An Unusual Neurological Syndrome of Crawling Gait, Dystonia, Pyramidal Signs, and Limited Speech

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ABSTRACT

Background: The purpose of the study was to identify and molecularly characterize a neurological syndrome in a consanguineous Pakistani family.
Methods: Five patients, their 2 siblings, and their parents were clinically examined. DNA from all 7 siblings was genotyped with Affymetrix SNP arrays and sequencing of selected candidate genes.
Results: An unusual neurological syndrome of crawling gait, predominant leg dystonia, pyramidal signs, microcephaly, and suspected deafness segregated in the family. Three patients ambulated on hands and knees,

either by hopping and crossing their legs, or by dragging the legs behind them. Two patients have acquired the ability to walk bipedally with a dystonic gait. Unexpectedly, no chromosomal region was homozygous in patients only. Under different disease models, we localized 7 chromosomal regions in the genome common to all patients. No pathogenic mutations were identified in selected candidate genes or the mitochondrial genome.
Conclusion: We describe an unusual movement disorder syndrome reminiscent of but distinct from Uner Tan syndrome. © 2011 *Movement* Disorder Society

Some movement disorders are characterized by distinct gaits or are part of rare syndromes with additional distinguishing phenotypes. For example, Uner Tan syndrome is characterized by a bear-like gait in which individuals walk on hands and feet (quadrupedal gait) and exhibit cerebellar ataxia.[1] In Woodhouse Sakati syndrome patients exhibit predominant dystonia of the lower limbs and dysarthria. In addition, extrapyramidal features, mental retardation, deafness, alopecia, hypogonadism, and diabetes mellitus are part of the clinical presentation.[2]

Mutations in many genes including those linked to mitochondrial integrity and function may cause movement disorder syndromes. For example *SUCLA2* encodes a subunit of a mitochondrial matrix enzyme, and its mutations cause a mitochondrial depletion syndrome that includes deafness and dystonia in the phenotype.[3] Mohr–Tranebjaerg syndrome is also a mitochondrial disease, and patients have deafness and dystonia with additional clinical manifestations.[4] In contrast, several unusual inherited movement disorders present with a combination of pyramidal and extrapyramidal signs in the absence of hearing loss. Complex hereditary spastic paraplegia[5] is an example of one such condition. Furthermore, disorders termed as neurodegeneration with brain iron accumulation (NBIA) may result in generalized dystonia with a severe gait disturbance along with optic degeneration.[6]

We report a neurological syndrome consisting of predominant dystonia with pyramidal signs, limited speech, and microcephaly segregating in 5 affected patients born to healthy, consanguineous parents in Pakistan. Three of 5 patients exhibit an unusual mode of locomotion in which they ambulate using all 4 limbs. This previously unreported syndrome is reminiscent of but distinct from Uner Tan syndrome and

thus adds to the current repertoire of movement disorders.

Patients and Methods

Family DYAF07 (Fig. 1A) is from a small village in Punjab, Pakistan. Patient VI:3 was examined by 1 of the authors (A.M.) at a hospital in Lahore. Samples were collected and processed (Appendix 1) after institutional review board approval at the School of Biological Sciences, University of the Punjab, with written informed consent for all participants. A motor exam was carried out (A.A.), and participants were videotaped at home. It was not possible to follow standard guidelines for neurological testing of the affected individuals because of limited cognition. These videotapes were reviewed by 2 of the authors (C.K., N.B.) blinded to diagnosis and pedigree position. Laboratory tests were carried out for patients VI:1 and VI:2 including blood counts, levels of copper and ceruloplasmin, and karyotyping as well as magnetic resonance imaging (MRI) of the brain. The hearing of 1 patient (VI:2) and his unaffected sibling (VI:4) was tested by audiometry.

Four genes connected with mitochondrial depletion syndromes, *SUCLA2, C10ORF2, RRM2B,* and *TK2,* were sequenced, and gene dosage analysis was performed by multiplex ligation-dependent probe amplification. Subsequently, gene mapping was carried out with Affymetrix Genome-wide Human SNP array 6.0 (Affymetrix, Santa Clara, CA). Data were analyzed under both recessive and dominant modes of inheritance with reduced penetrance. Linkage analysis was performed at a resolution of 0.5 cM using Allegro in EasyLINKAGE_v5.08.[7] Both parametric and nonparametric log odds scores were examined. Chromosomal haplotypes were generated with HaploPainter1.043.[8] Homozygosity mapping was performed with KinSNP[6] (Appendix 1). Microsatellite markers were used to confirm linkage regions (Appendix 1). In addition, 4 nuclear genes resulting as possible candidates after the linkage analysis, *CA9, TOMM5, MCART1,* and *GNAS,* were sequenced in patients VI:1 and VI:6. Finally, the mitochondrial genome of individual VI:6 was sequenced using DNA obtained from hair follicles (Appendix 1).

Results

Clinical Findings

Five individuals of family DYAF07 presented with an unusual neurological syndrome including generalized dystonia and variable degree of spasticity with lower-limb hyperreflexia and pyramidal signs (Videos 1–4 of affected individuals are available online). Bipedal locomotion was absent in 3 of the 5 affected individuals, whereas 2 patients who now walk bipedally had a distinct gait using
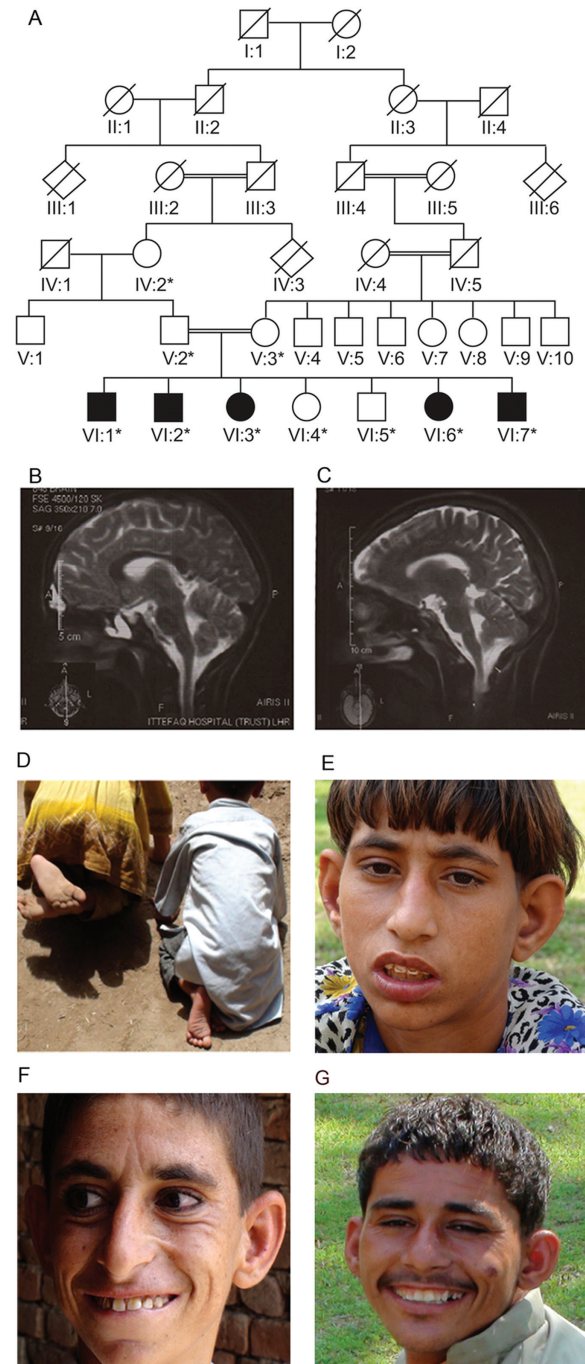

FIG. 1. Pedigree and clinical manifestations in family DYAF07. **A**: Family tree of DYAF07. Affected individuals are represented by filled symbols; deceased individuals are marked by a slash; double lines denote the presence of inbreeding loops in the pedigree; asterisks denote individuals who participated in the research. MRI findings and phenotypic presentation of the syndrome in family DYAF07. Sagittal T2-weighted MRI of patients VI:1 (**B**) and VI:2 (**C**) showing mild global brain atrophy, most pronounced in the medulla and the upper cervical spinal cord. Leukodystrophy or focal lesions could not be detected. **D**: Posture of VI:6 (left) and VI:7 (right) while ambulating. The legs are crossed at the back, and the patients are on their hands and knees. **E**: Photograph of VI:3, showing low-set ears and pointed face. **F**: Photograph of VI:2. Note pigmentation on the face and dysmorphic facial features. **G**: Individual VI:1 exhibits no dysmorphic facial features but presents with a dystonic risus sardonicus.

