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Brief Reports

Severe Forward Flexion of the Trunk in Parkinson's Disease: Focal Myopathy of the Paraspinal Muscles Mimicking Camptocormia

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Abstract: **Pronounced forward flexion of the trunk, often termed camptocormia, is a typical symptom of patients with Parkinson's disease. In 4 parkinsonian patients with camptocormia, paraspinal muscles were studied by electromyography (EMG) and axial computerized tomography (CT) or magnetic resonance imaging (MRI) scans and muscle biopsy. EMG of the lumbar and thoracic paravertebral muscles showed abundant fibrillations, positive sharp waves, and bizarre high-frequency discharges. Spinal CT and MRI scans revealed variable degrees of atrophy and fatty replacement of the thoracolumbar paraspinal muscles on both sides. No other signs of neuromuscular disease were found. Biopsy of the paraspinal muscles revealed end-stage myopathy with autophagic vacuoles, chronic inflammatory myopathy, unspecific myopathic changes, or mitochondrial myopathy. In parkinsonian patients with pronounced forward flexion of the trunk, myopathy confined to the erector spinae muscles must be considered.** © 2003 Movement Disorder Society

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Key words: Parkinson's disease; camptocormia; bent spine; focal myositis; mitochondrial myopathy

"Propensity to bend the trunk forward" is a recognized characteristic of Parkinson's disease and related conditions (see Fig. 3 in Goetz et al., 2001).[1,2] Higher degrees of forward flexion of the trunk, also referred to as camptocormia,[3] may cause considerable discomfort and handicap, and often poorly respond to dopaminergic treatment.[2] A similar feature is antecollis, or dropped head syndrome, thought to be caused by an increase of tone particularly in the anterior neck muscles.[3–5] Recently, isolated neck extensor myopathy was identified as another cause of the dropped head syndrome in patients with Parkinson's disease or multiple system atrophy (MSA).[5,6]

We report on 4 parkinsonian patients who developed progressive and severe forward flexion of the trunk combined in 1 patient with severe head drop. Detailed investigation by electromyography (EMG), axial computerized tomography (CT), or magnetic resonance imaging (MRI) scans of the spine and muscle biopsy disclosed focal myopathy of the paraspinal muscles.

PATIENTS AND METHODS

Patient 1

This 72-year-old machinist had a 6-year history of parkinsonian symptoms. Over the past 2 years, he developed progressive forward flexion of the trunk and mild axial rotation without head drop. On admission, active retroflexion of the trunk was possible up to 75 degrees. Passively, however, his spine could easily be extended. He presented with generalized akinesia and rigidity, severe postural instability, irregular tremor that was pronounced on the right, generalized myoclonic jerks, and action dystonia of his right hand. Deep tendon reflexes were brisk. A Babinski sign was present on the right. Memory function was impaired. He spoke with a distinct, quivering dysarthria and had signs of orthostatic dysregulation. Cranial MRI showed a few small bilateral subcortical lacunar lesions. He was diagnosed with multiple system atrophy. Motility (but not his stooped posture) improved with increasing doses of levodopa (L-dopa) plus benserazide (up to 500 mg/day) and bromocriptine (25 mg/day).

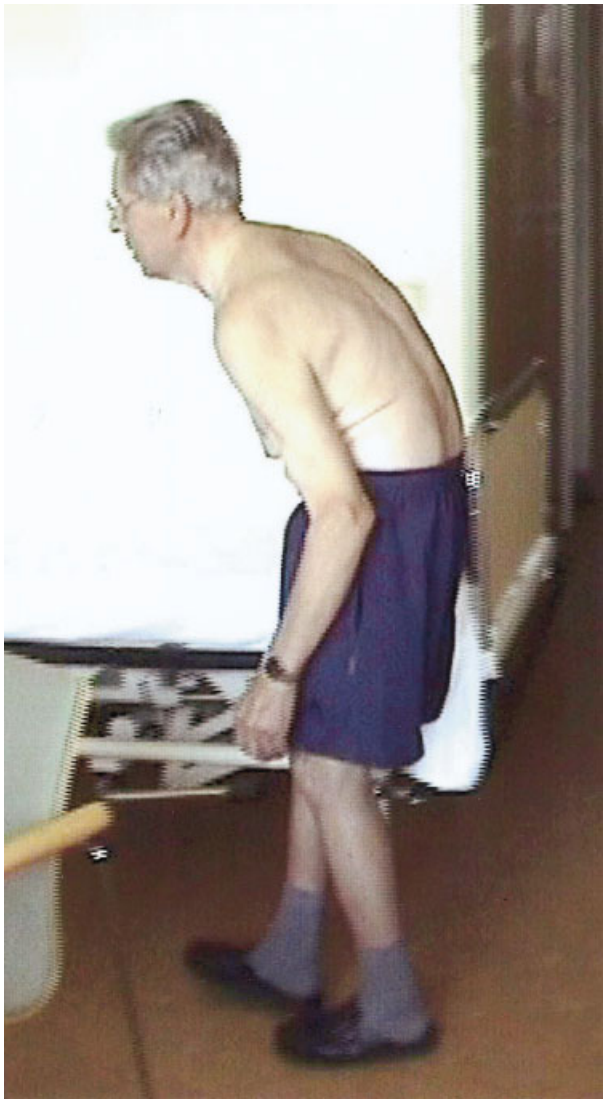

FIG. 1. Patient 2 with forward flexion of the trunk and a mild tilt to the left, but without head drop. Active retroflexion beyond this posture was not possible, although passively, the trunk could be easily erected.

Patient 2

This 69-year-old tradesman presented with idiopathic Parkinson's disease of 7 years with symptoms of pronounced right sided tremor, moderate rigidity, and mild akinesia. Intellectual function was normal. He initially was treated with budipine (60 mg) and amantadine (200 mg) for 1 year. For the past 3 years, he had been on L-dopa (300 mg) plus benserazide, pergolide (3 mg), and selegiline (10 mg) medication with good response. Over the past 18 months, he successively developed forward flexion of his trunk but not of the head, with a mild tilt to the left (Fig. 1), which proved refractory to increased medication. Active retroflexion of the trunk was not possible beyond 50 degrees. Passively, his trunk could easily be erected.

Patient 3

This 61-year-old worker had a 30-year history of idiopathic Parkinson's disease that had begun on the right side. He had been treated with L-dopa for 23 years with good response. Over 13 to 15 years, the patient developed dyskinesias and, therefore, received bilateral nucleus subthalamicus stimulation last year. During the past 4 years, the patient successively developed forward flexion of the trunk with a tilt to the right, but without head drop unresponsive to additional drug treatment. Active retroflexion was not possible. Two years prior to this report, spinal fusion surgery (L1–S1) reduced his forward flexion and improved gait and stance functions.

Patient 4

This 65-year-old tradesman suffered from familial essential tremor since childhood. Twelve years ago, he was diagnosed with idiopathic Parkinson's disease. Over the past 3 years, he developed progressive forward flexion of the head and trunk. For the past 3 years he was on L-dopa plus benserazide (300 mg), levodopa (100 mg), pramipexole (2.1 mg), metixen (15 mg), and propranolol (60 mg). Add-on treatment with budipine and pergolide did not improve the symptoms anymore. Therefore, he received bilateral nucleus subthalamicus stimulation. He now presented with a mild tremor at rest that involved both arms and legs, moderate rigidity, and mild akinesia. Truncal forward flexion and head drop did not respond to deep brain stimulation, in contrast to tremor and akinesia. Active retroflexion of the trunk and head was possible up to 70 degrees. Passively, his spine and head could be fully extended.

Methods

Lumbar and thoracic paraspinal muscles were studied by EMG and axial CT or MRI scans at the levels T3 to T10, and L1 to S4. CT scans of the lumbar spine obtained from a total of 421 consecutive patients from our neuroradiology (n = 162) and surgical radiology (n = 259) departments served as control. On either side, the fat content of the dorsal paraspinal muscles was estimated as $\leq$10%, 10 to 25%, 25 to 50%, 50 to 75%, or $\geq$75% of the respective muscle areas. EMG investigation of the thoracolumbar paraspinal muscles was performed in 15 control patients aged 52 to 75 years. Muscle biopsy specimens were taken from the erector trunci muscles at levels T11 (Patient 1), L1/L2 (Patients 2 and 4), and from the cervicothoracic area (Patient 3).

Muscle tissues were flash-frozen in liquid nitrogen and submitted to the following histological and enzyme histo-

chemical preparations: Modified Gomori trichrome, hematoxylin-eosin, elastica van Gieson, Congo red, oil-red O, myoadenylate deaminase, myophosphorylase, phosphofructokinase, acid phosphatase, oxidative enzymes NADH (nicotine adenine dinucleotide tetrazolium-H) reductase, MAG (menadione-linked α-glycerophosphate dehydrogenase), cytochrome-c oxidase (COX), succinic dehydrogenase (SDH), myofibrillar ATPase after alkaline (pH 10.4), and acid (pH 4.6 and 4.3) preincubations. Immunohistochemically, antibodies were used for leucocyte function associated antigene-β (LFA-β, Dako), intracellular adhesion molecule (I-CAM, Dako), B- and T-lymphocytes (Dako), CD_{68}-macrophages (Dako), major histocompatibility complex I (MHC-I, Dako), and C5b-9 complement (Dako).

Separate small slivers of biopsied muscle tissues were fixed in buffered glutaraldehyde, osmicated, and embedded in Epon for 1-μm–thick methylene-blue Azur-II–stained (Richardson) semithin sections and subsequent ultrathin sections, which were counterstained with uranyl acetate and lead citrate for electron microscopic investigation.

RESULTS

None of the patients showed wasting or weakness of the limb or girdle muscles suggestive of a neuromuscular disorder. Moreover, none of them had any laboratory abnormality including muscle-derived enzymes.

EMG

On EMG, multiple areas within the lumbar and thoracic and, in Patient 4, cervical paravertebral muscles demonstrated abundant fibrillations, positive sharp waves, and bizarre high-frequency discharges. Motor unit potential analysis demonstrated an increased proportion of small and short potentials and a considerable, although variable, proportion of polyphasic motor unit potentials (MUPs) with satellite potentials. EMG of gluteus, deltoid, and lateral vastus muscles in Patient 1; of abdominal, bilateral trapezius, anterior tibial, lateral vastus, and intrinsic hand muscles in Patient 2; and of abdominal, lateral vastus, deltoid muscles in Patient 3 were normal. In Patient 4, EMG of the paraspinal cervical muscles and cervical part of trapezius muscle demonstrated spontaneous activity with abundant fibrillations, positive sharp waves, some polyphasic MUPs. EMG of lumbar and thoracic paravertebral muscles of the control group was normal.

CT/MRI

Retrospective evaluation of 421 CT scans of the lumbar spine revealed a fat content of the dorsal paraspinal muscles below 50% as common (Fig. 2). Its degree depended on gender (women > men) and segmental level (L4 < L5 < S1), and increased with age and with the presence of spinal column disease. Moreover, the paraspinal fat content almost regularly was symmetric and showed a characteristic distribution along the bony and septal structures (Fig. 2, bottom right scan). Even the most caudal CT scans in the group older than 70 years revealed a fat content of ≥75% in not more than 5% of controls, and each of these control patients had a history with spinal surgery at the L5/S1 level. In our parkinsonian patients, CT and MRI scans of the thoracic and thoracolumbar spine revealed no abnormalities of the spinal cord and the spinal column (Fig. 2). In Patient 1 at and below the T10 level, the dorsal paraspinal musculature was diffusely interspersed with fat not exceeding 50% of the respective muscle compartments and pronounced on the right. The texture of the iliopsoas and gluteal muscles, in contrast, appeared normal. In Patient 2, MRI showed multifocal and asymmetric fatty replacement of paraspinal muscles between levels T5 and L4 with maximum degree (50–75%) at L4. In Patient 3, CT revealed the deep thoracic paraspinal musculature at the T5 to T10 levels on both sides mildly (10–25%) interspersed with fat, whereas the superficial muscle layer appeared normal. Lumbar levels could not be analyzed because of metal implants placed at the time of spinal fusion surgery. In Patient 4, fatty replacement of 25 to 50% of the deep thoracic paraspinal muscle areas with an asymmetric patchy pattern was evident. Muscle texture at the lumbar levels appeared normal. MRI of the thigh muscles was normal.

Muscle Morphology

Patient 1.

In densely fibrotic, embedded tissue, there were remnants of muscle fibres of varying diameters, many of them containing rimmed vacuoles and cytoplasmic bodies, whereas necrosis, regeneration of muscle fibres, and ragged-red fibres were absent as were inflammatory infiltrates. Some grouped muscle fibres that largely were of Type I appeared better preserved, however, with myopathic features, including fibre splitting. Scattered T-lymphocytes were found in fibrotic areas and CD_{68}-macrophages abounded. MHC-I was expressed on several muscle fibres (Fig. 3a). Ultrastructurally, these highly atrophic muscle fibers were largely devoid of sarcomeres, only few remnants mainly consisting of Z-disks, myelin-like lamellar, and amorphous material were seen in rimmed vacuoles (Fig. 3b) ,whereas aggregates of tubulofilaments were not unequivocally identified within muscle fibres or in their nuclei.

