malaria but had not yet received quinine, and injected the sample into nine patients with PGP. Six of the patients displayed marked improvements, and three of these were able to return to normal life. To avoid complications of malaria, in 1919 bacteriologist Doerr provided Wagner-Jauregg with a strain of *Plasmodium* that was safe and highly sensitive to quinine.[3] This seemed to be the onset of a new period in the prognosis of this type of dementia. In 1927, Wagner-Jauregg was awarded the Nobel prize in Physiology for his contributions to the treatment of PGP. Despite dramatic complications (some of the first patients died since they had been inoculated with a quinine-resistant *Plasmodium*), this was the first time that progression to severe and irreversible dementia could be stopped in its tracks. Some time later, Wagner-Jauregg himself combined malariotherapy with other such drugs as arsenic derivatives or bismuth, reporting, in 1939, 33% of satisfactory results and 14% of incomplete results; however, no cases of *restitutio ad integrum* were seen.[3] In some centres, malariotherapy continued to be used until well into the 1960s.[27]

Vallejo-Nágera,[28] one of the first psychiatrists to apply Wagner-Jauregg's therapy in Spain, and especially Rodríguez Lafora, made outstanding contributions in the field. The latter published many works on neurosyphilis, describing perineuronal calcareous degeneration in patients with juvenile general paresis[29] and introduced intrathecal treatment for tabes dorsalis and PGP in Spain.[30] In his lecture titled *Progresos recientes en el tratamiento intrarraquídeo de la neurosífilis* (Oporto, 1921), he stated that he had performed more than 1100 intrathecal injections combined with intravenous treatments (using mercuy and salvarsan).

Fleming's discovery of penicillin provided the definitive treatment for this disease. In 1943, Mahoney, Arnold, and Harris[31] proposed penicillin as the treatment of choice against treponemal infection after achieving promising results in four sailors with chancres. Penicillin treatment for syphilitic patients led to a decrease in both morbidity and mortality associated with paralytic dementia and today cases of PGP are anecdotal. An unfortunate exception was the 'Tuskegee experiment', a clinical study of 400 African-Americans with syphilis conducted in Alabama between 1932 and 1972 by the US Public Health Service. Although penicillin was available from the 1940s, these patients were denied treatment so that the natural progression of untreated syphilis could be analysed.[32]

Conclusions

Paralytic dementia provides a good example of how the scientific community persisted in determining the aetiology of a disease and finding a suitable treatment. Likewise, it is an example of long-term complications involving an infectious agent. It also demonstrates the importance of determining the aetiological factor of a disease before choosing a treatment in order to halt or reverse that process, either partially or completely. Doctors should fight against therapeutic nihilism, most especially when it concerns patients' mental health. After much trial and error, an effective treatment which reduced suffering and complications stemming from paralytic dementia was finally developed.

Conflicts of interest

The authors have no conflicts of interest to declare.

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