Table 1. Phenotypic details and results of the neurological examinations and laboratory and MRI findings for affected members of family DYAF07

	Subject				
	VI:7	VI:6	VI:3	VI:2	VI:1
Sex	M	F	F	M	M
Age at onset (y)	Birth	2.5	2	2.5	Birth
Age at examination (y)	3	7	14	17	19
Mode of locomotion	Hopping on hands and knees, legs crossed	Hopping on hands and knees, legs crossed	Dystonic gait	Dystonic gait	On hands and knees, legs crossed or dragged
Generalized dystonia	+	+	+	+	+
Reflexes	Brisk	Brisk	Brisk	Brisk	Brisk
Pyramidal signs	+	+	+	+	+
Speech	Sounds	Short words	Short words and sentences	Short words and sentences	Sounds and unclear short words
Hearing	NA	NA	NA	85 dB HL	NA
Head circumference[a] (cm)	NA	45.72	45.72	48.26	NA
Cognition	NA	NA	Limited[b]	Limited[b]	Extremely limited[c]
Facial morphology	Normal	Normal	Slightly dysmorphic with low-set ears	Mildly dysmorphic	Lower face dystonia (risus sardonicus)
MRI scan	NA	NA	NA	Minor global brain and upper cervical cord atrophy	Minor global brain and upper cervical cord atrophy
Serum copper and ceruloplasmin	NA	NA	NA	N	N
Karyotype	NA	NA	NA	46 XY	46 XY
Comments	Not able to feed himself	Has begun to walk a little by gripping and supporting herself with the help of furniture	Started ambulation by hopping on hands and knees like her younger iblings and then walked with a dystonic gait at around 6 years	Started ambulation by hopping on hands and knees like his younger siblings and then walked with a dystonic gait at around 6 years	Has never walked upright and his legs have become emaciated over the years

M, male; F, female; NA, not assessed; HL, hearing loss; CBC, complete blood counts; +, present; −, absent.
[a]2 standard deviations below normal for age and sex, according to the WHO head circumference chart.
[b]limited cooperation in carrying out a command, intelligent, recognizes well.
[c]does not follow commands, recognizes well.

all 4 limbs in childhood. A pronounced difference in dystonia of the lower extremities compared with the upper extremities exists in all affected individuals (Videos 1–4). The patients were able to straighten their legs completely when lying on their backs. Contractures of the hamstring muscles were excluded. All patients appear to have cognitive impairment, although this could not be formally tested. Head circumference is below the second standard deviation, consistent with microcephaly. Hearing loss is suspected in all 5 affected individuals. An audiogram of patient VI:2 revealed a severe degree of bilateral deafness (85 dB HL), though his cognitive impairment reduces the reliability of the test results. Speech production is severely limited in all patients, although enunciation is clear and dysarthria is absent. All affected individuals have extremely restricted activities of daily living.

Blood counts and ceruloplasmin and copper levels were within the normal range, ruling out Wilson's disease. Chromosomal abnormalities were absent. Cerebral MRI suggested minor global parenchymal atrophy, most prominent both frontally and infratentorially including the medulla and upper cervical cord (Fig. 1B,C). Acoustic neurinomas were excluded bilaterally. Short case reports of all patients are summarized in Table 1, and photographs of the patients illustrating the phenotype are shown in Figure 1D–G.

The paternal grandmother, parents, and 2 siblings were unaffected, and no neurological abnormalities were noticed on examination and in reviewing the videotapes of standardized neurological examinations. They have normal intelligence and hearing thresholds.

Molecular Findings

Sequencing of *SUCLA2* and additional genes linked to mitochondrial depletion syndromes (*C10ORF2*, *RRM2B*, and *TK2*) revealed no mutations. Other loci and genes in which mutations cause mitochondrial depletion syndromes or Uner Tan syndrome (*DGUOK*, *POLG*, *CA8*, *VLDLR*, and chromosome 17p13.3–p13.1) were excluded after single-nucleotide polymorphism (SNP) genotyping (Appendix 1). Analyses of SNP data did not identify any informative chromosomal region homozygous among the affected individuals of family DYAF07 (Appendix 1). An 8-cM region was identified on chromosome 9p21.1–p11.2 (Table e-1) at which the affected individuals were heterozygous for the same parental allele combinations, consistent with a recessive mode of inheritance with compound heterozygous mutations in the same gene. The 2 unaffected siblings carried different allele combinations. Under a dominant model of inheritance with reduced penetrance, there were 6 regions in the genome where affected individuals inherited the same chromosome from either parent. These regions are on chromosomes 1q42.3–q43, 3p26.3–p26.1, 9p21.1–q21.3, 16q21–q23.1, 20q13.2–q13.33, and 21q22.3 (Table e-1). Sequencing of candidate genes (Appendix 1) did not reveal any mutation. In addition, genes where mutations are known to result in Woodhouse Sakati syndrome (*C2ORF37*) or NBIAs (*PANK2*, *PLA2G6*, *FTL*, and *CP*) were not in these mapped intervals. No mutation was identified in the mitochondrial genome that segregated with the disease in the family.

Discussion

In this study, we have investigated a family with a previously unreported neurological syndrome presenting with a combination of signs of different movement disorders. Although ambulation may involve all 4 limbs in affected individuals, this syndrome differs from Uner Tan syndrome in several respects. This ambulation has no resemblance to the bear-like gait observed in Uner Tan syndrome in which patients sometimes may acquire bipedal gait first and lose it afterward. Patients with Uner Tan syndrome also have ataxia with cerebellar hypoplasia as a common feature. Although dystonia and, to a lesser degree, spasticity were the most prominent motor abnormalities in family DYAF07, ataxia was absent, and the patients had no cerebellar atrophy.

We hypothesize that the severe gait disturbance in patients in this family resulted from the combination of prominent leg dystonia and pyramidal involvement. Furthermore, the lower limb dystonia appeared to be in part action induced. Importantly, contractures did not contribute to the unusual type of locomotion. The crawling gait may be a compensatory strategy to overcome the restriction of locomotion in the affected individuals. Given the highly unusual type of locomotion that is not seen in other syndromes with combined dystonia and pyramidal signs, it is tempting to speculate that there may also be a neurodevelopmental defect that may lead not only to the unique gait pattern but also to the limited speech in the affected individuals.

Patients from consanguineous unions involving phenotypically unaffected parents are expected to have recessively inherited disorders and to be homozygous by descent for the disease gene. However, such a region was not identified in family DYAF07. Although unlikely because we used a high-resolution SNP array, we may have overlooked the disease gene–harboring homozygous region. The parents are third-degree cousins, and the region identical by decent may be small and localized in a region with low marker density. Notably, 21 small chromosomal regions were uninformative for linkage (Appendix 1). However, the phenotype observed in this family may be better explained by a different inheritance pattern. The affected individuals may be compound-heterozygous for mutations in a single gene, as has been observed for other recessive disorders segregating in consanguineous families.[9] Alternatively, 1 of the parents may be a carrier of the mutation without manifesting the phenotype because of incomplete penetrance of the disease gene or may have a mutation in an imprinted gene. There are 1 known (*GNAS*) and several predicted imprinted genes present in the mapped chromosomal locations.[10] Another possibility is that 1 of the parents exhibits germline mosaicism for a mutation in the disease-causing gene, as has been shown for other disorders.[11] We also cannot rule out the likelihood that mutations of 2 or more genes interact to produce the disease phenotype.

Because of the unknown mode of inheritance of the disorder segregating in family DYAF07 and the existence of many large chromosomal intervals that may harbor the disease gene, the responsible gene or genes may be identified in the future by sequencing the genomes of several affected and unaffected members from family DYAF07.[12]

Legends to the Video

Video 1 (VI:7). The patient ambulates on hands and knees by hopping and crossing his legs at the back. He propels his trunk with a hop while his legs are held in a dystonic posture.

Video 2 (VI:6). The first segment shows a "spontaneous" Babinski sign more pronounced on the left. Ambulation is similar to that of her brother (VI:7). With assistance, the patient displays a severely dystonic-spastic gait.

Video 3 (VI:3). The first segment shows leg spasticity and Oppenheim's reflex of the left leg. The patient and her brother (VI:2) are able to walk without

assistance, but present with a dystonic-spastic, hyper-lordotic gait.

Video 4 (VI:1). The patient has a severely dystonic gait; walking is only possible with assistance. He shows a dystonic smile when sitting. ∎

References

1. Tan U. Unertan syndrome: review and report of four new cases. Int J Neurosci. 2008;118:211–225.

2. Schneider SA, Bhatia KP. Dystonia in the Woodhouse Sakati syndrome: a new family and literature review. Mov Disord. 2008;23:592–596.

3. Carrozzo R, Dionisi-Vici C, Steuerwald U, et al. SUCLA2 mutations are associated with mild methylmalonic aciduria, Leigh-like encephalomyopathy, dystonia and deafness. Brain. 2007;130:862–874.

4. Koehler CM, Leuenberger D, Merchant S, Renold A, Junne T, Schatz G. Human deafness dystonia syndrome is a mitochondrial disease. Proc Natl Acad Sci U S A. 1999;96:2141–2146.

5. Gilbert DL, Leslie EJ, Keddache M, Leslie ND. A novel hereditary spastic paraplegia with dystonia linked to chromosome 2q24–2q31. Mov Disord. 2009;24:364–370.

6. Gregory A, Polster BJ, Hayflick SJ. Clinical and genetic delineation of neurodegeneration with brain iron accumulation. J Med Genet. 2009;46:73–80.