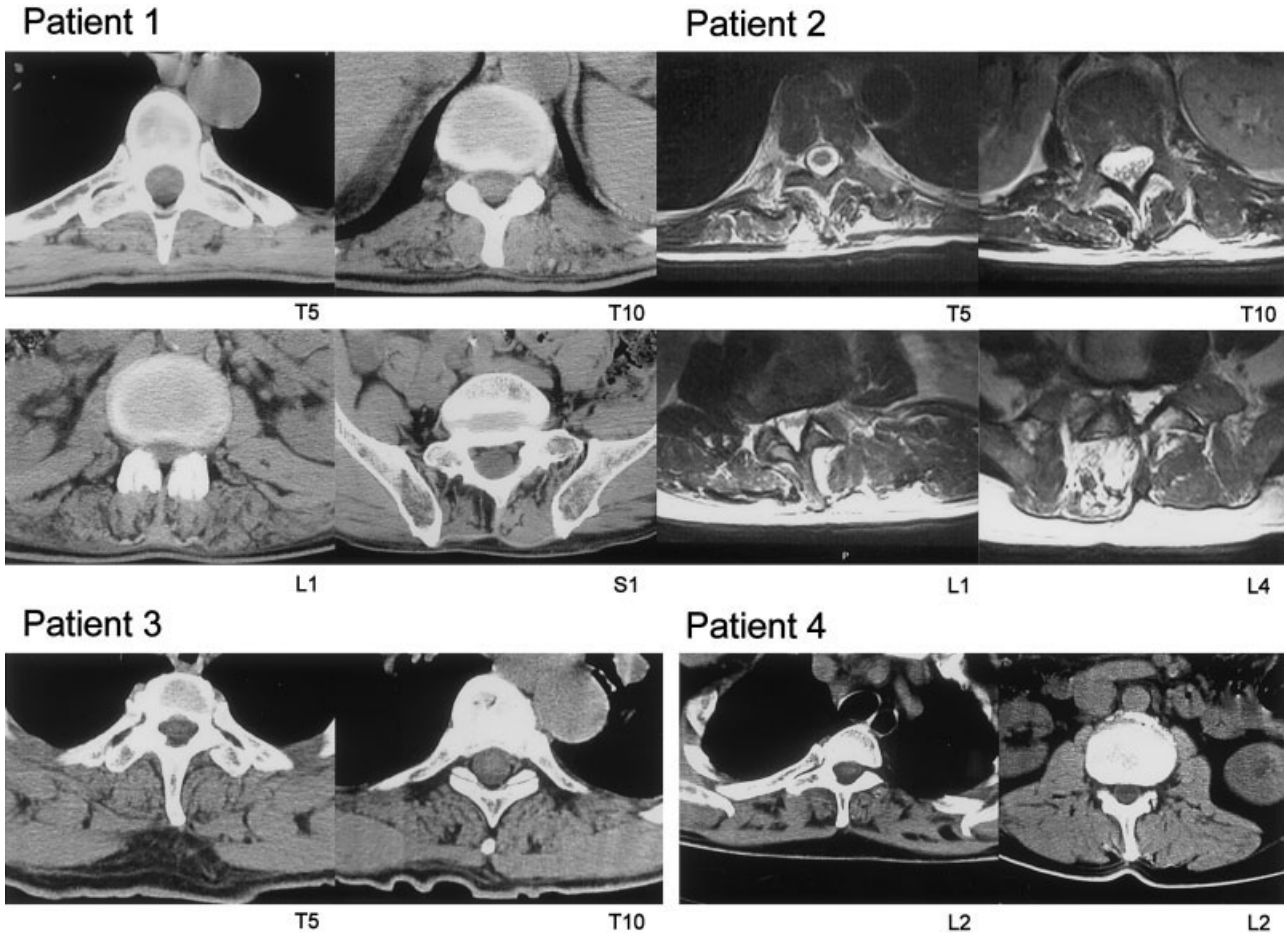

FIG. 2. Computed tomographic (CT) and magnetic resonance imaging (MRI) scans of the thoracic and thoracolumbar spine in all 4 patients revealed no abnormalities of the spinal cord or the spinal column. In Patient 1 at and below the T10 level, the dorsal paraspinal musculature was diffusely interspersed with fat, pronounced on the right (<50%). The texture of the iliopsoas and gluteal muscles appeared normal. In Patient 2, MRI showed multifocal and asymmetric fatty replacement of paraspinal muscles between levels T5 and L4 (50–75%). In Patient 3, CT revealed the deep thoracic paraspinal musculature at the T5 to T10 levels on both sides mildly interspersed with fat (10–25%), whereas the superficial muscle layer appeared normal. In Patient 4, grade 2 fatty replacement of the deep thoracic paraspinal muscles with an asymmetric patchy pattern was evident (25–50%). Muscle texture at the lumbar levels appeared normal.

Patient 2.

Muscle tissue showed considerable variation in fibre diameters and a slight increased number of nuclei. A few necrotic fibres as well as basophilic regenerating fibres were present. There was endomysial fibrosis and fatty replacement of muscle parenchyma. Several endomysial inflammatory infiltrates were present, containing B- and T-lymphocytes and abundant CD68-macrophages (3C, D). I-CAM and LFA-β were well expressed, and MHC-I (Fig. 3e) was present on each muscle fibre.

Patient 3.

Among the cross-sectioned muscle fibres, there were several scattered atrophic ones, including pyknotic nuclear clumps. There were several ragged red fibre segments, rare necrosis and basophilia of muscle fibres, and endomyosial fibrosis. Only rarely, small inflammatory infiltrates were present. The entire population of muscle fibres belonged to Type I only, a few highly atrophic fibres displaying a strong MAG reaction. CD68-macrophages abounded, whereas T-lymphocytes appeared scattered or in small aggregates. MHC-I (Fig. 3f) was only regionally expressed on the muscle fibre surface.

Patient 4.

Cross-sectioned muscle fibres showed considerable variation in fibre diameters with atrophic and hypertrophic fibres and an occasional angulated small fibre. Internal nuclei were numerically increased. Few muscle fibres contained vacuoles, some of the autophagic type.

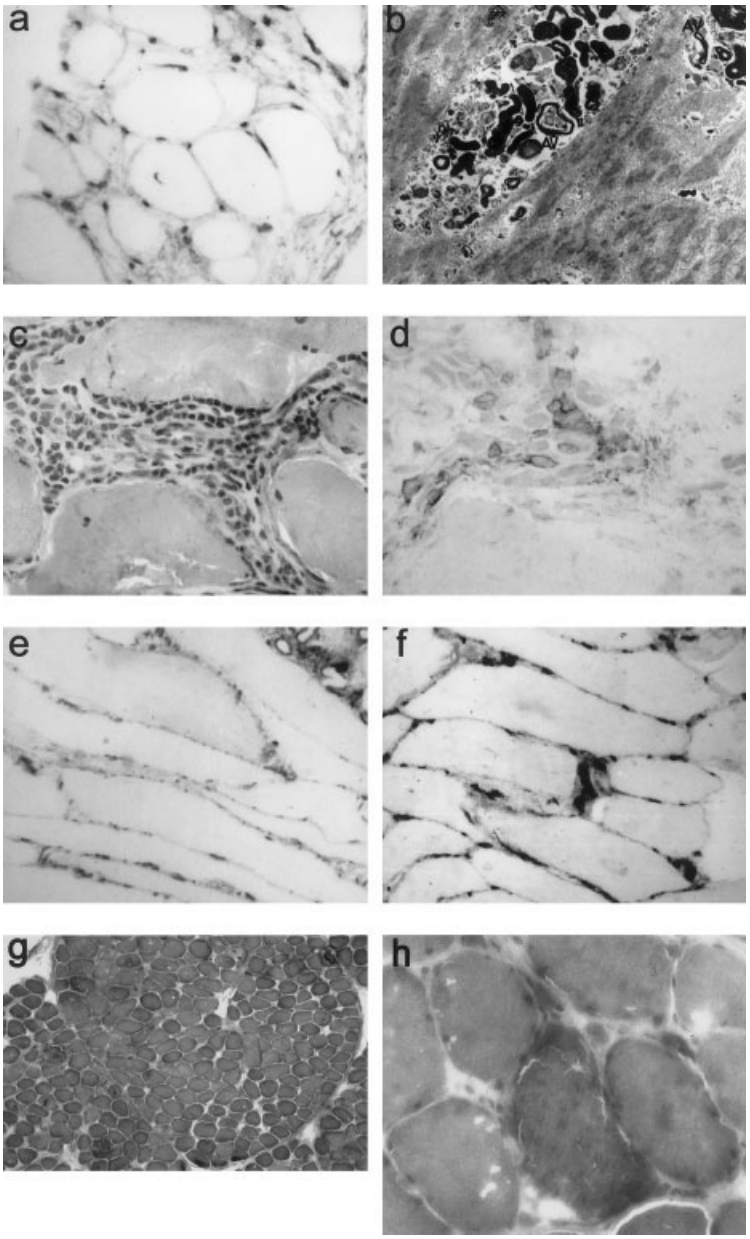

FIG. 3. a: Muscle fibers show variation in fiber diameters and display major histocompatibility complex I (MHC-I) on their surface; Patient 1, immunohistochemical reaction (original magnification, ×212). **b:** By electron microscopy, two autophagic vacuoles (AV) contain myelin-like lamellae and other debris; Patient 1 (original magnification, ×8,800). **c:** Distinct endomysial inflammatory infiltrates are present in a muscle biopsy from Patient 2 (hematoxylin and eosin stain; original magnification, ×400). **d:** Inflammatory infiltrates containing numerous T-cells in Patient 2 (anti-CD45R0, ×500). **e:** Muscle fibers show MHC-I on their surface; Patient 2, immunohistochemical reaction (original magnification, ×128). **f:** Muscle fibers display MHC-I on their surface; Patient 3, immunohistochemical reaction (original magnification, ×180). **g:** Cross-sectioned muscle fibrers vary considerably in fiber diameters. There are scattered ragged red fibers; Patient 4 (modified trichrome stain; original magnification, ×16). **h:** One ragged red fiber at higher magnification, Patient 4 (modified trichrome stain; original magnification, ×40).

There were numerous scattered ragged red fibres, and even more COX-negative muscle fibres showing SDH activity in a combined COX–SDH preparation (Fig. 3g and h).

In summary, Patient 1 had end-stage myopathy with autophagic vacuoles, Patient 2 had chronic inflammatory myopathy, Patient 3 had unspecific myopathic changes, and Patient 4 mitochondrial myopathy. After the diagnosis was made, all patients were treated with physiotherapy and Patients 1 to 3 with steroids for 2 months. Clinical examination showed a mild improvement of motor function in the paraspinal muscles, resulting in slightly reduced forward flexion of the trunk.

DISCUSSION

We report here that pronounced forward flexion of the trunk and head as a recognized feature of Parkinson's disease may be related to disease of the paraspinal muscles. None of our patients had evidence for systemic neuromuscular disease on clinical and laboratory testing. However, EMG or imaging studies, or both, suggested a circumscribed myopathy of the paraspinal muscles that

was then confirmed by biopsy. Microscopic investigation in 1 of our patients disclosed inflammatory infiltrates, was compatible with myositis in an advanced stage in 2 others, and disclosed mitochondrial myopathy in the fourth. The sole manifestation of myopathy in truncal muscles is uncommon.[6] The few cases reported include inclusion body myositis and myositis/polymyositis of the paraspinal muscles[7,8] as well as congenital and nemaline myopathy.[9,10] Possibly, nonspecific myopathy of the paraspinal muscles as a cause of forward flexion of the trunk[11–15] is not so rare; but there exists only one anecdotal report in a parkinsonian patient.[16]

The diagnosis of isolated trunk or neck extensor myopathy essentially relies on the clinical identification of back or neck muscle weakness as the cause of stooped posture. Axial CT or MRI scans of the spine or EMG investigation of the paraspinal muscles, or both, further substantiate the neuromuscular nature of disordered posture. Although etiologically unspecific, gross asymmetry or atypical patterns and particularly higher degrees of fat content ($\geq$75% on a given scan on either side) suggest fatty replacement of the paraspinal muscles due to a distinct pathologic condition rather than disuse atrophy.[17] Moreover, fibrillation potentials and substantial alterations of the motor unit potentials are not a feature of aging or immobile muscles.[8,9] CT or MRI scans of the vertebral column and its muscles are particularly helpful in disclosing multifocal involvement such as in our Patient 2 (Fig. 2), which might escape a screening EMG investigation.

Such pronounced forward flexion of the trunk has also been termed camptocormia, pleurothotonus or the Pisa syndrome.[18–20] Although clinically uniform, these terms reflect heterogenetic pathophysiologic states.[6] Camptocormia has been ascribed not only to excess activation of the abdominal wall muscles such as dystonia or to a reduced motor drive to the paraspinal muscles such as in Parkinson's disease[16,18] but also to skeletal diseases such as Bechterew's or neuromuscular disorders such as amyotrophic lateral sclerosis.[13,15] Parkinsonian disorders of posture, even if mild, often poorly respond to dopaminergic treatment.[16,18] Forward flexion of the trunk as a side effect of neuroleptic medication (pleurothotonus or the Pisa syndrome) may disappear with cholinesterase inhibitor treatment.[19–21] Stooped posture was also described to occur in patients with Alzheimer's disease and MSA and during antidepressant therapy.[20–23]

The nature of the observed association between Parkinson's disease and chronic myopathy confined to the trunk extensor muscles is obscure. So far, inflammatory myopathies are not known to coincide with Parkinson's diseases or with other disorders of posture such as Bechterew's disease, scoliosis, or osteoporosis. In 1 of our patients, pronounced flexion of the trunk was combined with the "dropped head syndrome," obviously due to a disorder of the paraspinal muscles at both thoracolumbar and cervical segments. In 5 of 7 parkinsonian patients with head drop, paracervical myopathy was confirmed by biopsy, and mitochondrial abnormalities, including ragged-red fibers, suggested mitochondrial disease.[5] Indeed, mitochondrial disease might be considered if two independent organ systems are involved. Although parkinsonian features are uncommon in mitochondrial DNA mutations, parkinsonism may occur with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).[24] Moreover, abnormality of mitochondrial function has been considered a pathomechanism in idiopathic Parkinson's disease.[24]

Our conclusion is that pronounced forward flexion of the trunk, a typical feature of Parkinson's disease, reflects various pathomechanisms. In addition to an imbalance of the central motor drive to the ventral or dorsal trunk musculature and primary vertebrogenic disease such as Bechterew's, myopathy confined to the neck or erector spinae muscles must be considered. In parkinsonian patients, the characteristic disorder of posture may mask weakness of the neck or trunk extensors due to focal neuromuscular diseases.

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Higher Incidence of Depression Preceding the Onset of Parkinson's Disease: A Register Study

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Abstract: **Although case histories of depression preceding Parkinson's disease (PD) point to a possible pathophysiological relationship between these two disorders, there is as yet no epidemiological evidence to support this view. We compared the incidence of depression in patients later diagnosed with PD with that of a matched control population. Using data from an ongoing general practice-based register study, the lifetime incidence of depressive disorder was calculated for patients until their diagnosis of PD and compared with that of a matched control population from the same register. At the time of analysis, the register held information on 105,416 people. At the time of their diagnosis of PD, 9.2% of the patients had a history of depression, compared with 4.0% of the control population (χ^2 = 22.388, df = 1, $P < 0.001$). The odds ratio for a history of depression for these patients was 2.4 (95% CI: 2.1–2.7). We concluded that the higher incidence of depression in patients who were later diagnosed with PD supports the hypothesis of there being a biological risk factor for depression in these patients.**

Key words: Parkinson's disease; depression; incidence; risk factor

Depression has long been recognized as a frequent accompanying syndrome of Parkinson's disease (PD). In PD patients, its prevalence ranges from 2.7% to 7.7% in community studies to an average of 40% in patients attending neurological outpatient clinics.[1–3] There have been several case reports of depression preceding the onset of PD.[4,5] In some cases, the diag-

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nosis of PD became apparent during pharmacological treatment of depression.[6–8] It has even been suggested that the emergence of parkinsonian symptoms during treatment with a selective serotonin re-uptake inhibitor (SSRI) is an early sign of future PD.[6] Several older studies have mentioned a history of depression before the onset of PD in a substantial number of participating patients.[9,10] Two studies have shown that depression is a risk factor for the later development of PD.[11,12] There is, however, no evidence from epidemiological studies that PD is a risk factor for depression. A higher incidence of depression in patients with PD than in a control population would support the existence of a biological risk factor, especially if the incidence of depression is already higher in patients before PD is diagnosed. Because the pathophysiological changes in PD are present long before clinical symptoms become apparent, a potential biological risk factor may also be present before the diagnosis of PD. Because patients are at that time not aware of their future diagnosis of PD, psychological factors, such as the stress of having to deal with this diagnosis, cannot explain a difference in incidence. Moreover, by looking at the incidence of depression preceding PD, other possible confounding factors are obviated, such as the level of invalidity and the use of antiparkinson medication.

