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

Key Words: movement disorders; dystonia; genetics; quadrupedal gait; crawling gait; microcephaly

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 paraplegia5 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. Both parametric and nonparametric log odds scores were examined. Chromosomal haplotypes were generated with HaploPainter1.043. Homozygosity mapping was performed with KinSNP (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
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 neuromas 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.

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

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

M, male; F, female; NA, not assessed; HL, hearing loss; CBC, complete blood counts; +, present; -, absent.

a2 standard deviations below normal for age and sex, according to the WHO head circumference chart.
bLimited cooperation in carrying out a command, intelligent, recognizes well.
cDoes not follow commands, recognizes well.

all 4 limbs in childhood. 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.
Molecular Findings

Sequencing of SUC2A2 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 descent 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. 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. 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. 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.

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-spatistic 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, hyperlordotic 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.

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References

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

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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]TGTATATGTGTGTACAGGGAG). 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 χ² 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,
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 characteristics explored, none reached compelling statistical significance after adjustment for multiple testing (although trends observed may justify further exploration in a much larger cohort).

**Discussion**

\(\alpha\)-Synuclein is central to the pathobiology of PD. Simply genetically increasing the expression of the \(\alpha\)-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

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**Table 1. Clinical characteristics of study participants**

<table>
<thead>
<tr>
<th>Disease status</th>
<th>PD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical findings (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications (%)</td>
<td></td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>n</th>
<th>MAF(^a) (%)</th>
<th>Additive(^b)</th>
<th>Dominant</th>
<th>Reccessive</th>
<th>Allelic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>( P )</td>
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<td></td>
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<td></td>
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<tr>
<td>PD specialist</td>
<td>375</td>
<td>275</td>
<td>54.53</td>
<td>45.94</td>
<td>1.00 (1.12–1.75)</td>
<td>.0026</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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. ●

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References


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

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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 quality of life as well as increasing physical problems. Such as depression, leading to a severe reduction in ability adjusted life years (DALYs).² In addition, the number of people who are likely to suffer from movement disorders, as age is, for most of them, the strongest risk.

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: G30.82); 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. 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. 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

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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.
illness was put forward. This encompasses not only disease frequency, but also the effective loss of working power, the years of life lost, and the social consequences of these diseases. Two important concepts were developed to quantify this burden: DALYs and quality adjusted life years. 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. Calculations of
the prevalence and incidence rates of dementia showed that the results are quite in line with international meta-analyses. 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. 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

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

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 19752 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.).

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),13 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 milligravities2). 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–f. 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 patients2–4 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.
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. Indeed, it has been shown that tremor was alcohol responsive in a mouse model deficient for the alpha-1 subunit of the GABA receptor. As alcohol-sensitive GABA receptors are specifically located in the cerebellum, it is conceivable that alcohol exerts its beneficial and specific effect on ET within the olivocerebellar circuit, which is commonly assumed to be

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**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: 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 milligravities²). 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.
related to the pathophysiology of ET. 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. 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. 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