7. Hoffmann K, Lindner TH. easyLINKAGE-Plus—automated linkage analyses using large-scale SNP data. Bioinformatics. 2005;21:3565–3567.

8. Thiele H, Nurnberg P. HaploPainter: a tool for drawing pedigrees with complex haplotypes. Bioinformatics. 2005;21:1730–1732.

9. Petukhova L, Shimomura Y, Wajid M, Gorroochurn P, Hodge SE, Christiano AM. The effect of inbreeding on the distribution of compound heterozygotes: a lesson from Lipase H mutations in autosomal recessive woolly hair/hypotrichosis. Hum Hered. 2009;68:117–130.

10. Luedi PP, Dietrich FS, Weidman JR, Bosko JM, Jirtle RL, Hartemink AJ. Computational and experimental identification of novel human imprinted genes. Genome Res. 2007;17:1723–1730.

11. Depienne C, Arzimanoglou A, Trouillard O, et al. Parental mosaicism can cause recurrent transmission of SCN1A mutations associated with severe myoclonic epilepsy of infancy. Hum Mutat. 2006;27:389.

12. Roach JC, Glusman G, Smit AF, et al. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. Science. 2010;328:636–639.

Association of *SNCA* with Parkinson: Replication in the Harvard NeuroDiscovery Center Biomarker Study

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ABSTRACT

Background: Mutations in the α-synuclein gene (*SNCA*) cause autosomal dominant forms of Parkinson's disease, but the substantial risk conferred by this locus to the common sporadic disease has only recently emerged from genome-wide association studies.

Methods: We genotyped a prioritized noncoding variant in *SNCA* intron 4 in 344 patients with Parkinson's disease and 275 controls from the longitudinal Harvard NeuroDiscovery Center Biomarker Study.

Results: The common minor allele of rs2736990 was associated with elevated disease susceptibility (odds ratio, 1.40; *P* = .0032).

Conclusions: This result increases confidence in the notion that in many clinically well-characterized patients, genetic variation in *SNCA* contributes to "sporadic" disease. © 2011 *Movement* Disorder Society

Key Words: Parkinson's disease; α-synuclein; GATA transcription factors; biomarker; genome-wide association study

Parkinson's disease (PD) is an aging-dependent, progressive neurodegenerative disease that poses an increasing threat to public health as life expectancy is improving worldwide. α-Synuclein has been correlated with sporadic PD since its discovery as a core constituent of Lewy bodies, but a considerable genetic contribution of noncoding *SNCA* variants to the sporadic disease has only recently emerged from genome-wide association studies. In this study we successfully replicated an association between the rs2736990 variant in *SNCA* intron 4 and PD highlighted by Simon-Sanchez et al (2009) in the Harvard NeuroDiscovery Center Biomarker Study (HBS).

Patients and Methods

Study Population

HBS is a Harvard-wide, longitudinal case–control study designed to accelerate the discovery and validation of molecular diagnostics that track or predict progression of early-stage PD and Alzheimer's disease (AD). Inclusion criteria for cases with PD are age ≥21, diagnosis of PD according to UK PD Society Brain Bank (UKPDSBB) criteria or according to movement disorders specialist assessment,[1] MMSE score >21 or next of kin present to provide informed consent, and ability to provide informed consent. Two modifications to UKPDSBB clinical diagnostic criteria were made to allow for more than 1 affected relative and response to dopamine replacement therapy. Exclusion criteria for cases with PD in HBS were diagnosis

of a blood or bleeding disorder, known hematocrit <30, or known active ulcer or active colitis. Inclusion criteria for healthy controls were no current diagnosis or history of a neurological disease, ability to provide informed consent, and age ≥21 (≥30 for spouses of AD patients). The controls were comparable to the PD cases in that they were drawn from the same source population and could be identified as a case if they had disease. Exclusion criteria for controls were analogous to those for cases. For the current genetic case–control association study nested in HBS, all cases with PD and healthy controls enrolled in HBS at the time of the analysis (February 2010) with available DNA specimens were included, yielding a total of 375 cases with PD and 275 controls. The institutional review boards of Brigham and Women's Hospital and Massachusetts General Hospital approved all studies.

Genetic Association Study

Genotyping was performed by TaqMan SNP assay on an ABI7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) for SNP rs2736990 (ACCTTATGAGCTGTTTAGGAAGAAG [A/G]TGTATATGTGTGTAACAGGGAGCAA). The genotyping completion rate was 98%, and the concordance rate was 100% for replicate assays included for 10% of randomly selected samples. Genotype frequencies were examined for deviation from the Hardy–Weinberg equilibrium using χ^2 tests. Logistic regression was used to estimate statistical significance, odds ratios (ORs), 95% confidence intervals (CIs) under allelic, dominant, and recessive models while adjusting for age and sex, using SAS software 9.2 for Windows (SAS Institute, Cary, NC). The Cochran–Armitage trend test was used to examine allelic additive effects. The primary analysis included cases meeting UKPDSBB diagnostic criteria. The secondary analysis included all cases based on a diagnosis of PD by a movement disorders specialist. $P < .05$ was considered statistically significant.

Results

Three hundred and forty-four of 375 patients (91.73%) diagnosed with PD by a neurology board-certified, movement disorders fellowship-trained neurologist met modified UKPDSBB criteria. An overview of baseline clinical characteristics is shown in Table 1. Allele frequency distribution of the rs2736990 polymorphism in *SNCA* is shown in Table 2. Hardy–Weinberg equilibrium was not violated in the controls. This SNP was highly present in the general population, with a minor allele frequency (G) of 45.9% in the controls and 54.5% in cases with PD. We found a significant association between the rs2736990 variant and PD in the HBS population (Table 2). For cases meeting UKPDSBB criteria, significant associations were obtained under dominant (OR, 1.60; 95% CI,

Table 1. Clinical characteristics of study participants

Disease status	PD	Control	P^b	PD Genotype AA[a]	Genotype AG[a]	Genotype GG[a]	P^c
n	375	275		80	181	114	
Age, mean ± SD	66.42 ± 10.83	68.57 ± 10.42	.0114	67.23 ± 13.89	66.18 ± 9.97	66.24 ± 9.73	.4942
Male	244 (65.07%)	94 (34.18%)	< .0001	56 (70.00%)	118 (65.19%)	70 (61.40%)	.4651
Age of onset	61.00 ± 11.51			61.56 ± 14.43	61.07 ± 10.37	60.44 ± 10.88	.8136
Clinical findings (%)							
Bradykinesia	374 (99.73)			80 (100.00)	181 (100.00)	113 (99.12)	1.0000
Resting tremor	265 (70.67)			61 (76.25)	130 (71.82)	74 (64.91)	.2006
Rigidity	366 (97.60)			79 (98.75)	176 (97.24)	111 (97.37)	.7006
Asymmetric onset	283 (75.47)			59 (73.75)	137 (75.69)	87 (76.32)	.8749
Postural instability	191 (50.93)			41 (51.25)	84 (46.41)	66 (57.89)	.1335
UPDRS total, mean ± SD	32.78 ± 15.70			33.12 ± 15.10	31.51 ± 15.06	34.47 ± 16.96	.2322
UPDRS subscale 1	1.83 ± 1.70			1.93 ± 1.68	1.70 ± 1.58	1.98 ± 1.89	.3412
UPDRS subscale 2	9.50 ± 5.84			9.98 ± 6.43	9.20 ± 5.49	9.66 ± 5.96	.5830
UPDRS subscale 3	19.32 ± 10.09			19.71 ± 9.47	18.31 ± 9.67	20.58 ± 11.01	.1628
UPDRS subscale 4	2.35 ± 2.18			2.13 ± 2.04	2.46 ± 2.32	2.33 ± 2.03	.5361
Hoehn and Yahr	2.16 ± 0.75			2.30 ± 0.84	2.06 ± 0.66	2.21 ± 0.81	.0459
MMSE	28.19 ± 2.46	29.27 ± 1.10	< .0001	28.00 ± 2.82	28.36 ± 2.24	28.03 ± 2.53	.2094
Medications (%)							
De novo	50 (13.33)			9 (11.25)	28 (15.47)	13 (11.40)	.5009
Carbidopa + levodopa	250 (66.67)			53 (66.25)	118 (65.19)	79 (69.30)	.6640
Ropinirole	53 (14.13)			12 (15.00)	26 (14.36)	15 (13.16)	.9466
Pramipexole	106 (28.27)			22 (27.50)	48 (26.52)	36 (31.58)	.5869
Amantadine	37 (9.87)			5 (6.25)	19 (10.50)	13 (11.40)	.4405
Entacapone	52 (13.87)			9 (11.25)	27 (14.92)	16 (14.04)	.7188
Trihexphenidyl	15 (4.00)			2 (2.50)	5 (2.76)	8 (7.02)	.1341
Carbidopa + levodopa + entacapone	39 (10.40)			9 (11.25)	17 (9.39)	13 (11.40)	.8155
Selegiline	25 (6.67)			3 (3.75)	15 (8.29)	7 (6.14)	.3843
Rasagiline	32 (8.53)			8 (10.00)	15 (8.29)	9 (7.89)	.8735
Other PD meds	36 (9.60)			6 (7.50)	21 (11.60)	9 (7.89)	.4790

[a]The right side of the table shows clinical characteristics of cases with PD carrying 2 (GG), 1 (AG), or no (AA) risk alleles.
[b]The t test or χ^2 test was used to estimate the significance of differences between cases and controls for numerical and nominal variables, respectively.
[c]The ANOVA or χ^2 test was used to explore differences in clinical characteristics within PD cases of distinct genotypes; note that P values shown were not adjusted for the multiple clinical characteristics explored.