We present an epidemiological study of the incidence of depression preceding the diagnosis of PD, based on a large, ongoing, general practice-based register.

PATIENTS AND METHODS

Registration Network Family Practices

A retrospective cohort study was carried out based on the data from the Registration Network Family Practices (RegistratieNet Huisartspraktijken, RNH). The RNH is a computerized database in which 53 general practitioners (GPs) working in 21 family practices in the southeast of the Netherlands participate.[13] The procedures of the RNH are in accordance with Dutch civil law and patients are informed about the participation of their practice. They are given the possibility of opting out individually, without consequences for their medical care.

Data are collected on all relevant current and past health problems. For this purpose, a health problem is defined as "anything that has required, does or may require health-care management and has affected or could significantly affect a person's physical or emotional well-being." These problems are coded according to the International Classification of Primary Care (ICPC), using the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2).[14,15] The register is updated continuously with information from all possible sources, including correspondence, reports and investigations from hospital-based specialists. The RNH has been in operation since 1985 and at the time of analysis (30 April 2000) held information on 105,416 people. Participation in the RNH ends when a patient moves to a non-participating practice or dies. With regard to demographic characteristics, the participating population is comparable to the regional Dutch population.[16]

Diagnostic Criteria

For the ICPC diagnosis of Parkinson's disease (ICPC-code N87), all of the following criteria must be met: coarse tremor, improving with active purposeful movement, muscular rigidity, and poverty of movements. Causes of parkinsonism other than PD, such as neuroleptic-induced parkinsonism, are not included in the analysis.

For the ICPC diagnosis of depressive disorder (ICPC code P76), patients should not be overtly psychotic and comply with three of the following six criteria: 1) sadness or melancholy more than can be explained by psychosocial stress, 2) suicidal thoughts or attempt, 3) indecisiveness, decreased interest in usual activities or diminished ability to think, 4) feelings of worthlessness, self-reproach, or inappropriate or excessive guilt, 5) early morning wakening, hypersomnia, or early morning fatigue, and 6) anxiety, hyperirritability, or agitation. Depressive syndromes other than depressive disorder, such as affective psychosis (including bipolar depression) and depressive feelings (ICPC codes P73 and P03 respectively), were not included in the analysis.

Analysis

All PD patients included in the RNH register participated in the analysis. Patients were followed up until 30 April 2000 or until they received a diagnosis of PD or left the register. For all PD cases, the presence and number of depressive episodes before the date of diagnosis were registered. The control population was formed by matching every case of PD with all people of the same gender and year of birth who did not suffer from PD at 30 April 2000, or the time they left the register. If there was more than 1 PD case with the same gender and year of birth, a proportionate number of control cases was randomly assigned to each of these PD cases. All of the matched controls were assigned the same exit date as the date of diagnosis of their matched PD case. This was done to make the number of person–years of the analysis equal for PD cases and controls. For the control patients, the presence and number of depressive episodes before their

assigned exit date were registered. Two analyses were carried out. First of all, the proportion of control subjects and patients with a history of depression before the diagnosis of PD in the patients were compared, and the difference tested with a χ^2-test. Second, the odds ratio (OR) for a history of depression was calculated. All analyses were carried out using *SPSS v. 10.0* for Windows (SPSS Inc., Chicago, IL).

RESULTS

From January 1985 to April 2000 the RNH gathered information on 105,416 people. In this period, there were 338 incident cases of PD (162 men and 176 women), with an average age of 70.2 years (SD 10.8) at the time of diagnosis. These PD cases were matched for age and gender with all other people in the register from the same birth-year. A total of 32,077 persons were matched with the 338 PD cases. At the time of diagnosis of PD, 31 of these 338 patients (9.2%) had a history of depression (95% confidence interval (CI): 6.1–12.3). Of the control population, 1,297 of 32,077 persons (4.0%) had a history of depression (95% CI: 3.8–4.2). The OR for a history of depression in patients with PD compared with control subjects was 2.4 (95% CI: 2.1–2.7). The difference in incidence was highly significant ($\chi^2 = 22.388$, $df = 1$, $P < 0.001$). In patients with PD, the time span between the first depressive episode and the diagnosis of PD varied widely, from 1 month to 36 years, with an average of 10.1 years (SD 10.4). The incidence seems to increase during the last few years before the diagnosis of PD is made, with 7 patients experiencing a first episode of depression in the year before the diagnosis of PD, 10 patients in the last 2 years, and 14 in the last 3 years before the diagnosis of PD.

A post hoc analysis was carried out to assess the proportion of patients in whom the diagnosis of PD was confirmed by a neurologist. We randomly selected 2 PD patients for every currently participating and every retired GP. The medical records of these patients were checked for specialist confirmation of the diagnosis. Of these 66 patients, the diagnosis of PD was confirmed by a neurologist in 53 (80.3%). Of the other 13 patients, 5 (7.6%) received the diagnosis 'parkinsonism,' 4 (6.1%) did not receive a diagnosis, and the other 4 (6.1%) received another diagnoses.

DISCUSSION

Methodological Issues

Although 2 studies have shown that depression may predispose to PD,[11,12] this does not imply that PD also predisposes for depression. It is this question that the authors addressed. They made use of the same general practice-based registration as Schuurman and associates in their study of depression as a risk factor for PD.[12] Because of the large number of people participating in the registration, and the fact that the studied population (PD patients in our study, vs. depressed patients in the study by Schuurman and associates), and thus the matched population, is different, it is possible to answer our research question independent of the study by Schuurman and associates.[12]

We found a significantly higher incidence of depression in patients before diagnosis of PD than in a matched control population, with an OR of 2.4 for a prior history of depression in patients with PD. The analysis was carried out with the RNH general practice-based register. Register studies have advantages as well as limitations. The large number of patients included in the register makes it possible to study disorders with a low incidence, such as depression in patients with PD. The representativeness of the study population, the completeness of the registration, the adequacy of diagnosis, and the detection rate must be established. Some of the methodological problems discussed below are inherent to the fact that the register was not designed specifically to answer our research question.

Because almost all people in The Netherlands are registered with a general practice, the subjects included in our study form a largely unselected group and can be considered representative for the regional general population.[16] The reliability and completeness of the registration have been determined earlier by comparison of the RNH data with disease-specific hospital-based registers, such as the regional Cancer Registry and the Maastricht Epilepsy Case Register.[16,17] To ensure the quality of the RNH database, participating general practitioners receive regular instruction and training sessions, and quality control interventions.

A number of authors have criticized the accuracy of the diagnosis of PD by GPs, and reported low detection rates.[18,19] For several reasons we do not think that this will have distorted our findings in a major way. First, a post-hoc analysis showed a high rate of specialist confirmation of the diagnosis of PD. Second, the crude incidence of PD for the RNH is 22.4 per 100,000 per year, which is comparable to that of other recent community-based studies.[20–22] This makes it unlikely that the diagnosis was missed in a substantial number of patients.

In a similar way, the recognition of depression by GPs has been criticized.[23–25] The crude annual incidence of depression in our sample is 0.3% (unpublished data), which is somewhat lower than that of two other general practice-based register studies: the CMR register in Ni-

jmegen, The Netherlands, and the Intego-network in Leuven, Belgium.[26,27] Differences in the healthcare system, as well as differences in registration and methodology make it hard to compare the reported figures. The possibility of underdiagnosis of depression, however, cannot be ruled out.

The ICHPPC-2 diagnostic criteria for PD differ somewhat from the more widely used operational criteria of the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDS-BB). Postural instability, which is included in the UK-PDS-BB criteria, is not part of the ICHPPC-2 criteria.[28] Likewise, the ICHPPC-2 criteria for depressive disorder differ from the criteria for major depressive disorder of the fourth edition of Diagnostic and Statistical Manual (DSM IV) of the American Psychiatric Association (APA).[29] The ICHPPC-2 criteria do not include 2 criteria of the DSM IV classification (reduced appetite and loss of energy/tiredness), and two other symptoms are combined as one item (slow mentation, and decreased interest and activities). The ICHPPC-2 criteria also do not include a time-threshold, like the 2 weeks minimum duration of symptoms that the DSM IV criteria for major depressive disorder require. There is no specific code for dysthymia in the ICPC classification.

Findings

Having addressed the methodological issues above, we think that our finding of a higher incidence of depression in patients who are later diagnosed with PD disease reflects a true difference in incidence. The only plausible explanation for this finding is the presence of a biological risk factor for depression in patients who will be diagnosed with PD in the future. This risk factor already exists before clinical symptoms become apparent. By looking at depression *preceding* PD, other possible PD-related causes of depression can be ruled out. Patients are not aware of their future diagnosis of PD, so that there is no psychological stress, they are not disabled, and do not use antiparkinsonian medication. Although unlikely, it cannot be ruled out that patients became depressed as a result of having to cope with restrictions in their functioning due to as yet not diagnosed PD. Our study confirms the results of a study by Gonera and associates.[30] In a retrospective case-control design, they showed that PD is preceded by a prodromal phase of 4 to 6 years, characterized by a greater incidence of a number of symptoms in different areas including mood disorders. The likelihood ratio for mood disorders in PD patients in the 10 years preceding the diagnosis was 1.8 ($P = 0.02$).[31]

A clinical implication of our finding is that in some cases, depression may be a predictor of later PD. Especially in primary care settings, practitioners should be aware of this possibility. Future PD may be especially likely if parkinsonian signs emerge during SSRI treatment for depression.[6]

Two hypotheses have linked the pathophysiologic changes in PD before the formal diagnosis and an increased risk of depression: the serotonergic and the dopaminergic hypothesis. The serotonergic hypothesis, proposed by Mayeux and associates, interprets the overall reduction of serotonin in PD as a physiological compensatory mechanism for the reduced availability of striatal dopamine.[31,32] At the same time a reduced serotonin activity is considered a risk factor for depression.[33] The dopaminergic hypothesis of Fibiger is based on the fact that not only the nigrostriatal, but also the mesocortical and mesolimbic dopaminergic projections degenerate in PD. As these projections play an important role in self-reward mechanisms, it is hypothesized that damage to these reward-related systems may be a risk factor for depression.[34] Given the presence of a biological risk factor for depression in patients with future PD, these two hypotheses should be investigated further.

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Efficacy of Piribedil as Early Combination to Levodopa in Patients with Stable Parkinson's Disease: A 6-Month, Randomized, Placebo-Controlled Study

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Abstract: **Piribedil is a non-ergot D2/D3 agonist with a significant antagonist action on α2A and α2C adrenergic receptor subtypes. This double-blind placebo-controlled study was undertaken to confirm the efficacy of 150 mg/day piribedil po in improving motor symptoms of idiopathic Parkinson's disease (PD) in nonfluctuating patients insufficiently controlled by a stable daily dose of levodopa (L-dopa). Efficacy was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) III score as primary criterion over 4 months. A second comparison was planned at 6 months, after possible adjustment of L-dopa. At 4 months, the rate of response, defined as a 30% decrease from baseline on UPDRS III score, was significantly greater with piribedil compared with placebo (56.4% vs. 37.7%; $P = 0.040$). At 6 months, the better efficacy of piribedil was maintained (61.8% of responders vs. 39.6% on placebo; $P = 0.020$). The difference between groups on UPDRS III change from baseline reached statistical significance only at 6 months: −10.0 points in the piribedil group vs. −6.7 points in the placebo group ($P = 0.037$). Secondary endpoints were not significantly different. The most frequently**

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reported adverse events were gastrointestinal symptoms (27 of 61 patients in the piribedil group vs. 13 of 54 patients in the placebo group). In conclusion, a 6-month oral administration of 150 mg/day piribedil in combination with L-dopa is well tolerated, except for minor gastrointestinal symptoms at the beginning of the treatment and significantly improves motor symptoms compared with placebo in PD nonfluctuating patients.

Key words: piribedil; L-dopa; Parkinson's disease; nonfluctuating patients

Over time and as therapeutic response becomes insufficient, parkinsonian patients already on levodopa (L-dopa) may maintain adequate control of motor symptoms by progressively increasing their daily dose or by combining another anti-Parkinson drug. In fact, although L-dopa substitution is still regarded as the criterion standard of Parkinson's disease (PD) drug therapy, motor response oscillations and dyskinesia were shown to develop in the majority of PD patients who undergo L-dopa monotherapy for more than 5 years.[1–3]

Therefore, a current therapeutic strategy recommends early treatment with dopamine agonists, either alone, or in combination with L-dopa.[4] Piribedil (Trivastal retard 50 mg; [(methylenedioxy-3,4 benzyl)-4 pyperazinyl-1] -2 pyrimidine) is a centrally acting dopamine agonist[5,6] with a balanced affinity for D_2 and D_3 receptors.[7,8] Recently, binding and efficacy studies have shown that piribedil presents antagonist actions at the two main adrenergic receptors subtypes present in the central nervous system: α_{2A} and α_{2C}.[9,10] Of interest, piribedil shows a similar affinity for dopamine and adrenergic receptors, suggesting that, at therapeutically relevant doses, the blockade of central adrenergic receptors may contribute to its functional profile.[11] The antiparkinsonian activity of piribedil has been first demonstrated in experimental models[5,12–14] and in the MPTP-treated marmosets.[15] Moreover, repeated oral administration of piribedil compared to an equieffective dose of L-dopa, as judged by the reversal of motor deficits, is less likely to induce dyskinesia than L-dopa and is superior to L-dopa on items related to vigilance and balance control.[16,17]

After repeated oral administration of 150 mg/day to parkinsonian patients, piribedil plasma levels remain stable over 24 hours, the median terminal half-life being 21 hours, and the compound shown to be more active in patients with higher piribedil plasma levels.[18]

Many clinical studies were performed to evaluate the effects of piribedil on Parkinson's symptoms. The antiparkinsonian effect of piribedil has been shown in a pioneer clinical study of Chase and colleagues[19] and has been shown to be active either as a monotherapy or in combination with L-dopa or amantadine in the treatment of PD.[20–25] An interesting therapeutic profile was suggested in de novo patients after a 3-month monotherapy in an open-label study.[26] Previous clinical studies have also suggested that piribedil is efficacious as an adjunct to L-dopa.[22,27,28] The present prospective, randomly assigned, double-blind study was carried out in L-dopa –treated, nonfluctuating patients to demonstrate the therapeutic benefit of piribedil, in comparison to placebo, as early combination to L-dopa.

PATIENTS AND METHODS

This study was conducted in agreement with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the relevant institutional ethics committee, and all patients freely gave their written informed consent before participation.

Patients

Male and female patients, 35 to 75 years of age, with a clinical diagnosis of idiopathic PD (complete parkinsonian syndrome, or predominant tremor, or pure akinetic hypertonic syndrome) of less than 10 year's duration (stages I–III on the Hoehn and Yahr's scale)[29] could be recruited. Previous treatment with dopamine agonists, anticholinergics, and amantadine had to be discontinued for at least 1 month before screening. Eligible patients had to be receiving L-dopa treatment for more than 6 months and less than 8 years and suffering from stable residual parkinsonism on a stable dosage of L-dopa ($\geq$150 mg and $<$800 mg) combined with carbidopa or benserazide for at least 1 month before inclusion.