1.08–2.36), recessive (OR, 1.54; 95% CI, 1.04–2.28), and allelic models (OR, 1.41; 95% CI, 1.11–1.78); see Table 2. For each minor allele, there was a 40% increase in the risk of PD (OR, 1.40; 95% CI, 1.12–1.76; $P = .0032$) in the carriers. A secondary analysis that included all 375 cases based on a diagnosis of PD by a movement disorders specialist produced virtually identical results (Table 2). Exploratory analyses of clinical phenotypes of cases with PD carrying 2 (GG), 1 (AG), or no (AA) risk allele are shown on the right side of Table 1. Considering the many clinical charac-

teristics explored, none reached compelling statistical significance after adjustment for multiple testing (although trends observed may justify further exploration in a much larger cohort).

Discussion

α-Synuclein is central to the pathobiology of PD. Simply genetically increasing the expression of the α-synuclein gene (*SNCA*) by 50%–100% through locus multiplication unequivocally causes autosomal dominant Parkinson's disease.[2] Over the years these increases in wild-type

Table 2. Association between the intron 4 *SNCA* polymorphism rs2736990 and risk of PD

Diagnostic criteria	n PD	Control	MAF[a] (%) PD	Control	Additive[b] OR (95% CI)	P	Dominant OR (95% CI)	P	Recessive OR (95% CI)	P	Allelic OR (95% CI)	P
UKPDSBB	344	275	54.51	45.94	1.40 (1.12–1.76)	.0032	1.60 (1.08–2.36)	.0183	1.54 (1.04–2.28)	.0297	1.41 (1.11–1.78)	.0052
PD specialist	375	275	54.53	45.94	1.40 (1.12–1.75)	.0026	1.59 (1.09–2.34)	.0173	1.55 (1.06–2.28)	.0245	1.41 (1.14–1.78)	.0043

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for minor allele, adjusted for age and sex.
[a]Minor allele frequency.
[b]Linear trend for 0, 1, or 2 minor alleles.

SNCA expression, although small, are sufficient to bring death to a majority of vulnerable dopamine neurons. Whereas mutations in *SNCA* have long been linked to rare autosomal dominant forms of PD, a substantial genetic contribution of this gene to sporadic PD has only recently been appreciated.[3] A recent genome-wide association study highlighted an association between the rs2736990 variant in *SNCA* intron 4 and common sporadic PD.[3] Here we confirmed this association in an independent, clinically well-characterized population. This intronic variant, together with the REP1 *SNCA* promoter polymorphism[4] and other implicated 5′ and 3′ variants,[3,5] suggests a genetic role for noncoding variants in *SNCA* in conferring susceptibility to some forms of the common "sporadic" disease. How such polymorphisms enhance susceptibility to PD is unclear. It is possible that rs2736990 or an as yet unidentified linked causal sequence variant may regulate transcription of *SNCA* either directly through a *cis*-acting mechanism or indirectly through interaction with transcriptional enhancers[6] and repressors. Pinpointing the true PD-associated variants in *SNCA* and their mechanism and clarifying the relation to early mitochondrial dysfunction[7] will be important challenges for future research. ∎

References

1. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain. 2002;125:861–870.

2. Singleton AB, Farrer M, Johnson J, et al. Alpha-Synuclein locus triplication causes Parkinson's disease. Science. 2003;302:841.

3. Simon-Sanchez J, Schulte C, Bras JM, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009;41:1308–1312.

4. Chiba-Falek O, Nussbaum RL. Effect of allelic variation at the NACP-Rep1 repeat upstream of the alpha-synuclein gene (*SNCA*) on transcription in a cell culture luciferase reporter system. Hum Mol Genet. 2001;10:3101–3109.

5. Mueller JC, Fuchs J, Hofer A, et al. Multiple regions of alpha-synuclein are associated with Parkinson's disease. Ann Neurol. 2005;57:535–541.

6. Scherzer CR, Grass JA, Liao Z, et al. GATA transcription factors directly regulate the Parkinson's disease-linked gene alpha-synuclein. Proc Natl Acad Sci U S A. 2008;105:10907–10912.

7. Zheng B, Liao Z, Locascio JJ, et al. PGC-1α, a potential therapeutic target for early intervention in Parkinson's disease. Sci Transl Med. 2010;2:52ra73.

Projected Numbers of People With Movement Disorders in the Years 2030 and 2050

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ABSTRACT

Background: Movement disorders are chronic diseases with an increasing prevalence in old age. Because these disorders pose a major challenge to patients, families, and health care systems, there is a need for reliable data about the future number of affected people.

Patients and Methods: We searched the literature to identify epidemiological studies to obtain age-specific prevalence data of movement disorders. We combined the age-specific prevalence data with population projections for Europe, the United States, and Canada.

Results: Movement disorders will increase considerably between 2010 and 2050. The highest increase will be for dementia with Lewy bodies. In several countries, we project a near doubling of patients with PD.

Conclusions: There will be a strong increase in the number of people affected by most movement disorders between 2010 and 2050. This increase will mostly depend on the future aging of populations in terms of their age structure and future life expectancy. © 2011 *Movement* Disorder Society

Key Words: neurodegeneration; prevalence; movement disorders

Life expectancy has increased during the past 160 years by approximately 3 months per decade.[1] Both increasing life expectancy and decreasing fertility result in a growing proportion of elderly people. In particular, the occurrence of neurological disorders and, above all, movement disorders is a growing concern, as age is, for most of them, the strongest risk. Brain disorders account for the highest number of disability adjusted life years (DALYs).[2] In addition, the majority are associated with psychiatric disorders, such as depression, leading to a severe reduction in quality of life as well as increasing physical problems. A high level of care along with losses of output to the economy and increased medical expenditure render mental diseases the most costly disease group.[3,4] These increasing costs pose major challenges to societies and health care systems. For long-term planning, however, it is important to estimate the future number of people who are likely to suffer from movement disorders.

To date, a large number of studies have focussed on the prevalence and incidence of different neurological disorders.[5–8] However, only a few projections of the number of people who are likely to suffer from movement disorders over the next 40 years are available. An analysis of Parkinson's disease (PD) was performed to project the number of PD patients in the year 2030,[9] revealing an increase, by a factor of 2, from 4 to nearly 9 million affected people in 2030. To close the epidemiological gap of missing projections for neurological disorders, we projected the number of people who will suffer from several major movement disorders in the year 2050.

Patients and Methods

The following 12 movement disorders were included in our search: Wilson's disease (ICD-10: E83.0); Gilles de la Tourette syndrome (GTS; ICD-10: F95.2); Huntington's disease (ICD-10: G10); ataxias (ICD-10: G11); idiopathic PD (ICD-10: G20); progressive supranuclear palsy (PSP; ICD-10: G23); corticobasal degeneration (CBD; ICD-10: G23); focal and generalized dystonia (ICD-10: G24); essential tremor (ET; ICD-10: G25); restless legs syndrome (RLS; ICD-10: G25.81); Lewy body dementia (LBD; ICD-10: G31.82); and multiple system atrophy (ICD-10: G90.3).

We performed a systematic literature search in the electronic databases, MEDLINE and PreMEDLINE, using a combined search strategy, including the respective disease terms and the term, prevalence/epidemiology. As inclusion criteria, each publication had to contain an adequate epidemiological evaluation according to current standards. A standardized assessment form was used to extract the data. For diseases with insufficient data, prevalence rates were calculated using data from the German sickness funds (GKV), which were provided by the research centers from the Statistical Office Germany.[10] This applied to Huntington's chorea, ataxias, PD, and PSP. It must be noted that CBD has been assigned the code G23, as well as progressive supranuclear palsy. Therefore, these two diseases could not be differentiated. The prevalence for GTS was based on two sources: First, the mean prevalence rate was calculated from literature sources; second, age profiles from the GKV data for ages 0 to 9 and 10 to 19 were applied. A detailed description of the methods underlying the prevalence-based projections is given in two recent publications.[11,12] An overview of the data sources can be found in Supporting Material Table 1. Wilson's disease was excluded because of missing prevalence data.

In a second step, age-specific population projections for all countries were used. We projected the number of people who are likely to suffer from movement disorders in 2050 by combining the age-specific population figures with age-specific prevalence rates of the diseases assuming constant prevalence (for a detailed method description, see Supporting Information).

Results

The number of patients with movement disorders is going to increase during the next 40 years, up until 2050 (Table 1; Figs. 1 and 2).

From the 12 analyzed disorders, RLS is the most prevalent disease, with 9.22 million people above the age of 65 who were affected in 2010 in Europe (EU27) (1.8% of the total population), 3.78 million in the United States (1.2%), and 0.50 million in Canada (1.5%). By 2050, the numbers will increase to 14.9 million in Europe (2.9%), 8.33 million in the United States (1.9%), and 1.12 million in Canada (2.7%) Table 1.

PD is a major reason for disability among the affected elderly. Approximately 0.4% to 0.5% of the total population were found to be affected in 2010, increasing to approximately 0.8% in Europe and Canada and 0.6% in the United States.

The other investigated disorders were found to be much less prevalent in the populations, for example, from 0.06% for LBD to approximately 0.002% for MSA. Because they occur more frequently in higher age groups, the number of people affected by these diseases is going to increase.

To make a comparison feasible between the different disorders, we used an indexed illustration. Figure 1 shows the indexed increase of people in the projected age groups with the respective disorders for all countries combined. Starting from a base (2010) of 100, the increase up to 2050 is shown. The largest increase of more than 131% up to 2050 is seen for LBD, followed by PD with 92%. GTS shows the smallest change, of only approximately 4%. In addition, we calculated the indexed change in overall prevalence up to 2050 for the different countries stratified

by the respective movement disorders (Fig. 2). Increases were found to vary considerably across countries, as well as across the different movement disorders.

Discussion

Up to the year 2050, the number of people with movement disorders in developed countries is going to increase considerably. In this projection, the rate of change depends not only on population changes, but also on gender- and age-specific prevalence rates and on the size of the equivalent gender- and age-specific populations.

Other projections of single disorders obtained similar results. Dorsey et al. examined the increase in prevalence of PD in Western European countries.[9]

They found an increase by a factor of 2 between 2005 and 2030. Approximately 9 million people will suffer from PD in the year 2030 in the 10 most populous countries. We projected PD for 27 European countries, as well as for the United States and Canada, up to 2050. Our results showed an increase by a factor of 1.6 between 2010 and 2035 and are, therefore, comparable with those of Dorsey et al.[9]

Our data on the development of movement disorders over the forthcoming years are essential when considering the burden imposed by this disease group on society. To more comprehensively calculate the impact of movement disorders, further measures will have to be considered in addition to mere epidemiological data. Recently, the concept of the burden of

Table 1. Projected Prevalence Cases For All Diseases, Provided For the Years 2010, 2030, and 2050

	PD			Ataxia		
Year	EU27	United States	Canada	EU27	United States	Canada
2010	2,325,436	1,129,024	131,712	202,958	114,287	12,941
2030	3,270,782	1,878,223	237,439	238,076	152,737	17,635
2050	4,245,257	2,539,630	317,269	254,410	183,139	20,117

	LBD			PSP/CBD		
Year	EU27	United States	Canada	EU27	United States	Canada
2010	301,140	128,758	18,912	59,349	31,860	3,677
2030	455,899	210,597	35,058	73,638	45,256	5,437
2050	691,300	310,047	55,533	82,909	55,656	6,454

	ET			RLS		
Year	EU27	United States	Canada	EU27	United States	Canada
2010	5,776,481	3,001,897	350,888	9,221,431	3,777,974	499,560
2030	7,702,637	4,586,688	574,439	12,733,919	6,179,263	941,849
2050	9,143,046	5,830,989	718,879	14,916,025	8,325,575	1,115,829

	Huntington's chorea			GTS		
Year	EU27	United States	Canada	EU27	United States	Canada
2010	64,772	37,156	4,236	1,759,336	1,402,500	124,511
2030	73,067	47,004	5,405	1,695,493	1,624,183	127,670
2050	73,696	55,113	5,950	1,616,360	1,880,188	128,185

	MSA			Dystonia		
Year	EU27	United States	Canada	EU27	United States	Canada
2010	10,257	5,171	615	77,698	42,108	4,930
2030	12,864	7,793	964	96,457	56,549	6,965
2050	13,153	8,538	1,029	103,024	68,366	8,158

Data for Canada are 2011, 2031, and 2051.
Abbreviations: PD, Parkinson's disease; LBD, Lewy body dementia; PSP, progressive supranuclear palsy; CGB, corticobasal degeneration; ET, essential tremor; RLS, restless legs syndrome; GTS, Gilles de la Tourette syndrome; MSA, multiple system atrophy.
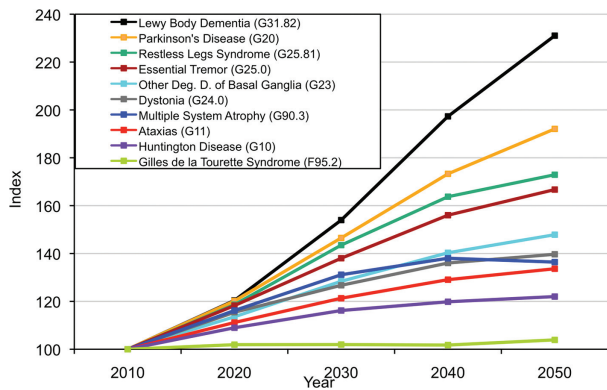
FIG. 1. Indexed increase for the respective movement disorders until 2050 for all countries combined.

illness was put forward.[8] This encompasses not only disease frequency, but also the effective loss of working power, the years of life lost, and the social conse-

quences of these diseases. Two important concepts were developed to quantify this burden: DALYs[13] and quality adjusted life years.[14] These imply information about disease stages, measurements of disability, therapy costs, and socioeconomic factors. Unfortunately, these data are currently not available for movement disorders.

Despite a systematic selection of the studies included, the statistical analysis, and the standardized projection, our study had some limitations. First, the currently available data on movement disorders are incomplete. However, we could use GKV data whenever literature results were not available or were insufficient. Second, in these cases, we had to use three-digit ICD codes and not the more detailed four-digit ICD codes. However, the advantage of the GKV data set is its sample size of more than 2 million people in Germany.[11] Calculations of
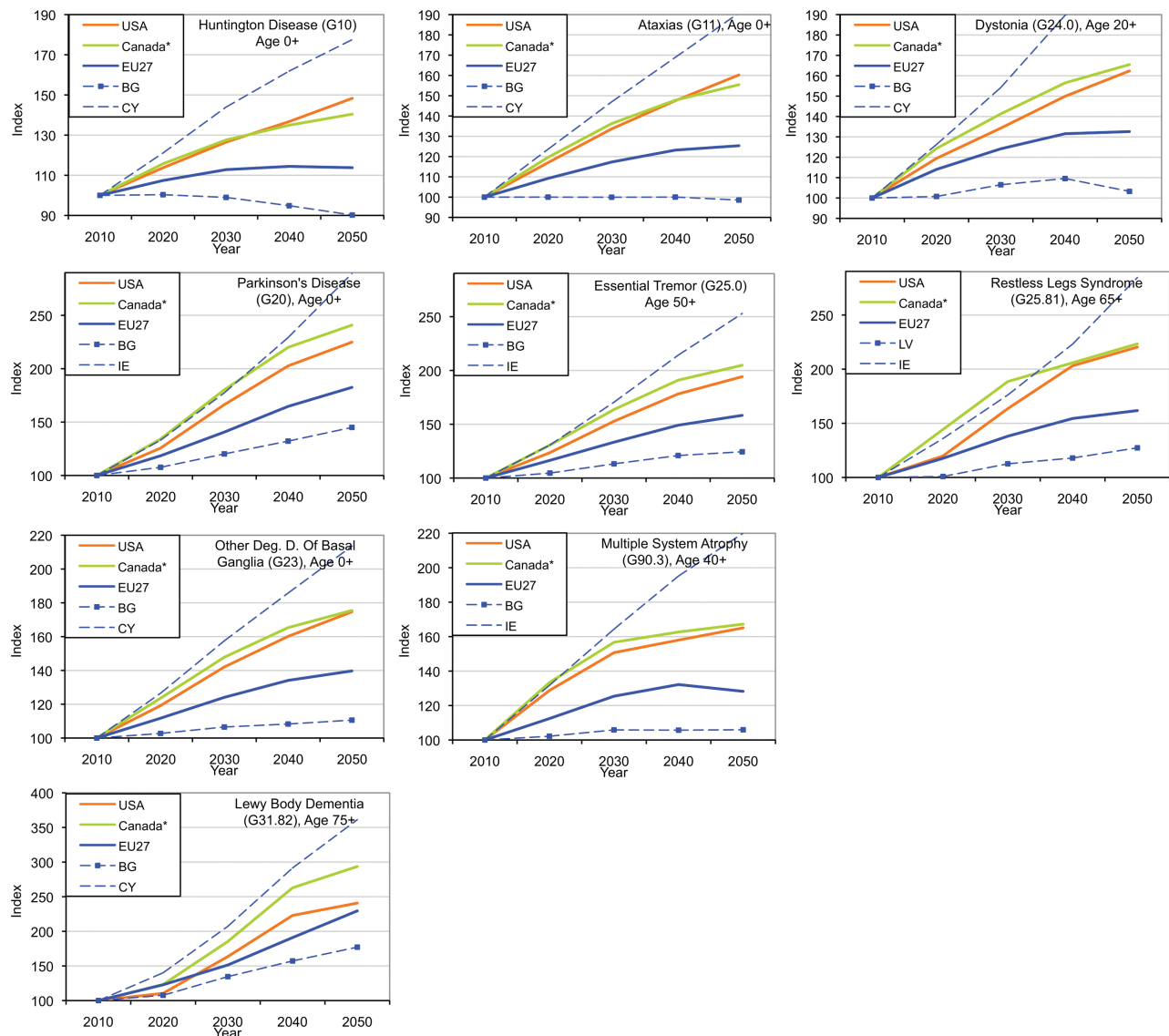

FIG. 2. Indexed increase in the United States, Canada, and Europe (EU27, Norway, and Switzerland) and the countries with the highest/lowest increase in Europe (BG, Bulgaria; CY, Cyprus; IE, Ireland; LT, Lithuania). Note the different values of the *y*-axis.

the prevalence and incidence rates of dementia showed that the results are quite in line with international meta-analyses.[15] Thus, it seems justified to use these data for calculating the prevalence of diseases for which insufficient literature data exist. Third, we had to exclude Asian and African countries because of insufficient data on incidence and prevalence rates.