Patients treated with selegiline could participate as long as they were on stable dosage for at least 1 month before enrolment. Current treatments with anxiolytic, hypnotic, and antidepressant drugs (except for MAOI, amineptine, medifoxamine, fluoxetine, and fluphenazine with nortriptyline) were continued unchanged throughout the trial. Patients with motor fluctuations were excluded.

Study Design

The study used a randomly assigned, double-blind two-group parallel design. Patients underwent a run-in placebo period of 15 days and then were randomly assigned to one of the protocol treatment sequences for up to 6 months: piribedil plus L-dopa or placebo plus L-dopa.

Efficacy was assessed using the Unified Parkinson Disease Rating Scale Part III (UPDRS III) score[30] as primary efficacy criterion: the percentage of responders defined by a 30% decrease from baseline on the UPDRS III[31] and the change from baseline were compared be-

tween the two groups on an intention-to-treat (ITT) basis. A second analysis was performed at 6 months after a possible adjustment of L-dopa daily dose.

Experimental Procedures and Efficacy Measurements

Piribedil was taken as 50-mg tablets or matching placebo tablets, which were identical in aspect and conditioning. The starting dose was 50 mg o.d., increased every 2 weeks in increments of 50 mg up to a recommended dose of 150 mg t.i.d. Daily dose could be eventually adjusted: titrated up by 50 mg in case of insufficient therapeutic efficacy or titrated down by 50 mg in case of clinical intolerance. By the fifth week and up to 6 months, subjects received the treatment at the dosage level achieved in the titration phase. L-Dopa was kept stable until the fourth month but could be adjusted afterward if therapeutic efficacy was not maintained. Domperidone (10 or 20 mg t.i.d.) could be prescribed to control gastrointestinal disorders.

Initial screening visit included a complete medical history with a particular attention to the stability of the patient's symptoms over the day; none complained of motor fluctuations or dyskinesias. Clinical and safety assessments were performed at baseline and after 6 weeks, 4 months (M4), and 6 months (M6). Clinical outcome measures included the UPDRS III score,[30] Schwab and England scale,[32] UPDRS II (activities of daily living) and L-dopa daily dose (to evaluate the need for supplementary L-dopa intake). At M6, overall efficacy was assessed both by the patient and the clinician. Safety evaluations included vital signs measurements (in particular blood pressure and heart rate). Supplementary follow-up visits were scheduled at 2 weeks, 4 weeks, and 3 months, during which only vital signs were assessed. At each visit, an open-question interview concerning unexpected events was carried out and compliance was calculated by the count of unused medication.

Statistical Analysis and Sample Size Considerations

The comparability of the two groups was tested at baseline for the main end-point (UPDRS III score) and clinical characteristics. As stated by the protocol, the UPDRS assessments were to be performed at the inclusion, after 4 months and at the end of the study. Piribedil and placebo groups were compared over the 4 and 6 months periods by a one-sided Student *t* test and on an ITT basis.

The ITT population included all randomly assigned patients who had at least one evaluation visit on treatment, taking into account for the analysis of the last observation carried forward. Secondary statistical analyses included Student *t* test or Mann-Whitney's test for bradykinesia, rigidity, and tremor subscores of UPDRS III, UPDRS parts II and VI, and a chi squared test was carried out for the number of early withdrawals due to adverse events.

In a one-sided approach with a minimal difference of 4 points between the two groups on UPDRS III change from baseline, a standard deviation estimated at 6.4 points and an α risk of 0.05, at least 50 patients with at least one UPDRS III score assessed during treatment were necessary in each treatment group. Randomisation was stratified on country. A block size of 4 with a treatment ratio of 1:1 was used. Separate blocks were supplied to each centre.

RESULTS

One hundred fifteen patients participated to this multicentre study, recruited by 31 centres in France and Portugal. A total of 61 patients were randomly assigned in the piribedil group and 54 in the placebo group. Treatment groups were statistically homogeneous at inclusion (Table 1), and the mean duration of study treatment was 155 days in both of them.

Efficacy

The ITT population taken into account for the ITT main analysis of the treatment efficacy consisted of 108 patients who had undergone at least one motor evaluation during the comparative period: 55 patients in the piribedil group and 53 in the placebo group (Fig. 1). At M4, piribedil significantly increased the percentage of

TABLE 1. *Demographics and characteristics of the randomised population at baseline (D0)*

Parameters	Piribedil (n = 61)	Placebo (n = 54)
Men (%)	66	52
Women (%)	34	48
Age (yr)	63.4 ± 7.3	64.8 ± 7.6
Duration of the disease (mo.)	55 ± 33	48 ± 28
Previous treatment with dopamine agonist (%)	29.5	24.2
Hoehn and Yahr		
I–I$\frac{1}{2}$ (%)	9 (15)	12 (22)
II (%)	32 (52)	25 (46)
II$\frac{1}{2}$–III (%)	20 (33)	17 (32)
UPDRS III	28.0 ± 9.8	29.1 ± 10.3
Purely akinetic type (%)	17 (28)	11 (20)
Tremoric type (%)	3 (5)	5 (9)
Classical type (%)	41 (67)	38 (71)
L-Dopa daily dose, D0 (mg)	423 ± 154	398 ± 159

Comparison of the two groups: P = NS for all parameters.

NS, not significant; UPDRS, Unified Parkinson's Disease Rating Scale.

responders compared with placebo (56.4% vs. 37.7%; $P = 0.040$, Fig. 2A), although the difference between groups observed on the improvement of UPDRS III score from baseline (9 and 6.8 points in piribedil and placebo groups, respectively) did not reach statistical significance ($P = 0.088$, Fig. 2B). A significant difference from baseline on the UPDRS III score versus placebo was observed over 4 months in the akinetic hypertonic subset of patients, with −10.1 points from baseline in piribedil group (n = 16) versus −1.4 in placebo group (n = 11) ($P = 0.029$). After 4 months, L-dopa dosage was slightly modified: mean change was +15.1 mg in the placebo group and −8.8 mg in the piribedil group, always in favour of piribedil.

At M6, the second analysis confirms the trends observed at M4 and shows that both UPDRS III parameters were significantly different on the ITT analysis between treatment groups: 61.8% of responders versus 39.6% ($P = 0.017$) in the piribedil group versus placebo (Fig. 3B) and 10 points versus 6.7 points ($P = 0.037$) for the change from baseline (Fig. 3A). Secondary efficacy endpoints (Table 2) did not reach any statistically significant change overall, although tremor at rest change was close to significance at M4 ($P = 0.088$).

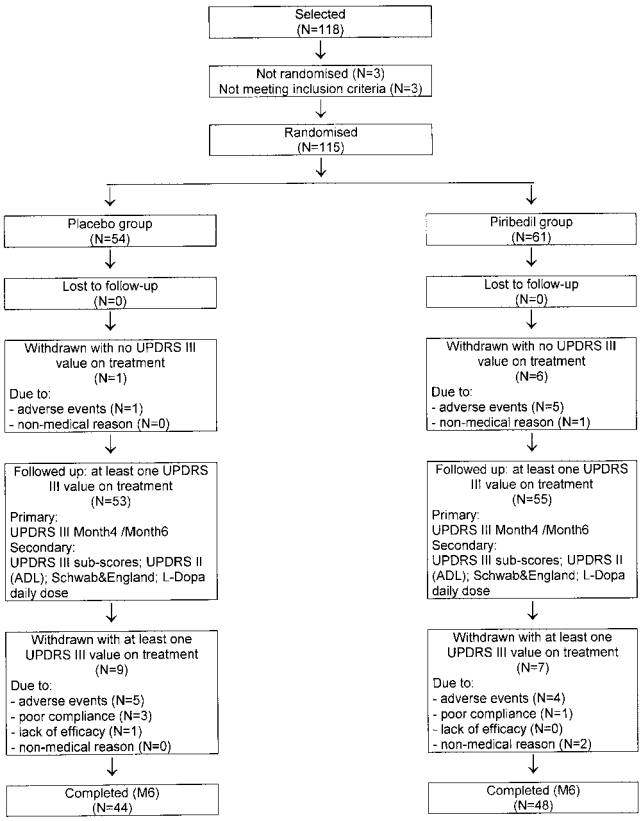

FIG. 1. Disposition of patients according to the CONSORT statement.

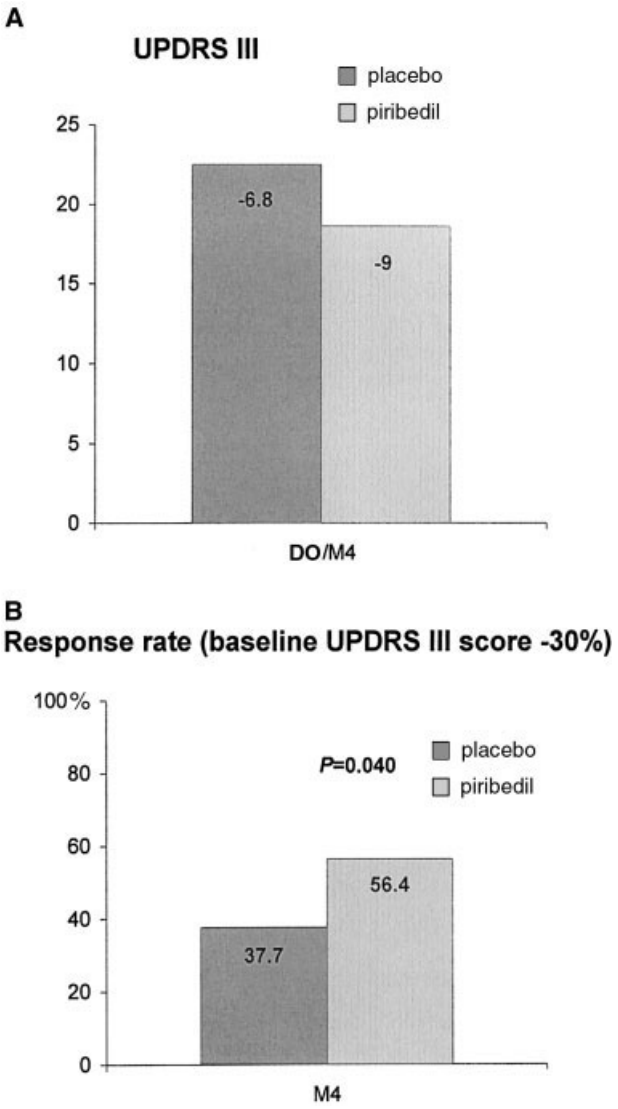

FIG. 2. Efficacy analysis at month 4 (M4) in the intention-to-treat population (n = 108). **A:** Change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) III score. **B:** Response rate defined as a 30% decrease from baseline on the UPDRS III score.

Safety and Tolerability

Among 115 randomly assigned patients, 9 patients (14.7%) in the piribedil group and 6 patients (11.1%) in the placebo group (difference between groups = not significant), withdrew from the study due to the occurrence of an adverse event as shown in Table 3.

Considering the pattern of adverse events leading to withdrawal from the study (Table 3), more withdrawals related to gastrointestinal adverse events were observed in piribedil (5 patients) versus placebo (1 patient). No meaningful difference from placebo was found for withdrawals related to other adverse events.

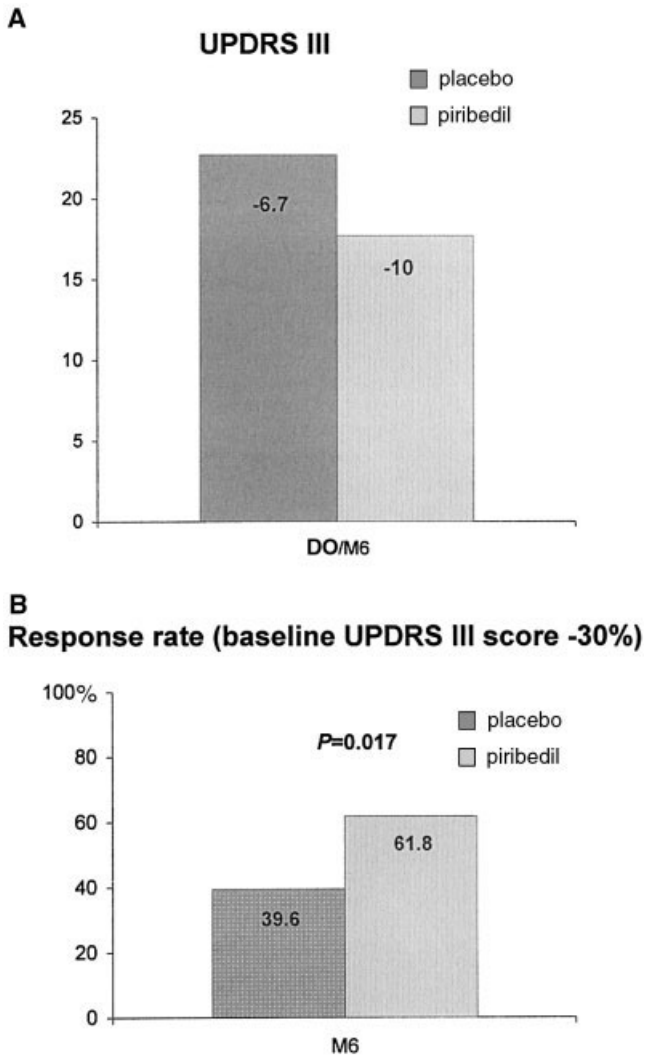

FIG. 3. Efficacy analysis at month 6 (M6) in the intention-to-treat population (n = 108). **A:** Change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) III score. **B:** Response rate defined as a 30% decrease from baseline on the UPDRS III score.

TABLE 3. *Withdrawals due to adverse events*

Adverse events	Piribedil (n = 61)	Placebo (n = 54)
Gastrointestinal symptoms	5 (8.2%)	1 (1.9%)
Hypotension/orthostatic hypotension	1 (1.6%)	1 (1.9%)
Delirium	0 (0%)	1 (1.9%)
Dizziness	2 (3.3%)	1 (1.9%)
Vasodilation hands	0 (0%)	1 (1.9%)
Dystonia	0 (0%)	1 (1.9%)
Headache	1 (1.6%)	0 (0%)
Total AE-related withdrawals[a]	9 (14.7%)	6 (11.1%)

[a]Statistical significance of the comparison, not significant.
AE, adverse events.

During the treatment, 73.8% of the patients in the piribedil group and 55.6% in the placebo group reported the emergence of at least one adverse event (regardless of relationship to study medication; Table 4). The most common adverse events were gastrointestinal symptoms: 27 of 61 patients in the piribedil group versus 13 of 54 patients in the placebo group reported some gastrointestinal symptoms (frequently nausea and/or vomiting), mostly at the beginning of active treatment. Sixteen and 8 patients were treated with domperidone in the piribedil and placebo group, respectively. Among other symptoms, sweating, hypotension, and dizziness were more frequently reported on piribedil plus L-dopa than on placebo plus L-dopa. The sleep-related disorders pattern was similar in piribedil and placebo patients: somnolence, 2 (3.3%) versus 1 (1.9%); dreaming abnormal, 0 (0%) versus 1 (1.9%); paroniria, 1 (1.6 %) versus 0 (0%); yawning, 1 (1.6%) versus 0 (0%); and other sleep disorders, 0 (0%) versus 1 (1.9%), respectively, on piribedil and placebo. No case of sudden sleep attack was reported. During the study, only one patient reported dyskinesia (at M6, in the piribedil group).