Finally, the population projection also bears uncertainties. Mortality assumptions are especially important here, as movement disorders are most prevalent in higher age groups. If the decline in mortality is underestimated, as was generally the case in earlier projections and if the rise in life expectancy is larger than projected, there will be more and, on average, older elderly people in 2050, with a subsequent increase of patients and affected subjects with movement disorders.

Our estimates would have been more precise if country-specific prevalence rates were available. These are not yet available for every country included in this analysis, and these data are incomplete for European countries.[4] Therefore, further studies will be required to obtain detailed data on country-specific prevalence rates and to correct these data according to country. However, our data are still a valuable parameter for underlining the economic burden of disease development over the next 40 years.

Conclusion

In conclusion, the number of people with movement disorders is going to increase because of the aging population. However, these estimates are conservative, as a so-called "status-quo model" with constant prevalence rates was applied, which neglects societal changes and medical progress. It is most likely that, by 2050, there will be therapeutic options for many of the diseases analyzed in this study. This would result in a decrease of age-specific prevalence, which, in turn, would result in lower numbers of patients. These gains may, however, be offset by a faster rise in life expectancy, resulting in an even larger number of elderly people than assumed today. Accordingly, these disorders pose a major threat to both patients and health care systems, as patients will grow older with these disorders.

References

1. Oeppen J, Vaupel JW. Demography. Broken limits to life expectancy. Science 2002;296:1029–1031.
2. Kaplan W Laing R. Priority medicines for europe and the world. World Health Organization. 2004. [Available at: http://mednet3.who.int/prioritymeds/]. Accessed on February 2010.
3. WHO. Neurological disorders. Public health challenges. Geneva: World Health Organization; 2006.
4. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J. Cost of disorders of the brain in Europe. Eur J Neurol 2005;12(Suppl 1):1–27.
5. Alves G, Forsaa EB, Pedersen KF, Dreetz Gjerstad M, Larsen JP. Epidemiology of Parkinson's disease. J Neurol 2008;255(Suppl 5):18–32.
6. Berger K, Kurth T. RLS epidemiology—frequencies, risk factors, and methods in population studies. Mov Disord 2007;22(Suppl 18):S420–S423.
7. Harper PS. The epidemiology of Huntington's disease. Hum Genet 1992;89:365–376.
8. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology 2007;68:326–337.
9. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007;68:384–386.
10. Lugert P. Sample data from the statutory health insurance—foundation and structure of the data. Wiesbaden, Germany: Federal Statistical Office; 2007.
11. Ziegler U, Doblhammer, G. Projection of people with dementia in germany—projections of the number of people with dementia through 2047 In: Doblhammer G, ed. Ageing, Care Need, and Quality of Life—The Perspective of Care Givers and People in Need of Care. Wiesbaden, Germany: VS Verlag; 2010.
12. Doblhammer G, Ziegler U, Muth, E. Trends and patterns in life expectancy and health, and dementia projections for Germany until 2050. In: Kumbier E TS, Herpertz SC eds. Ethics and remembrence: the responsibility of psychiatry in the past and present. Lengerich, Germany: Pabst Science Publishers; 2009:91–108.
13. Murray CJ, Lopez AD. Evidence-based health policy—lessons from the Global Burden of Disease Study. Science 1996;274:740–743.
14. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253–1258.
15. Ziegler U, Doblhammer, G. Prevalence and incidence of dementia in Germany - a study based on data from the public sickness funds in 2002. Das Gesundheitswesen 2009;71:281–290.
16. The Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group. A prevalence study of primary dystonia in eight European countries. J Neurol 2000;247:787–792.
17. Wenning GK, Kiechl S, Seppi K, et al. Prevalence of movement disorders in men and women aged 50–89 years (Bruneck Study cohort): a population-based study. Lancet Neurol 2005;4:815–820.
18. Dogu O, Sevim S, Camdeviren H, et al. Prevalence of essential tremor: door-to-door neurologic exams in Mersin Province, Turkey. Neurology 2003;61:1804–1806.
19. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. Neurology 2000;54:1064–1068.
20. Chrysostome V, Tison F, Yekhlef F, Sourgen C, Baldi I, Dartigues JF. Epidemiology of multiple system atrophy: a prevalence and pilot risk factor study in Aquitaine, France. Neuroepidemiology 2004;23:201–208.

A Clinical Test for the Alcohol Sensitivity of Essential Tremor

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ABSTRACT

Background: The objective of the study was to develop a simple diagnostic test for alcohol sensitivity of essential tremor patients. Here we describe the controlled measurements of tremor severity after alcohol ingestion and the practicability of using it as a home test. **Methods:** Ten patients were tested for alcohol sensitivity under controlled conditions in the laboratory (blood alcohol, quantitative tremor recordings, modified Fahn scale, visual analog scale, Archimedes spirals), and 15 patients were instructed to perform an alcohol test at home (visual analog scale, Archimedes spirals) following an adapted dosage of alcohol. **Results:** The time course of the antitremor effect showed significant improvement of up to 50% in both groups for all the outcome parameters. Tremor deteriorated after 3 hours. A quarter of the patients noticed the alcohol effect for the first time during the test. **Conclusions:** Alcohol is an effective drug for essential tremor. Its effect is only short-lived and exhibits a rebound after > 3 hours and the next morning. We propose this essential tremor home test as a diagnostic tool to confirm the alcohol sensitivity of essential tremor. © 2011 Movement Disorder Society

Key Words: essential tremor; alcohol sensitivity; Archimedes spirals; Fahn scale; rebound

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Essential tremor (ET) is among the most common movement disorders, with a prevalence of approximately 4% in persons older than 65 years.[1] The tremor-suppressing potential of alcohol on ET was first reported in 1975[2] and later confirmed by several studies.[3–6]

Meanwhile, alcohol sensitivity is part of the secondary criteria for the diagnosis of ET.[7] Alcohol specifically reduces ET severity at low blood levels, with a reduction of tremor amplitude of 50%–70%.[8]

The idea of this study is to develop a standardized test for the responsiveness of an individual patient to alcohol. As a first step, the alcohol effect needed to be quantified. Both the time course and the amount of tremor suppression were systematically studied, and spiral drawing and the visual analog scale (VAS) were found to be valid markers. As a proof-of-principle, we asked 15 patients to drink a defined amount of alcohol at home and to document the response with these measures.

Patients and Methods

Patients suffering from ET were selected from the in- and outpatient clinics of the Department of Neurology Kiel. The patients fulfilled the diagnostic criteria of classic ET as defined by the consensus statement of the Movement Disorder Society.[9] Inclusion criteria were definite essential tremor and age > 18 years. Patients suffering from diseases prohibiting alcohol ingestion were excluded. The study protocol was approved by the local ethical committee, and all patients gave written informed consent.

Assessment of Alcohol Response under Controlled Conditions

Ten patients were included (mean age, 57 ± 20 years; mean disease duration, 29 ± 23 years; 6 patients with a positive family history in first-degree relatives) to undergo an alcohol test in the laboratory. Eight patients reported that ingestion of alcohol produced a positive effect on their tremor. One reported no significant effect, and 1 patient has never tested the effect of alcohol.

The dosage of alcohol was adapted for each individual according to weight and sex to receive a target response of approximately 0.8‰ blood alcohol according to the published Widmark formula.[10] The test started between noon and 1 PM after a full breakfast but without lunch. The patients were asked to drink their predetermined amount of alcohol as fast as possible (5–10 minutes). For the tremor recordings, each patient was seated in a comfortable chair. Tremor was measured with a modified Fahn scale (rating only upper extremities),[11] a 100-point visual analog scale (VAS),[12] drawing of Archimedes spirals,[13] and Fourier transform of accelerometry (totalpower).[14]

The tests were obtained before alcohol ingestion and after 10, 20, 30, 40, 50, 60, and 90 minutes, in the

evening of the same day and the next morning. For each of these times, the blood alcohol level was measured from venous blood, and tremor was examined with the scales and tests mentioned above. The spirals were blinded and analyzed by 2 trained reviewers (K.K., and D.L.).[13]

Home Test

Fifteen patients suffering from definite ET (mean age, 60 ± 13 years; mean disease duration, 34 ± 17 years; 7 patients with a positive family history) completed the test at home. Ten patients reported ingestion of alcohol had a positive effect on their tremor severity. Five reported no significant effect. The patients received an instruction manual, the patient information, an informed consent, a short questionnaire, and Archimedes spirals and VAS sheets to complete. Using weight, sex, and volume percent of the alcohol, the individual dosage of alcohol could be calculated based on a conversion table in the instruction manual. Before drinking alcohol and every 5 minutes after alcohol ingestion, they drew 1 spiral with each hand and estimated their tremor via VAS (5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, and 90 minutes, in the evening and the next morning). The whole material was posted back and again blindly evaluated (see above).

Statistical Analysis

The t test was applied to assess correlation coefficient using Pearson's r (SPSS 17). The results were analyzed by comparing the baseline scores (Fahn scale, Archimedes spirals, VAS, Fourier transform of accelerometry [totalpower]) with those from follow-up examinations (20, 30, 40, 50, and 60 minutes) using repeated-measures ANOVA. Changes for the different times were analyzed post hoc using Bonferroni/Dunn corrections. $P < .05$ was considered significant.

Results

The 10 patients who underwent the laboratory-test program showed that alcohol had a profound effect on their tremor according to the different measures. Figure 1a–d shows the time course of the mean values of all parameters: Spiral values improved by 2.4 to 3.1 points on the Bain tremor scale (0–10),[15] the VAS (0–100) by 20 to 31 points, the Fahn scale (0–24) by 2.7 to 4.8, and totalpower between −0.75 and −0.53 (log milligravities^2). Repeated-measures ANOVA was significant for all measures, and post hoc comparisons using the Bonferroni/Dunn corrections showed significant results in the laboratory test between 20 and 60 minutes, as indicated by asterisks in Figure 1a–d. Figure 1g shows a synopsis of the findings, with the improvement of the different outcome parameters in percentages of baseline. It is evident that all the parameters show almost the same time course depending

on the blood alcohol level. Improvement began within the first 10 minutes after ingestion but was short lasting and faded after 60–90 minutes. All patients suffered a severe tremor rebound the next morning. Tremor totalpower deteriorated up to −10^3 %, Fahn score up to −31%, VAS up to −21%, and Archimedes spirals up to −10% (Fig. 1).

All 15 patients who completed the ET home test also showed that alcohol had a pronounced effect (Fig. 1e–f): improvement of the VAS (0–100) between 14 and 32 points and of the Archimedes spirals between 1.8 and 2.2 points. Again, the repeated-measures ANOVA was significant for both VAS and Archimedes spirals, and post hoc comparisons were significant between 20 and 60 minutes, as indicated by asterisks in Figure 1e–f. The correlation coefficient between home VAS and home spirals was 0.8 (Pearson r, $P < .005$). The best effect of alcohol was obtained 45 minutes after alcohol ingestion.

Laboratory tests and home tests revealed very similar results for the Bain scale and the VAS tests. The correlation coefficient between home and clinical laboratory VAS and home and clinical laboratory spirals by using Pearson r was 0.9 ($P < .005$).

The amount of best improvement might give an estimate of the variability of the response to alcohol of these outcome parameters. Figure 2 shows the best individual effect for each of the patients in the laboratory group (Fig. 2a–d) and in the home-test group (Fig. 2e–f). For the Archimedes spirals, average improvement was 7 to approximately 3 points for the laboratory group and 5.6 to 2 points for the home-test group; best individual improvement was from 10 at baseline to 3 after alcohol ingestion for the laboratory group and from 9 to 2 for the home-test group. VAS average improvement was from 71 to 38 points for the laboratory group and from 64 to 27 points for the home-test group; best individual effect was from 70 at baseline to 0 after alcohol for the laboratory group and from 88 to 5 for the home-test group. It is noteworthy that improvements of 2 points on the Bain scale and >10 on the VAS scale were found in all patients during the test.

Discussion

The alcohol response of patients with ET has never been studied under controlled laboratory conditions. Our study confirms the well-known qualitative effect of alcohol on tremor in ET patients[2–4] with a quantifying approach and proposes a test for quantification of the alcohol response. The strong effect of alcohol within the first 90 minutes after alcohol ingestion is followed by a severe rebound effect. The response of the patients was highly consistent. Therefore, the test qualifies for home testing and can be used as a screening tool for confirmation of the diagnosis. Usually an office-based test of this kind is not feasible.
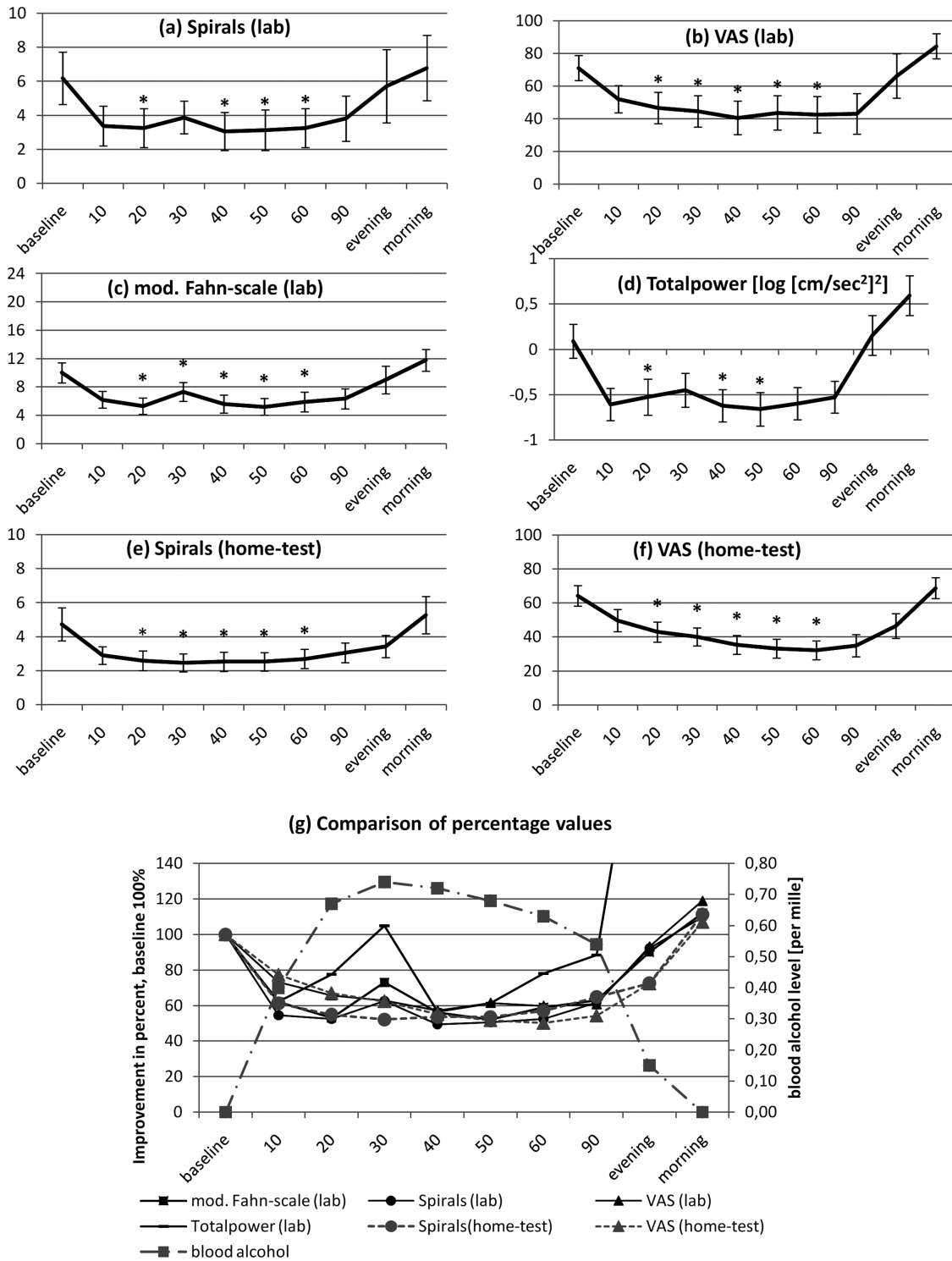
FIG. 1. Mean absolute improvement and SEM of outcome parameters during the alcohol test in the laboratory (**a–d**) and at home (**e–f**). **a, e**: Spirals (0–10): 2 patients in the laboratory group were excluded; they could not draw either without or with alcohol. **b, f**: VAS (0–100). **c**: Modified Fahn scale (0–24). **d**: Tremor amplitude measured as totalpower (log milligravities^2). Statistical testing was only performed between times 20 and 60 minutes (baseline compared with 20, 30, 40, 50, and 60 minutes); *significant change at $P < .05$. **g**: Different outcome parameters in improvement by percentage in order to show the similar time course and the relation with blood alcohol level.