TABLE 2. *Subscores recorded for the comparative analysis of efficacy (ITT): mean (SD) and percentage of change versus baseline (D0)*

	Piribedil (n = 55)		Placebo (n = 53)	
	M4-D0	M6-D0	M4-D0	M6-D0
Rigidity (item 22 UPDRS III)	−1.7 (1.9) 33%	−2.0 (2.4) 39%	−1.4 (2.3) 26%	−1.4 (2.3) 25%
Bradykinesia (items 23–27 UPDRS III)	−4.0 ± 3.6 36%	−4.5 ± 4.3 40%	−3.1 ± 4.1 25%	−3.2 ± 4.2 26%
Rest tremor (item 20 UPDRS III)	−1.4 (2.0) 40%	−1.1 (2.1) 33%	−0.7 (2.0) 25%	−0.5 (2.4) 16%
UPDRS II (ADL)	−2.4 (3.4) 22%	−2.4 (3.5) 23%	−1.8 (3.5) 17%	−1.9 (3.7) 18%
Schwab & England	+3.1 (6.0) 4%	+2.5 (7.3) 3%	+2.3 (5.6) 3%	+2.3 (6.7) 3%

ADL, activities of daily living; ITT, intention-to-treat; m, month; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 4. *Emergent adverse events*

Adverse events system	Piribedil (n = 61)	Placebo (n = 54)
Gastrointestinal system	27 (44.3%)	13 (24.1%)
General disorders	13 (21.3%)	10 (18.5%)
Central peripheral nervous system	11 (18.0%)	9 (16.7%)
Psychiatric disorders[a]	7 (11.5%)	7 (13.0%)
Respiratory system	7 (11.5%)	3 (5.6%)
Autonomic nervous system	6 (9.8%)	1 (1.9%)
Musculoskeletal system	4 (6.6%)	3 (5.6%)
Skin disorders	2 (3.3%)	0 (0%)
Vascular (extracardiac) disorders	1 (1.6%)	1 (1.9%)
Others	3 (4.9%)	3 (5.6%)

[a]Including sleep-related disorders.

Five patients (two in the piribedil group, three in the placebo group) had at least one serious adverse event: one case of orthostatic hypotension; one case of suspicion of a rectum neoplasm, which was not confirmed on piribedil; one case of dehydration leading to a confusional syndrome, one case of agitation and delirium, and one case of ischemic colitis on placebo.

Data on blood pressure and heart rate, at inclusion and on the discharge day at M6, are displayed in Table 5. They show no noticeable variation of these parameters during the study, in none of the two groups.

DISCUSSION

We have conducted this prospective, double-blind, placebo-controlled trial to confirm the therapeutic benefit of piribedil (Trivastal retard 50 mg, 150 mg/day) as an adjunct to L-dopa to improve the control of PD-induced motor symptoms. The present results confirm a significantly greater efficacy of 6-month piribedil administration (150 mg/day) over placebo in stable patients insufficiently controlled by L-dopa alone.

The planned main criteria was the improvement of motor symptoms evaluated by the change in UPDRS III score from baseline and the number of responders at 4 months, on an ITT basis. The part III of UPDRS was chosen because it is largely validated and has a good inter-rater reliability. Response defined by at least a 30% reduction from baseline is generally believed to represent a clinically relevant improvement.[31]

At 4 months, the number of responders was significantly higher in the piribedil group (56.4%) than in the placebo group (37.7%). On the other hand, although there was a greater improvement on UPDRS changes in the piribedil group than in the placebo group, this difference did not reach statistical significance ($P = 0.088$), probably due to an unexpectedly large placebo effect, which reduced the power of the study. Of interest, UPDRS III score changes were greater on piribedil than on placebo in the small subset of purely akinetic hypertonic patients, whereas it is a frequent clinical observation that piribedil is mostly active on tremor. At 6 months and despite possible adjustment of L-dopa daily dose, difference was significant for both primary outcomes. None of the UPDRS III subscore, UPDRS II, or UPDRS VI showed a statistically significant difference at M4 or M6, although these parameters are not considered sensitive enough in early PD patients.

The beneficial therapeutic effects of piribedil may be related to its specific receptorial profile that couples a balanced agonist activity on D_2 and D_3 dopamine receptor to a similar extent antagonist action on the two main α-2 adrenergic receptor subtypes in the central nervous system.[9,10] Such a receptorial profile may explain the locomotor, vigilance, or balance control improvements observed in preclinical models.[33]

The present study showed that piribedil had satisfactory clinical acceptability except for gastrointestinal symptoms (nausea or vomiting), often mild and occurring at the beginning of the active treatment. Recently, Hundemer and coworkers[34] also reported that digestive adverse events were common with the use of pergolide in early-stage PD. The clinical pattern of adverse events observed with piribedil was basically the same as with ropinirole and bromocriptine,[35,36] although no difference from placebo was observed for orthostatic hypotension and sleep-related disorders. The present study was not aimed at evaluating somnolence,[37–39] but no major safety problem due to somnolence or other sleep-related disorder was detected in this study: only 2 of 61 patients (3.3%) reported somnolence on piribedil.

Combination treatment with a dopamine agonist and L-dopa is frequently proposed in the treatment of PD.[40–43] Dopamine agonists may be recommended as early treatment,[44,45] either alone or later combined with

TABLE 5. *Blood pressure and heart rate at inclusion and at the end of the study*

	Piribedil (n = 55)		Placebo (n = 52)	
	BP (mm Hg)	HR (bpm)	BP (mm Hg)	HR (bpm)
Day 0				
Supine	136/81	72	134/79	72
Standing	129/79	76	129/79	75
Month 6				
Supine	133/80	71	133/78	73
Standing	127/79	76	125/76	77

BP, blood pressure; HR, heart rate; bpm, beats per minute.

L-dopa.[4] The present data show that the association of piribedil to L-dopa significantly improves parkinsonian motor symptoms in stable patients with approximately 5 years of PD history. Its global efficacy on motor symptoms was not confined to tremor, and it was well accepted. Further studies, with a longer duration of follow-up, in a larger population of patients should be considered to confirm the therapeutic benefit of using long-term piribedil to prevent late motor complications as expected according to available preclinical studies.

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SCA2 May Present as Levodopa-Responsive Parkinsonism

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Abstract: **Some kindreds with familial parkinsonism exhibit genetic anticipation, suggesting possible involvement of trinucleotide repeat expansion. Recent reports have shown trinucleotide repeat expansions in the spinocerebellar ataxia 2 (SCA2) gene in patients with levodopa-responsive parkinsonism. We tested 136 unrelated patients with familial parkinsonism for SCA2 mutations. Two probands had borderline mutations; the rest were normal. (≤31 repeats is normal, 32–35 is borderline, ≥36 is pathogenic). The expanded allele segregated with neurological signs in one kindred. The absence of borderline mutations in the normal population, and the co-segregation of the expanded allele with neurological signs in one kindred suggest that SCA2 mutations may be responsible for a subset of familial parkinsonism.**

Key words: parkinsonism; SCA2 mutation; levodopa

The causes of parkinsonism are mostly unknown, but the evidence increasingly implicates genetic factors.[1] Anticipation has been described in familial parkinsonism, leading to the suggestion that in some families a trinucleotide repeat expansion may be a cause for disease.[2] Furthermore, previous studies have identified fam-

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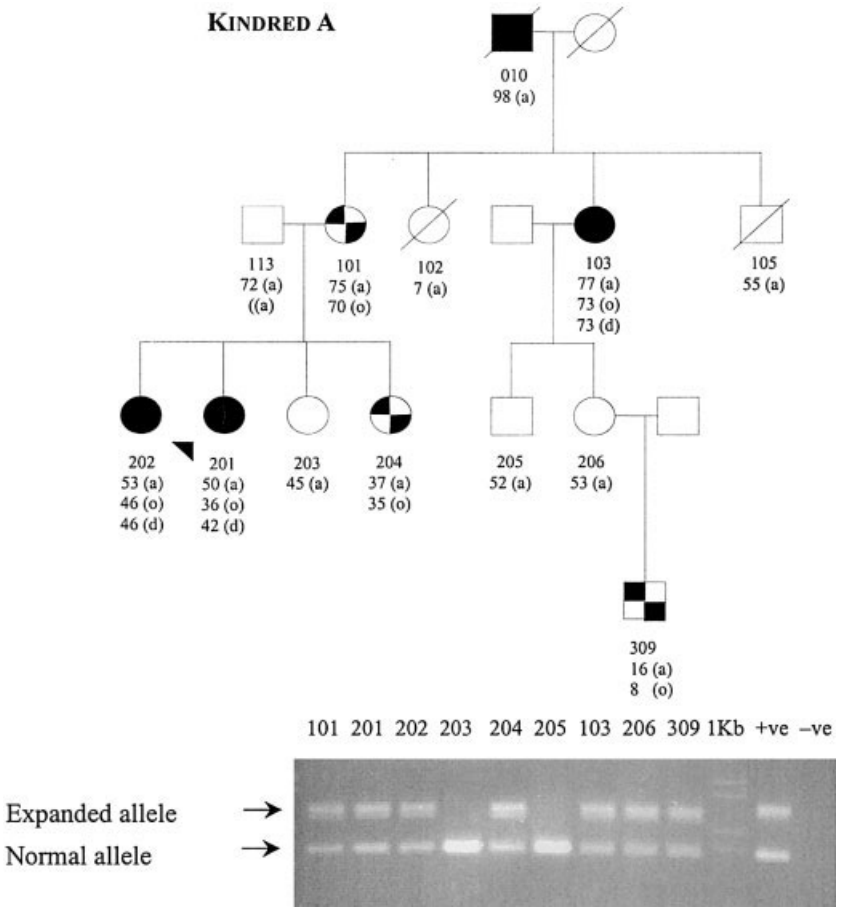

FIG. 1. Solid symbol, clinical idiopathic parkinsonism; hatched symbol, neurological signs or symptoms; a, age at last contact or death; o, age at onset of symptoms; d, age at diagnosis.

ilies with SCA2 repeat expansions in which probands presented with parkinsonism.[3,4] For these reasons, we examined the presence of SCA2 mutations in clinically diagnosed patients with parkinsonism with positive family history.

SUBJECTS AND METHODS

We studied 136 probands with idiopathic parkinsonism and a history of first- or second-degree relative with parkinsonism (83 men, 53 women; 133 Caucasian, 2 Hispanic, 1 Native American). All probands were evaluated by neurologists at the movement disorder clinics at the Oregon Health and Science University (OHSU) and the University of Washington (UW) and had the clinical diagnosis of idiopathic parkinsonism, according to the British Parkinson's Disease Brain Bank criteria,[5] except that family history was not an exclusion criteria. The affected relatives were reported by the proband to have had a diagnosis of parkinsonism by a physician. All subjects signed an Informed Consent approved by the Institutional Review Boards at OHSU and UW.

Genomic DNA was extracted from blood using standard techniques. SCA2 expansions were assessed by PCR amplification followed by high-resolution acrylamide electrophoresis.[3] In addition, when PCR showed an expansion, PCR products were TA cloned, following the manufacturer's recommendation (Invitrogen, Carlsbad, CA), and normal and expanded alleles sequenced to verify the expansion.

We also studied the affected and unaffected family members of Proband A-201, who had a SCA2 mutation, to determine if the mutation segregates with disease in the kindred (Fig. 1). The family members had been evaluated by neurologists before this study and the diagnoses were made before they were suspected to have SCA2 mutations. Every member of the A kindred who was included in the SCA2 testing had been evaluated clinically, except A-203 who had no symptoms and did not wish to be examined. Genotyping for SCA2 was blind to phenotype.

LOD scores were calculated using LINKAGE (online at ftp://linkage.rockefeller.edu/software/linkage) under

an autosomal dominant model. Model specifications were set at 0.0003, 0.003, and 0.5 to 0.99, respectively for disease frequency, phenocopy rate and penetrance. Two scenarios were considered: first, affecteds-only analysis of parkinsonism; second, individuals with parkinsonism or other neurological signs were considered affected, all other family members were considered at risk.

RESULTS

Two probands (A-201 and B-201) had expanded SCA2 alleles with 33 and 35 repeats respectively; the remaining 134 probands had normal SCA2 repeat lengths of 19 to 30. Proband A-201 had an uninterrupted CAG repeat whereas Proband B-201 had a single CAA in the repeat sequence. Subsequent sequencing confirmed the expansions and showed 36 repeats for both A-201 and B-201. The first results (33 and 35 repeats) were based on PCR, whereas the second results (36 repeats) were based on sequence. Given that the diagnostic standards for SCA2 are based on the PCR method, where $\leq$31 repeats is normal, 32 to 35 is borderline and $\geq$36 is the full mutation, the expanded alleles in A-201 (33 repeats) and B-201 (35 repeats) would be considered borderline pathogenic.

Kindred A

Proband A-201 is a 50-year-old Caucasian woman who first developed back pain, gait difficulties, imbalance, and bradykinesia at age 36. She was diagnosed as having parkinsonism at age 42 and started on benztropine that improved all of her symptoms. Subsequent addition of levodopa (L-dopa) further improved her symptoms. Her exams have markedly differed from clinic visit to visit while she has been followed at OHSU. After reducing her L-dopa on her initiative and seen 12 hours after her last dose, she had rigidity in all limbs, rest tremor in her left leg, global bradykinesia, reduced facial expression, a slow gait and reduced associated movements and postural instability (motor UPDRS = 42). She did not have abnormal eye movements, pyramidal signs, sensory loss, ataxia, or significant dysautonomia. Subsequent examinations at various times within L-dopa dose cycles sometimes showed her to be essentially normal with no stigmata of parkinsonism when *on*; some times to have mild truncal and leg dyskinesias; and at other times to exhibit dystonic posturing of the legs and feet as L-dopa was wearing off. A MRI done at age 50 was normal. Subject A-201 has no mutation or deletion in the parkin gene, as determined by sequence analysis and dosage assays.

Proband A-201 is one of 4 sisters (Fig. 1, Table 1). The eldest sister (A-202), age 53, presented at age 46 with a history of deterioration in handwriting and gait. She described shuffling, a tendency to drag her feet, and impaired balance. She had masking, mild rigidity, bradykinesia, no tremor, and impaired postural responses. She responded to L-dopa and has had minimal progression of her signs to present. Her brain MRI, done at age 46, was normal. The youngest sister (A-204), age 37, reports problems with balance and speech starting at age 35, particularly brought out by alcohol or fatigue, but has a normal neurological exam. The fourth sister (A-203) is healthy. The 2 sisters with parkinsonism and the sister with speech and gait symptoms but no signs have the expanded allele; the sister without symptoms or signs does not.

Their mother (A-101) developed mild postural instability and a wide based gait at age 70; she has no other neurological signs at age 75. Her sister (A-103), age 77, was diagnosed with parkinsonism at age 73 and started on L-dopa at that time, with good response. Remainder of her neurological exam was normal. MRI showed mild white matter ischemic changes and mild T2 hyperintensity in the globus pallidus bilaterally but no cerebellar or brainstem atrophy. Both A-101 and A-103 have the expanded allele. The proband's maternal grandfather (A-010) was reportedly affected with parkinsonism in his 90s and was treated with L-dopa. The proband's cousin (A-206) has the expansion but has no neurological signs or symptoms at age 53. Her son (A-309), who also has the expansion, was noted to have abnormal eye movements at age 8. When examined at age 16, he had severe vertical gaze palsy and mild masked facies, but did not have ataxia, dysarthria or nystagmus.

Segregation of the expanded allele with parkinsonism and neurological signs was examined using linkage analysis. LOD score analysis of this pedigree gave suggestive evidence for linkage to SCA2 (Z = 1.2–1.5, θ = 0, depending on whether parkinsonism or parkinsonism/other neurological signs was considered as the trait).

Kindred B

The proband (B-201) is a 76-year-old, Hispanic man who noted cramps in his legs at age 60, and at age 62 began to experience burning sensation in his feet that extended to the knees by age 65. When evaluated at age 64, he was found to have evidence of a sensorimotor neuropathy but also he had brisk deep tendon reflexes, bilateral Babinski signs, spastic catch in the legs and a neurogenic bladder. MRI of cervical and thoracic spine showed degenerative disc disease from C4 to C7 with a prominent spondylotic bar at C6-7 for which he underwent a posterior decompressive laminectomy with mild

TABLE 1. *Phenotypic characteristics of affected individuals in the families*

Phenotype	Subject						
	A-101	A-103	A-201	A-202	A-204*	A-309	B-201
Age at onset (yr)	70	73	36	46	35	8	60
Parkinsonism							
Rest tremor	−	±	+	−	−	−	+
Rigidity	−	+	+	+	−	−	+
Bradykinesia	−	+	+	+	−	−	+
Impaired postural responses	+	NA	+	+	−	−	+
Levodopa response	−	+	+	+	NT	NT	+
Levodopa induced dyskinesia	−	NA	+	+	NT	NT	−
Ataxia							
Wide based and/or ataxic gait	+	−	−	−	−	−	−
Limb ataxia	−	−	−	−	−	−	−
Action/kinetic tremor	−	−	−	−	−	−	−
Ataxic speech	−	−	−	−	−	−	−
Peripheral neuropathy							
Decreased or absent DTRs	+	−	−	−	−	−	+
Sensory changes	−	−	+	−	−	−	+
Corticospinal dysfunction							
Increased DTRs	−	−	−	+	−	−	+
Babinski signs	−	−	−	−	−	−	+
Abnormal eye movements							
Slowed saccades	−	−	−	−	−	+	−
Opthalmoplegia	−	−	−	−	−	+	−

*A-204 has symptoms but no signs.
NA, unknown or could not be tested; NT, not treated; −, sign absent; +, sign present.

improvement in his gait. Examination at age 65 showed signs of peripheral neuropathy and myelopathy but also signs consistent with parkinsonism, namely masking, reduced arm swing, rigidity and mild resting tremor in arms and legs. He was felt to have three unrelated disorders, peripheral neuropathy, myelopathy from cervical stenosis and idiopathic parkinsonism. Over the next 10 years, restless leg syndrome became the patient's predominant complaint. His deep tendon reflexes became less prominent and eventually disappeared. The parkinsonism became more apparent and responded to L-dopa. He had no abnormalities of eye movements, no dysarthria, no dysmetria, and his gait remained narrow based. Ambulation was markedly impaired at last examination due to weakness in his legs, shuffling, and impaired postural responses. Diabetes was diagnosed at age 72 and treated with oral agents. Chronic lymphocytic leukemia was also diagnosed at this time.

The proband was one of 4 children. His older brother had tremor, shuffling gait, and dysarthria that was diagnosed as parkinsonism in Mexico. He died at age 80. His other 2 brothers had no recognized neurological disorders. The patient's father was said to have died of complications of alcoholism at age 33. The patient's mother had severe diabetes. Restless leg syndrome was said to run in the mother's side of the family. We could not assess segregation of SCA2 in the B-201 kindred because the affected relatives of the proband were deceased and DNA was not available.

DISCUSSION

In our clinical series of 136 patients with familial idiopathic parkinsonism, 2 (1.4%) had borderline SCA2 mutations. In a study of Chinese patients with familial parkinsonism, SCA2 mutations were found in approximately 10% of the patients.[4] The size of the expansions in our parkinsonian patients would be considered borderline pathogenic for SCA2. Riess and associates[6] defined the range of the normal SCA2 allele size as 17 to 31 CAG repeats. The full pathogenic mutations had 36 to 64 repeats. The intermediate/borderline repeat sizes, which were found in our parkinsonian patients, were absent in 241 neurologically normal elderly individuals. It is possible that other as yet undetected genetic or environmental factors caused or contributed to the parkinsonism in our patients. Absence of borderline mutations in the normal population and co-segregation of the expanded allele with neurological signs in Kindred A suggest, however, that SCA2 mutations may be responsible for a subset of familial parkinsonism. The collective evidence

from this and other reports suggest that patients with an autosomal dominant family history of possible Parkinson's disease, and those with L-dopa-responsive atypical parkinsonism should be screened for SCA2 mutations.

Three of our cases (A-103, A-201, and A-202) were diagnosed as idiopathic parkinsonism by the standard criteria. Case B-201 was also felt to be idiopathic parkinsonism with coexisting cervical spinal stenosis explaining the myelopathy and diabetes being the etiology of his peripheral neuropathy. Only after discovering that he carried the SCA2 mutation, were the progressive peripheral neuropathy, myelopathy, and parkinsonism recognized likely to be caused by the same condition. Although, with the benefit of hindsight, each patient had some mild features that were atypical, the symptoms were overwhelmingly those of sustained L-dopa–responsive parkinsonism. These cases, like two previous reports,[3,4] show that SCA2 expansions can produce the clinical picture of L-dopa responsive idiopathic parkinsonism without cerebellar signs. The case descriptions of these three reports suggest that onset with gait and balance complaints, leg tremor, sustained response to L-dopa and borderline expansions are characteristics of parkinsonism associated with SCA2 mutations. Interestingly, borderline expansions of SCA3 may also be associated with the L-dopa–responsive parkinsonism.[7,8]

The pathology of SCA2 includes a marked degeneration of the substantia nigra compacta and the surprise is that patients with the SCA2 mutation do not more frequently exhibit parkinsonism.[9] Perhaps concurrent degeneration in other brainstem and cerebellar nuclei may mask the expected clinical manifestations of degeneration of the substantia nigra compacta just as subthalamic nucleus lesions or DBS may mask the effects of selective degeneration of substantia nigra compacta in idiopathic Parkinson's disease.

Kindred A exhibits genetic anticipation, but strikingly, there is no correlation between age at onset and repeat size. Unless there is mosaicism with larger repeats in the central nervous system than white blood cells, other factors must exist to explain the variable expression of this mutation. The possibility that anticipation in this family is due to ascertainment bias or other genetic or environmental causes unrelated to SCA2 expansion is not ruled out. Although we had suggested previously that anticipation may occur in idiopathic parkinsonism and thus expanded repeats may be found; we had found none using the Repeat Expansion Detection (RED) technique.[10] The RED technique, however, would have not picked up less than 50 repeats. We did not find SCA2 expansions in 134 of 136 probands with familial parkinsonism, but it remains possible that borderline expansions of other triplet repeats may be present in some of them.

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Reduced Genital Sensitivity in Female Patients with Multiple System Atrophy of Parkinsonian Type

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Abstract: **According to the consensus statement on the diagnosis of multiple system atrophy (MSA), erectile dysfunction is required for male patients to fulfil the urinary incontinence criterion. However, there is no equivalent item for female patients. We questioned 19 female patients with MSA of the parkinsonian type (MSA-P), 28 female patients with Parkinson's disease (PD), and 27 healthy controls on their genital sensitivity. A total of 47% of the MSA patients but only 4% of the PD patients and 4% of the control group admitted to reduced genital sensitivity, a highly significant difference ($P < 0.001$). Moreover, the appearance of reduced genital sensitivity in female MSA patients showed a close temporal relation to the onset of the disease. If these preliminary results can be confirmed and further specified in a larger sample, a historical item of reduced genital sensitivity in female patients might become a diagnostic feature for MSA, comparable to erectile dysfunction in male patients.**

Key words: multiple system atrophy; parkinsonian syndrome; genital sensitivity; female gender; diagnosis

Multiple system atrophy (MSA) is characterized clinically by a combination of autonomic symptoms with parkinsonian, pyramidal, and/or cerebellar signs.[1,2] The consensus statement on the diagnosis of multiple system atrophy[3] defines three levels of diagnostic certainty: possible, probable, and—at post mortem—definite. Whereas a possible diagnosis of MSA can be made on the presence of one criterion plus two features from the given domains (autonomic and urinary dysfunction, parkinsonism, cerebellar dysfunction), a probable diagnosis requires the presence of autonomic dysfunction. One study has shown impotence (erectile dysfunction) to be the most frequent autonomic symptom in male patients with MSA.[4] However, studies on MSA lack information on sexual dysfunction in female patients. Erectile dysfunction in male patients is an additional requirement to fulfil the autonomic dysfunction criterion of urinary incontinence according to the consensus statement, but there is no comparable requirement in female patients. Therefore, in this pilot study, we have investigated, as an item corresponding to male erectile dysfunction, the historical item of reduced genital (clitoral) sensitivity in female patients with MSA of parkinsonian type (MSA-P).

SUBJECTS AND METHODS

We investigated by means of a standardized semi-structured interview the presence and onset of reduced genital sensitivity in female individuals suffering from MSA-P or PD and in healthy controls. Nineteen female patients diagnosed with possible (n = 5) or probable(n = 14) MSA[4] of the parkinsonian type (MSA-P) were identified at the Department of Neurology, University of Marburg, and at the Paracelsus-Elena Hospital in Kassel, Germany, a specialised clinic for Parkinson's disease. All of them agreed to be questioned on sexual dysfunction, including libido and presence and onset of reduced genital sensitivity. The key question was: "have you experienced reduced sensitivity in your genital body region (original question in German: "haben Sie eine Verminderung des Gefühls im Genitalbereich erlebt?") and, if so, was its onset related to the onset of motor symptoms? Reduced genital sensitivity was defined and explained as marked reduction or absence of sensitivity of the clitoris or within the genital region. We deliberately used this rather global question and did not differentiate between sensitivity, lubrication, or reduced blood circulation. Interviews were conducted face-to-face by the same male physician at the Department of Neurology in Marburg. In 12 patients who were too handicapped to come to the clinic, the interview was done via telephone.

An additional 28 female patients with Parkinson's disease (PD) were recruited at the Department of Neurology of the University of Marburg. These women were significantly older than those with MSA-P ($P = 0.03$), and their mean disease duration non-significantly longer. All of them responded well to levodopa medication, and only four complained of autonomic features (urge incontinence).

Finally, 27 healthy female control volunteers (HC), including a few spouses of inpatients of the Department of Neurology, were interviewed. Their age did not differ

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TABLE 1. *Demographic data of patients (MSA-P, PD) and healthy controls*

	MSA-P (n = 19)		PD (n = 28)		HC (n = 27)	
	Mean	SD	Mean	SD	Mean	SD
Age (yr)	63.5	6.6	69.2	9.6	64.2	9.0
Disease duration (yr)	4.2	2.3	7.0	5.2		

MSA-P, multiple system atrophy of Parkinsonian type; PD, Parkinson's disease; HC, healthy controls.

significantly from the group of MSA-P patients, and none of them suffered from neurological diseases or autonomic dysfunction. The demographic data of the three groups are given in Table 1. Interviews of patients with Parkinson's disease and of control volunteers were also conducted face to face by the same male physician.

Statistical analysis was done using the SPSS standard version for windows. The mean demographic scores were compared using the Student's *t* test. Comparison of frequency of autonomic dysfunction was done using Fisher's exact test.

RESULTS

Seventeen of the 19 patients with MSA-P were able to answer the questions on reduced genital sensitivity. Eight (47%) of these 17 admitted to reduced genital sensitivity, whereas only 1 of 28 patients with PD and 1 of 27 healthy controls admitted to this symptom (Table 2). The difference between the patients with MSA-P and the PD patients as well as the healthy controls was significant ($P < 0.001$). In addition to those patients with reduced genital sensitivity, 3 further MSA-P patients, 7 PD patients, and 8 HCs had loss of libido. Two patients with MSA-P could not comment on their genital sensitivity—a weakness of the approach using a questionnaire and a semistructured interview. The reduced genital sensitivity in most MSA-P patients occurred within the 3 years before their akinetic–rigid symptoms appeared or the disease was diagnosed, and most of them reported a subacute onset of reduced sensitivity over a period of 3 months or less. In only 2 MSA-P cases did the reduced sensitivity start after their clinical diagnosis. In those patients with PD and healthy controls with loss of libido, this finding had occurred shortly after the death of the sexual partner and was not temporally related to the diagnosis of PD.

DISCUSSION

This clinical study is the first to address reduced genital sensitivity in female patients with possible and probable MSA-P. One possible weakness of the methodology is obvious, in that the results rely solely on the reply of the respondents. However, patients responded without hesitation, and those who reported reduced genital sensitivity immediately knew what the question was related to. Moreover, male erectile dysfunction is also normally elicited by questioning the individual patient, rather than by any objective methods. Our survey indicates that reduced genital sensitivity is far more frequent in women suffering from MSA-P than in female patients with PD or healthy controls, despite longer disease duration and older age in the former. Also, in the vast majority of

TABLE 2. *Differences in sexual dysfunction between patients with MSA, PD, and healthy controls*

Symptom	MSA-P (N = 17)*	PD (N = 28)	Controls (N = 27)
Normal genital sensitivity, n (%)	9 (53)	27 (96)	26 (96)
Reduced genital sensitivity, n (%)	8 (47)	1 (4)[a]	1 (4)[a]
Loss of libido, n (%)	3 (17)	7 (25)	8 (29)
Latency from reduced genital sensitivity to onset of akinetic-rigid symptoms, yr (mean ±SD)	−0.5 ± 2.0 (n = 6)[b]	+1 (n = 1)	N/A

*Two of the 19 MSA patients were not able to answer the question on reduced genital sensitivity.

[a]Difference compared to patients with MSA-P was highly significant ($P < 0.001$), Fisher's exact test.

[b]Six of eight MSA patients with reduced genital sensitivity were able to state its time of onset.

MSA-P, multiple system atrophy of parkinsonian type; PD, Parkinson's disease.