Alcohol sensitivity is one of the mysterious clinical features of most patients with essential tremor. This may be related to its specific effect on GABA receptors.[16] Indeed, it has been shown that tremor was alcohol responsive in a mouse model deficient for the alpha-1 subunit of the GABA receptor.[17] As alcohol-sensitive GABA receptors are specifically located in the cerebellum,[18] it is conceivable that alcohol exerts its beneficial and specific effect on ET within the olivocerebellar circuit, which is commonly assumed to be
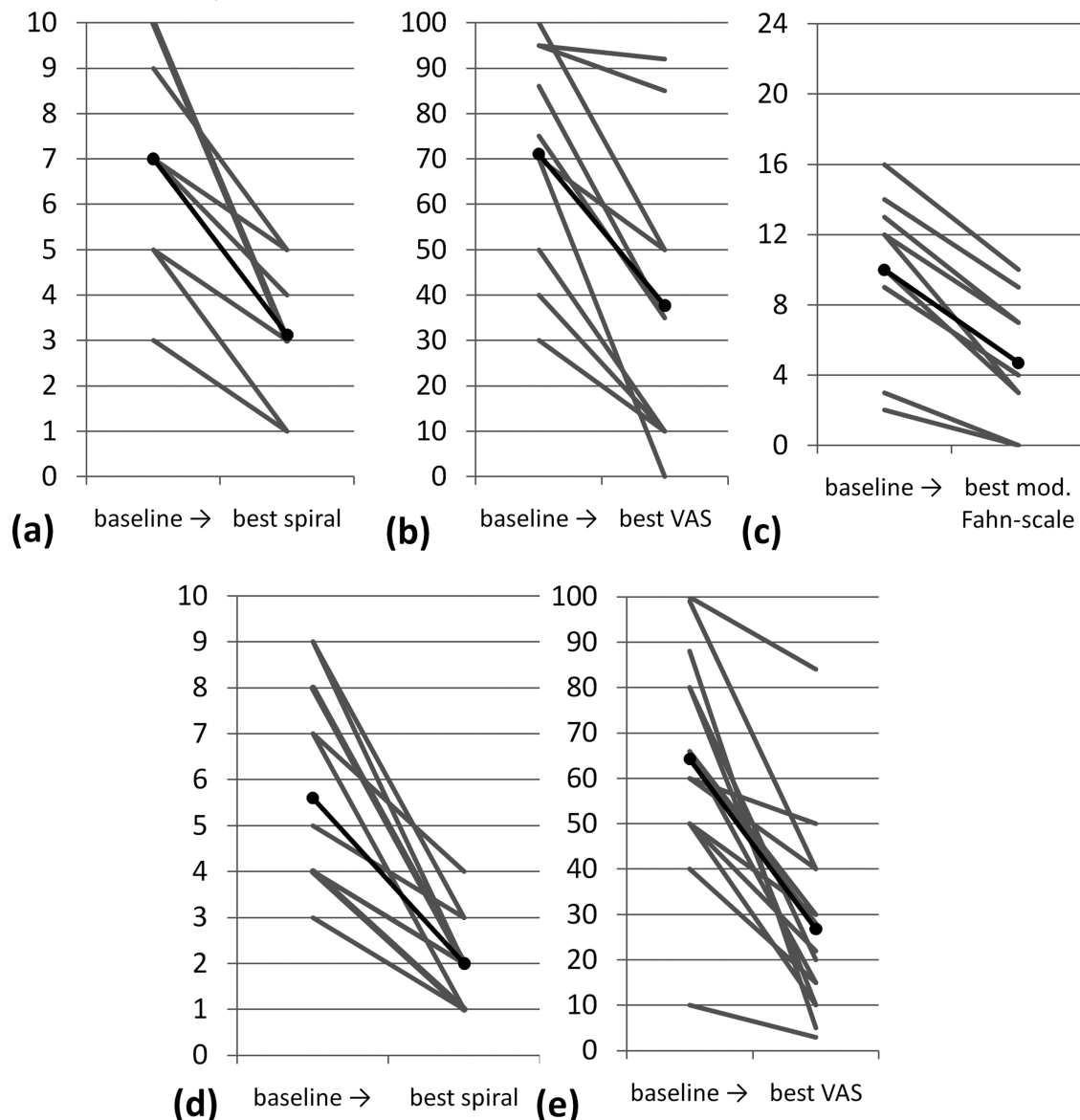
FIG. 2. Best individual tremor improvements of all patients during the laboratory test (**a–c**; 10 patients) and the home test (**d–e**; 15 patients), shown by gray lines (black line, mean value). **a**: Spiral drawing (0–10): 2 patients improved from 10 at baseline to 3, and 2 patients were excluded, as they could not draw without and with alcohol. **b**: Visual analog scale (0–100). **c**: Modified Fahn scale (0–24). **d**: Spiral drawing (0–10): 5 patients improved from 4 at baseline to 2, 2 patients improved from 8 at baseline to 2, and 2 patients improved from 4 at baseline to 1. **f**: Visual analog scale (0–100).

related to the pathophysiology of ET.[19,20] Therefore, the alcohol responsiveness may be a key physiological feature of ET.

We transferred our laboratory findings to a test to be performed at home that helps to confirm the secondary criterion "alcohol sensitivity of tremor" in a given patient. The diagnosis of definite essential tremor in our home-test patients had already been made during earlier outpatient visits, but even among these well-informed patients, we found one third who were not aware of their favorable alcohol response. This aspect underlines the importance of testing patients suspected of ET, even though they may deny improvement of tremor after alcohol ingestion. For this ET home test, only the subjective measure VAS and Archimedes spirals as an objective measure were included. Such simple and easy-

to-be-performed methods to confirm alcohol sensitivity and thereby the diagnosis of ET are also important in epidemiologic and genetic field studies of ET.

So far, it is unknown if the alcohol test can also be used as a differential diagnostic tool. About 1 in 3 patients with tremor have been found to be misdiagnosed as having ET, with the most frequent false diagnoses being Parkinson's disease and dystonia.[21] Further confirming criteria would be highly welcome. To the best of our knowledge, there is no other tremor entity that responds as well to alcohol as essential tremor.[8] Certainly more research is necessary to accept alcohol-sensitivity as a reliable differential diagnostic tool for ET against all other tremor entities.

We conclude that the time course of the alcohol response is consistent and comparable in different

individuals with ET. It can be tested with the simple procedure proposed here.

References

1. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25:534–541.

2. Growdon JH, Shahani BT, Young RR. The effect of alcohol on essential tremor. Neurology. 1975;25:259–262.

3. Koller WC, Biary N. Effect of alcohol on tremors: comparison with propranolol. Neurology. 1984;34:221–222.

4. Koller WC, Busenbark K, Miner K. The relationship of essential tremor to other movement disorders: report on 678 patients. Essential Tremor Study Group. Ann Neurol. 1994;35:717–723.

5. Klebe S, Stolze H, Grensing K, Volkmann J, Wenzelburger R, Deuschl G. Influence of alcohol on gait in patients with essential tremor. Neurology. 2005;65:96–101.

6. Zeuner KE, Molloy FM, Shoge RO, Goldstein SR, Wesley R, Hallett M. Effect of ethanol on the central oscillator in essential tremor. Mov Disord. 2003;18:1280–1285.

7. Bain P, Brin M, Deuschl G, et al. Criteria for the diagnosis of essential tremor. Neurology. 2000;54(11 Suppl 4):S7.

8. Mostile G, Jankovic J. Alcohol in essential tremor and other movement disorders. Mov Disord. 2010;25:2274–2284.

9. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13(Suppl 3):2–23.

10. Widmark EMP, ed. Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung. Berlin Wien, 1932.

11. Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, eds. Parkinson's disease and movement disorders. Baltimore, MD: Williams & Wilkins; 1993:271–280.

12. Lord BA, Parsell B. Measurement of pain in the prehospital setting using a visual analogue scale. Prehosp Disaster Med. 2003;18:353–358.

13. Lorenz D, Papengut F, Frederiksen H, et al. Evaluation of a screening instrument for essential tremor. Mov Disord. 2008;23:1006–1012.

14. Raethjen J, Lauk M, Koster B, et al. Tremor analysis in two normal cohorts. Clin Neurophysiol. 2004;115:2151–2156.

15. Bain F, ed. Assessing Tremor Severity:. A Clinical Handbook. London: Smith-Gordon; 1993.

16. Breese GR, Criswell HE, Carta M, et al. Basis of the gabamimetic profile of ethanol. Alcohol Clin Exp Res. 2006;30:731–744.

17. Kralic JE, Criswell HE, Osterman JL, et al. Genetic essential tremor in gamma-aminobutyric acidA receptor alpha1 subunit knockout mice. J Clin Invest. 2005;115:774–779.

18. Wallner M, Hanchar HJ, Olsen RW. Low-dose alcohol actions on alpha4beta3delta GABAA receptors are reversed by the behavioral alcohol antagonist Ro15–4513. Proc Natl Acad Sci U S A. 2006;103:8540–8545.

19. Jankovic J, Noebels JL. Genetic mouse models of essential tremor: are they essential? J Clin Invest. 2005;115:584–586.

20. Elble RJ, Deuschl G. An update on essential tremor. Curr Neurol Neurosci Rep. 2009;9:273–277.

21. Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? Arch Neurol. 2006;63:1100–1104.