MSA-P patients reduced genital sensitivity had been noticed before the appearance of the akinetic–rigid symptomatology. These findings show that reduced genital sensitivity is common among, and perhaps characteristic of, female patients with MSA-P. However, the frequency of reduced genital sensitivity (47%) in our group of 17 female MSA-P patients is not as high as the frequency of impotence (90%) reported by Wenning and coworkers[5] among 67 male patients with MSA. This finding might be due to the smaller number in our sample, to sociocultural differences between male and female recognition of sexual dysfunction, or may represent a real difference. As noted before, 2 of the female MSA-P patients could not comment on their genital sensitivity.

We are aware that this is a pilot study. Improved self-report measures or a physical investigation are needed to ascertain whether the reported reduction of sensitivity represents a true hypo- or anaesthesia or simply is an interpretation of reduction in lubrication or blood circulation. Thus, a future study should use an appropriate scale and to relate the reported reduced genital sensitivity to sexual practices, frequency of intercourse, or mood disturbances that may affect these variables. A further study is needed to assess whether women with MSA of cerebellar type (MSA-C) have a similar rate of reduced genital sensitivity. At present, it remains unknown to what extent the reduced genital sensitivity reported is a central or peripheral process, and the degree to which it is equivalent to the erectile dysfunction experienced by male patients with MSA.

The absence of a recognized female equivalent of erectile dysfunction in males can potentially affect both diagnosis and estimates of disease duration. Thus, because the consensus diagnostic criteria insist on the additional presence of erectile dysfunction in men for them to fulfil the urinary incontinence criterion for autonomic failure, they may be less likely to be diagnosed with MSA, or diagnosed later, than women. Conversely, when disease duration and survival are considered, because for many men erectile dysfunction precedes any other symptom, they may have apparently longer survival than women with MSA that is artificial and that disappears when survival from onset of motor symptoms alone is considered.[6]

If our observation is confirmed and further specified in a larger prospective study in MSA in comparison to PD patients, reduced genital sensitivity may become a further symptom to be added to the list of autonomic features[3,7] that can be used to diagnose and differentiate MSA from PD in women.

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Factors Associated with Increased Risk of Head Tremor in Essential Tremor: A Community-Based Study in Northern Manhattan

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Abstract: **Head tremor is one of the major expressions of essential tremor (ET). It is not well understood why some patients develop head tremor, whereas others do not. A**

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study of the characteristics of patients with head tremor has not been undertaken. Our goal was to estimate the prevalence of head tremor and to identify demographic and clinical characteristics associated with an increased risk of head tremor in ET. Cases were ascertained from a community-based study of ET in northern Manhattan, New York. Arm tremor severity was rated with a total tremor score. Logistic regression analyses resulted in odds ratios (OR). Head tremor was present in 37 (34.9%) of 106 ET cases. Female gender was associated with a fourfold increased risk of head tremor (OR = 3.73; $P = 0.005$). Total tremor score was divided into quartiles; individuals in the lowest or highest quartile were four times more likely to have head tremor (OR = 4.16; $P = 0.001$). Individuals with both risk factors (female gender and lowest or highest total tremor score quartile) were 16 times more likely to have head tremor (OR = 15.88; $P = 0.0006$). Being related to a proband with head tremor marginally increased the risk of head tremor (OR = 11.30; $P = 0.08$). Age and tremor duration did not influence the risk of head tremor. We identified several factors that were associated with an increased risk of head tremor in ET; female gender, coexisting arm tremor that was either very mild or extremely severe, and relation to an ET case with head tremor. These disease associations require further exploration, and might provide insight into the mechanisms underlying head tremor.

Key words: essential tremor; head tremor; epidemiology; community; risk factors

Head tremor is common in patients with essential tremor (ET)[1–3] and is one of the main expressions of the underlying disease. Head tremor is important in other ways as well. Head tremor and hand tremor do not necessarily respond in the same way to treatments, including beta blocking agents,[4] methazolamide,[5] and barbiturates.[6] The reasons why some patients develop head tremor whereas others do not are not well understood. Initial clues about the mechanisms that underlie head tremor may be gained through an epidemiological approach, and more specifically, a study of the characteristics of the patients who have developed this type of tremor. We studied a group of ET cases who participated in a community-based study of ET.[7,8] An advantage of this group over previous cohorts is that the ET cases were not ascertained through clinics, doctors offices, or hospital rosters. They were not selected because of health-seeking behavior or because of the severity or type of their disease manifestations. Our goals were to estimate the prevalence of head tremor, and to determine which demographic and clinical characteristics were associated with an increased risk of head tremor in ET.

PATIENTS AND METHODS

The Washington Heights-Inwood Genetic Study of Essential Tremor is a family study of ET in the Washington Heights–Inwood community in northern Manhattan, New York.[7,8] Subjects included two types of probands (ET cases and control subjects) and their respective first- and second-degree relatives. ET was diagnosed based on a neurological examination and standardized diagnostic criteria.[7,8] There were 106 ET cases from 70 families. This group included 59 probands with ET, 33 of their relatives with ET and 14 affected relatives of control probands.[8] All subjects underwent a demographic and medical history and a videotaped tremor examination. During the videotaped tremor examination, tremor was assessed during six tasks performed with the dominant arm and nondominant arms. Two neurologists, who viewed videotaped examination, rated the tremor during each task using a 0 to 3 clinical rating scale and assigned a total tremor score (0–36 maximum).[7,8] The final total tremor score was the average of the two raters' scores. The total tremor score is a clinical measure of tremor severity that correlates with physiological measures of tremor severity including a modified Klove Matthews Motor Steadiness Test Battery[9] and quantitative computerized tremor analysis results.[10] ET of the head, which was assessed while the patient was seated, standing, and walking, was noted as present or absent. Hence, the head was observed in many situations in which the arms were either resting in the lap or at the sides. In this way, the examiner was able to examine head tremor without the effects of simultaneous arm tremor. ET of the head was distinguished from dystonic tremor by the absence of 1) twisting or tilting movements of the head, 2) jerk-like or clonic neck deviation, and 3) hypertrophy of neck muscles. Head tremor severity was rated as mild or moderate to severe.

Chi-square (χ^2) tests were used to analyze proportions and Student's t tests to examine group differences in continuous variables. Total tremor score was stratified into quartiles. Univariate and multiviariate logistic regression analyses were performed in which the dependent variable was head tremor (present vs. absent) and in different models, independent variables included age, gender, total tremor score quartile, taking a tremor medication (yes vs. no), or being related to a proband with head tremor. This approach resulted in odds ratios (OR) with 95% confidence intervals (CI). Strata of gender by total tremor score quartile were created, including men in quartiles 2 or 3, men in quartiles 1 or 4, women in quartiles 2 or 3, and women in quartiles 1 or 4. A univariate logistic regression analysis was performed in which the dependent variable was head tremor, and the independent variable was gender by total tremor score quartile (women in quartiles 1 or 4 vs. men in quartiles 2 or 3). All statistical analyses were performed using *SPSS v. 9.0* (SPSS, Chicago, IL).

TABLE 1. *Comparison of patients with and without head tremor*

	Head tremor	No head tremor	Significance
N	37	69	
Age (yr)	73.1 ± 18.4	68.0 ± 18.3	t = 1.36, $P = 0.18$
Female, n (%)	29 (78.4%)	34 (49.3%)	$\chi^2 = 8.46$, $P = 0.004$
Ethnicity			$\chi^2 = 1.03$, $P = 0.60$
Caucasian	10 (27.0%)	15 (21.7%)	
Hispanic	19 (51.4%)	33 (47.8%)	
African-American	8 (21.6%)	21 (30.4%)	
Total tremor score	17.7 ± 8.6	17.6 ± 5.1	t = 0.06, $P = 0.95$
Tremor duration	15.5 ± 17.5	15.4 ± 20.0	t = 0.03, $P = 0.97$
Previously diagnosed with ET*	7 (18.9%)	8 (11.6%)	$\chi^2 = 1.06$, $P = 0.30$
Taking a medication for ET	4 (10.8%)	1 (1.4%)	Fisher's exact test, $P = 0.05$

*Previously received a diagnosis of ET during a routine visit to their primary care physician.
Values are expressed as either mean (SD) or n (%).
ET, essential tremor.

RESULTS

The mean age of 106 ET cases was 69.8 ± 18.4 years (range, 18–96 years) and 63 (59.4%) were women. The mean total tremor score was 17.6 ± 6.5. Tremor duration was known by 60 subjects in whom the mean was 15.4 ± 18.8 years (range, 0.1–74 years). None had consulted a primary care physician or a neurologist for tremor. Fifteen (14.2%) previously had received a diagnosis of ET during a routine visit to their primary care physician. Five (4.7%) were taking a medication to treat their tremor. Three (2.8%) had isolated head tremor (i.e., tremor ratings of greater or equal to 2 on 0 tasks).

Head tremor was present in 37 (34.9%) cases; in 10 (27%) of 37 it was mild. Cases with mild head tremor did not differ from those with moderate to severe head tremor by age, gender, ethnicity, tremor duration, or total tremor score.

Cases with and without head tremor differed by gender but not by ethnicity, total tremor score, or tremor duration (Table 1). The age difference did not reach significance (Table 1). Cases with head tremor were more likely to be taking a medication for their ET than were those without head tremor.

Female gender was associated with a nearly fourfold increased risk of head tremor; 29 (46.0%) women and 8 (18.6%) men had head tremor (OR = 3.73; 95% CI, 1.50–9.31; $P = 0.005$). Total tremor score was divided into quartiles. The mean (SD, range) total tremor score in each quartile was 9.5 (3.4, 2–13), 15.0 (1.0, 13.5–16.5), 18.9 (0.8. 17.5–20), and 25.7 (4.6, 20.5–36). Cases in the lowest or highest quartile were four-times more likely to have head tremor than were cases in the two intermediate quartiles (OR = 4.16; 95% CI, 1.76–9.82; $P = 0.001$; Table 2). When we excluded the three cases with isolated head tremor, all of whom were in the lowest quartile, results were similar (OR = 3.70; 95% CI, 1.54–8.79; $P = 0.003$; Table 2).

We also examined the associations of gender and total tremor score quartile, separately and in combination, with head tremor (Table 3). Only 6.9% of men in the two intermediate total tremor score quartiles (quartiles 2 and 3) had head tremor. In cases who were either in the highest or lowest total tremor score quartile or were women, 34.6 to 42.9% had head tremor (Table 3). The group that had the highest proportion with head tremor (54.1%) was women who were in the highest or lowest

TABLE 2. *Head tremor by total tremor score quartile*

Total tremor score quartile	Head tremor (%)	No head tremor (%)
Lowest quartile	12 (32.4)	11 (15.9)
Quartile 2	2 (5.4)	26 (37.7)
Quartile 3	9 (24.3)	18 (26.1)
Highest quartile	14 (37.8)	14 (20.3)
Total	37 (100)	69 (100)
Lowest or highest quartile	26 (70.3)	25 (36.2)
Quartile 2 or 3	11 (29.7)	44 (63.8)
Total	37 (100)	69 (100)

All percentages are column percentages.
For two-by-four table, $\chi^2 = 15.35$, $P = 0.002$. After excluding the 3 subjects with isolated head tremor, $\chi^2 = 13.43$, $P = 0.004$. For two-by-two table, $\chi^2 = 11.18$, $P = 0.001$. After excluding the 3 subjects with isolated head tremor, $\chi^2 = 9.03$, $P = 0.003$.

TABLE 3. *Head tremor by gender and total tremor score quartile*

Gender and total tremor score quartile	Head tremor (%)	No head tremor (%)
Male and quartile 2 or 3	2 (6.9)	27 (93.1)
Male and quartile 1 or 4	6 (42.9)	8 (57.1)
Female and quartile 2 or 3	9 (34.6)	17 (65.4)
Female and quartile 1 or 4	20 (54.1)	17 (45.9)

Percentages are row percentages.
Quartile = total tremor score quartile. $\chi^2 = 16.37$, $P = 0.001$.

total tremor score quartile. In a univariate logistic regression analysis, risk of head tremor was nearly 16 times higher in women who were in the highest or lowest total tremor score quartile than in men who were in the intermediate total tremor score quartiles (OR = 15.88; 95% CI, 3.29–76.71; $P = 0.0006$).

In a multivariate logistic regression analysis, female gender (OR = 2.69; 95% CI, 1.03–7.05; $P = 0.04$) and total tremor score quartile (highest or lowest vs. quartiles 2 or 3, OR = 3.03; 95% CI, 1.22–7.50; $P = 0.02$) were independently associated with an increased risk of head tremor, whereas age ($P = 0.48$) and taking a tremor medication ($P = 0.33$) were not.

We also performed logistic regression analyses restricted to the 47 relatives with ET. The risk of head tremor was marginally higher in relatives of ET probands with head tremor than in relatives of control probands (OR = 11.30; 95% CI, 0.73–174.61; $P = 0.08$), while adjusting for age, gender, total tremor score quartile (highest or lowest vs. quartiles 2 or 3), and taking a tremor medication.

DISCUSSION

We studied the correlates of head tremor in a group of ET cases who participated in an ethnically mixed community-based study in northern Manhattan, New York. ET cases were not ascertained through health care settings and, therefore, were not self-selected because of the severity or localization of their disease manifestations. Approximately 35% of ET cases had head tremor. In clinic-based studies of ET,[1–3] the proportion of patients with head tremor ranged from 40.9% to 52.9% (group proportion = 43.9%), which is marginally higher than the proportion in our sample ($\chi^2 = 3.09$; $P = 0.08$). One possible explanation is that head tremor, which can be conspicuous to family members and friends, may trigger a visit to the doctor. Female gender does not explain this difference as the proportion of women in clinic-based studies (45.6–52.9%)[1–3] was lower than that in our sample (59.4%).

Female gender was associated with a fourfold increased risk of head tremor. In a study of ET at the Tremor Clinic at the University of Kansas Medical Center,[1] head tremor was twice as common in women than men. As noted by the authors,[1] health-seeking behavior might have influenced their results. Our study corroborates the finding that women are more likely to develop head tremor in ET. The explanation for these findings is not clear, although one possibility is that sex hormones may influence the risk or expression of ET.

The majority of individuals with head tremor fell into two categories: namely, those with minimal or very mild arm tremor and those with extremely severe arm tremor. This finding suggests that there may be two forms of head tremor: 1) that which occurs in ET cases who have little or no arm tremor, and 2) that which accompanies a severe form of the illness characterized by the most severe arm tremor. In the latter, it has long been noted that the tremor typically begins in the arms and later spreads to involve the head as well.[11] Somatotopic maps of the cerebellum indicate that the head and neck regions are located medially in the vermis and the limb representations are located in the cerebellar hemispheres. One hypothesis is that the first form of head tremor (isolated head tremor) may reflect a pathological process restricted to the medial/vermal region. The second form of head tremor (accompanied by severe overall disease) may reflect a pathology that begins in the arm representation region and then progresses by both increasing within the arm region and by extending to the more medial/vermal head region. This hypothesis requires further exploration.

ET cases who were related to probands with head tremor were themselves more likely to have head tremor than were ET cases who were relatives of control subjects. This finding suggests that there is familial aggregation of the phenotypic expression of ET. To our knowledge, this relationship has not been reported previously, although in the clinical and genetic population study of ET in Sweden,[12] there was clear evidence that, in some families, multiple members had head tremor, whereas in others, none had head tremor.

In summary, in an epidemiological study, we identified several factors that were associated with an increased risk of head tremor in ET; female gender, coexisting arm tremor that was either very mild or extremely severe, and relation to an ET case with head tremor. These disease associations require further exploration, and might provide insight into the mechanisms underlying head tremor in ET.

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Globus Pallidus Internus Deep Brain Stimulation for Dystonic Conditions: A Prospective Audit

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Abstract: **In the current era of functional surgery for movement disorders, deep brain stimulation (DBS) of the globus pallidus internus (GPi) is emerging as the favoured target in the treatment of patients with dystonia. The results of 25 consecutive patients with medically intractable dystonia (12 with generalised dystonia, 7 with spasmodic torticollis, and 6 with other types of dystonia) treated with GPi stimulation are reported. Although comparisons were limited by differences in their respective neurological rating scales, chronic DBS benefited all groups, resulting in clear and progressive improvements in their condition. This study clearly demonstrates that DBS of the GPi provides amelioration of intractable dystonia.** © 2003 Movement Disorder Society

Key words: dystonia; pallidum; stereotactic; stimulation

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Surgical interventions for the treatment of dystonia, preceding the stereotactic era, have proved ineffective or of little benefit, consequently being replaced by functional stereotactic procedures. As in other hyperkinesias, medial pallidotomy was the first stereotactic operation to be performed,[1] although initially only a few small series of pallidotomy for dystonia were published. The establishment of pallidal surgery, for the treatment of the motor symptoms of Parkinson's disease,[2–4] together with the amelioration of levodopa-induced dystonic dyskinesias and *off* period dystonic symptoms, observed in parkinsonian patients after pallidotomy,[5–8] has renewed interest in pallidal surgery for the treatment of patients with dystonia.[3,4] Encouraging results after pallidotomy have also been reported for clinically and etiologically varying forms of dystonia.[9–11]

There are, however, only a few reports detailing the effects of globus pallidus internus (GPi) deep brain stimulation (DBS) in dystonia, most of which have been published as case reports or small case series.[7,12–18] We report on a series of 25 patients with medically intractable dystonia treated by GPi DBS in our centre.

PATIENTS AND METHODS

Patients

A total of 25 consecutive patients, with dystonia refractory to medical intervention and eligible for GPi DBS were included in this study, 12 with primary generalised dystonia, 7 with spasmodic torticollis (3 of whom have been described previously in Parkin et al.[17]), and 6 with miscellaneous manifestations of the condition. The patients in the miscellaneous group comprised four with varying forms of myoclonic dystonia, one with tardive dystonia after long-term treatment with antipsychotic medication and one with post-traumatic left hemidystonia. All patients had been treated medically, resulting in either inadequate response or intolerance to side effects.

Medications used included benzhexol, tetrabenazine, clonazepam, diazepam, mirtazapine, and co-careldopa.

Botulinum toxin was used in the treatment of the patients with spasmodic torticollis and also for the control of focal symptoms in one of the patients from the miscellaneous group. All patients underwent operation between 1999 and 2001. The degree of dyskinesia was assessed according to the Burke, Fahn, and Marsden Dystonia Rating Scale (BFMDRS)[19] for generalised dystonia and the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)[20] for spasmodic torticollis. Assessments were performed preoperatively and then at 3- to 6-monthly intervals thereafter. Because of the heterogeneity of the miscellaneous group, the Abnormal Involuntary Movement Scale (AIMS)[21] was used in an attempt to provide comparable data, conveying disease severity within this patient group.

Surgical Methods

After detailed explanations of the risks and potential benefits of the procedure, written informed consent was obtained from each patient. The patients underwent bilateral implantation of Medtronic quadripolar 3387 DBS electrodes into the posteroventral GPi using Image Fusion and Stereoplan[22] to localise the targets by fusing the MRI to the stereotactic CT scan.[23] Under general anaesthesia, the electrodes were passed to the target nuclei whilst monitoring the impedance with a Radionics electrode of 1.8-mm diameter and 2.0-mm exposed tip. A more detailed explanation of surgical technique has been described by our group previously.[22] Having identified the targets, the TM electrode was removed and replaced by a Medtronics 3387 electrode that was then plated to the skull. These were then connected to a subcutaneous programmable pulse generator (Kinetra or Synergy, Dual Channel Itrel; Medtronic, Minneapolis, MN) implanted in the subclavicular tissue. No significant perioperative complications occurred. Postoperative MRI scan confirmed the electrode positions. Initial stimulator parameters aimed for settings in the region of: 4.0–7.0 V, 130–180 Hz, and 150–240 μsec as tolerated by the individual patient with progressive adjustment of electrical parameters at each follow-up visit. Bipolar stimulator settings were used for all patients in accordance with the standard practice of our group. The DBS electrodes used were those that did not produce any side effects on unipolar stimulation. The deepest available electrode was set to negative, the most superficial to positive, whilst any intervening electrodes remained neutral.

Analysis of Results

Because the BFMDRS, TWSTRS, and AIMS record ordinal data, analysis of results was performed by applying the Wilcoxon signed rank test to compare rating scales within each group, before surgery and at the most recent outpatient visit. A statistical threshold of $P < 0.05$ was considered significant.

RESULTS

GPi DBS was performed on 25 patients (11 men, 14 women) between 1999 and 2001. Mean follow-up was 12.3 months (range, 4–24 months). Individual clinical data are displayed in Table 1. A breakdown of mean pulse generator parameter settings, for each subgroup at discharge and most recent follow-up, is given in Table 2. After surgery, it was no longer necessary for most patients to be maintained on any medical therapy for dystonia. Of those that were still on medication (Patients 3, 13, 14, 19, and 25), all but one (Patient 19) had their medication regimen reduced considerably. Two patients from the spasmodic torticollis group (Patients 6 and 8) and one from the miscellaneous group (Patient 25) have also received further botulinum toxin therapy since DBS was commenced.

The postoperative course of Patient 12 was complicated by the left DBS lead slipping from its position several months after surgery. This migration gave rise to deterioration in neurological function. Replacement of the lead was further complicated by infection, necessitating removal of both deep brain stimulators. This removal resulted in further deterioration, requiring admission to the intensive care unit for intubation and ventilation, after the development of severe spasmodic dysphonia. Gradual sustained improvement in her condition recommenced after the DBS leads were successfully replaced for a second time. This rebound phenomenon occurred in two further patients (Patients 3 and 5), one of whom had a damaged lead connector, whilst in the other patient the pulse generator battery had run out suddenly. Both patients began to recover rapidly within a few hours of the appropriate hardware being replaced.

Patient 6, whose dystonic symptoms were in part responsive to alcohol, opted to have his stimulators removed, because the improvements in neurological function had removed the need to suppress his symptoms with alcohol. He requested that the system be removed in preference to decreasing his level of alcohol intake.

Generalised Dystonia

Individual preoperative and outcome data at most recent follow-up is displayed in Table 3. The mean age at the time of surgical procedure was 31.9 years (range, 7 to 48 years) with a mean follow-up period of 9.2 months (range, 4 to 18 months). Statistically significant reductions were observed in the mean severity of the dystonia, resultant disability and total scores ($P < 0.02$ for each score). All patients with generalised dystonia demonstrated benefit with greatest im-

TABLE 1. *Clinical features of 25 consecutive patients treated with GPi DBS*

Patient no.	Gender	Clinical details	Age at onset (yr)	Age at operation (yr)	Length of follow-up (mo)
01	F	Spasmodic torticollis	59	68	24
02	M	Myoclonic dystonia	15	28	24
03	F	Spasmodic torticollis	21	37	24
04	M	Left post-traumatic hemidystonia	17	41	12
05	F	Generalised dystonia	15	36	18
06	F	Spasmodic torticollis	17	23	21
07	M	Generalised dystonia	12	39	12
08	F	Spasmodic torticollis	21	27	21
09	F	Spasmodic torticollis	21	29	12
10	M	Spasmodic torticollis	36	44	18
11	F	Generalised dystonia	14	28	12
12	F	Generalised dystonia	3	7	18
13	F	Generalised dystonia, DYT1+	15	30	12
14	F	Spasmodic torticollis	44	47	12
15	M	Tardive dystonia	35	40	12
16	M	Generalised dystonia, DYT1+	7	20	6
17	M	Generalised dystonia	42	48	6
18	F	MS with spasmodic torticollis	41	51	10
19	F	Generalised dystonia	29	34	6
20	M	Generalised dystonia	3	33	6
21	F	Generalised dystonia	46	48	6
22	M	Generalised dystonia	7	21	4
23	M	Generalised dystonia	37	39	4
24	M	Myoclonic dystonia	33	51	4
25	F	Myoclonic dystonia	15	20	4

GPi, globus pallidus internus; DBS, deep brain stimulation; MS, multiple sclerosis.

provement occurring in the severity score aspect of the BFMDRS evaluation. All changes were progressive and sustained with relief of pain the first improvement observed in most patients (Fig. 1, top left and top right).

Spasmodic Torticollis

The data related to this group are displayed in Table 4. The mean age at the time of surgical intervention was 39.3 years (range, 23 to 68 years) with a mean follow-up time of 18.9 months (range, 12 to 24 years). Statistically significant improvements were observed in the mean severity, disability, pain, and total scores ($P < 0.05$ for each score) (Fig. 1, middle left and middle right images). Again, relief of pain preceded improvements observed in other aspects of the TWSTRS rating scale. One patient (Patient 10) did not appear to receive any benefit. It later transpired that this patient had repeatedly turned his stimulator off, with the use of his patient-controlled hand-held programmer. He, therefore, would not have received continuous sustained DBS and, hence, was excluded from any further analyses of results.

Miscellaneous Group

Most patients within this group also benefited greatly from treatment. Individual patient outcomes are displayed in Table 5. The mean percentage improvement in

TABLE 2. *Implanted pulse generator settings*

	Parameters at discharge			Parameters at last follow-up		
Group	Amplitude (V)	Pulse width (μsec)	Frequency (Hz)	Amplitude (V)	Pulse width (μsec)	Frequency (Hz)
Generalised dystonia	3.1 ± 1.0	135.0 ± 43.0	138.0 ± 24.3	5.0 ± 0.7	210.5 ± 60.0	140.0 ± 24.4
Spasmodic torticollis	3.9 ± 0.7	157.5 ± 61.8	142.5 ± 51.4	5.8 ± 0.6	168.8 ± 66.4	143.8 ± 24.3
Miscellaneous group	2.8 ± 0.4	110.0 ± 14.1	165.0 ± 21.2	3.8 ± 0.4	165.0 ± 63.6	125.0 ± 35.4
All groups	3.3 ± 0.9	141.4 ± 47.7	139.3 ± 32.0	5.2 ± 0.8	198.2 ± 62.3	141.1 ± 23.5

Values are expressed as mean ± SD.
Stimulator settings at the time of hospital discharge and at the most recent follow-up are displayed.

TABLE 3. *Preoperative and most recent postoperative BFMDRS recorded from patients with generalised dystonia*

Patient no.	Preop severity score	Preop disability score	Preop total score	Postop severity score	Postop disability score	Postop total score	% Improvement in severity score	% Improvement in disability score	% Improvement in total score
05	48	15	63	4.5	5	9	81	67	85
07	22	6	28	13	4	17	41	33	39
10	18	7	25	3.5	2	5.5	81	71	68
11	66	12	78	7.5	5	12.5	89	58	84
12	103	28	131	36	10	46	65	64	65
15	109	28	137	78	17	95	28	39	31
16	66	6	72	28	4	32	58	33	56
18	108	23	131	84	22	106	22	4	19
19	80	20	100	63	17	80	21	15	20
20	62	12	74	49	9	58	21	25	22
21	50	10	60	28	8	36	44	20	40
22	48	9	57	38.5	7	45.5	20	22	20
Mean ± 1 SD	65.0 ± 30.6	14.7 ± 8.2	79.7 ± 38.0	36.1 ± 27.8	9.2 ± 6.3	45.3 ± 33.7	47.6 ± 26.3	37.6 ± 26.3	45.8 ± 25.0

Mean postoperative follow-up 9.2 months, range 4–18 months. Individual severity, disability, and total scores as well as percentage improvements in each field are displayed.

BFMDRS, Burke, Fahn, and Marsden Dystonia Rating Scale.

AIMS evaluation was 37.1 ± 28.5% (± 1 SD). Patient 4 showed dramatic improvement in his dystonic left arm and leg with recovery to near normal function within 48 hours of surgery. Unfortunately, these improvements were only short-lived, and disease severity returned to preoperative levels over the subsequent few weeks. Figure 1 (bottom-left and bottom-right images) demonstrates a patient in the miscellaenous group successfully treated with GPi DBS. A video illustration of this patient has been published previously.[24]

FIG. 1. Evidence of clinical effect of deep brain stimulation (DBS) of the globus pallidus internus on patients from each of the three main subgroups. A 7-year-old girl (**top left**) with severe idiopathic torsion dystonia showing dramatic improvement 6 months after surgery (**top right**). A 21-year-old woman with spasmodic torticollis before (**middle left**) and after (**middle right**) receiving DBS. A 40-year-old man with severe camptocormic tardive dyskinesia (**bottom left**) as a result of antipsychotic medication. Pallidal stimulation resulted in dramatic improvement in posture (**bottom right**).

DISCUSSION

Although the first stereotactic surgery for dystonia involved the pallidum, this did not initially make it the favoured target for DBS, probably because of the success of thalamic surgery and neurophysiological evidence implicating the thalamus in the pathogenesis of dystonia.[25]This strategy was first described by Mundinger in 1977, who successfully treated spasmodic torticollis by implantation of stimulators into the thalamus and zona incerta.[26] Since then, it has been demonstrated that targeting thalamic nuclei can produce favourable results in several different forms of dystonia.[27–29] More recent evidence, however, favours the pallidum as the target of choice.[30,31]

Unfortunately to date there are only a few reports detailing the effects of pallidal stimulation in dystonia.[7,12–18] Our results further corroborate the substantial improvements, observed by other groups in this field, in dystonia patients treated with GPi stimulation. Our 12 patients with generalised dystonia, however, did not exhibit improvements as dramatic as Coubes' DYT1-positive series,[14] who, on average, demonstrated a greater than 90% resolution of their preoperative condition at 1 year after surgery. This finding may in part be a reflection of the greater variability in clinical background in

TABLE 4. *Spasmodic torticollis group showing preoperative and most recent postoperative TWSTRS scores recorded for each patient*

Patient no.	Preop severity score	Preop disability score	Preop pain score	Preop total score	Postop severity score	Postop disability score	Postop pain score	Postop total score	% Improvement in severity score	% Improvement in disability score	% Improvement in pain score	% Improvement in total score
01	18	13	14	45	11	3	11	25	39	77	21	44
03	23	20	13.8	56.8	7	8	2.3	17.3	65	60	94	70
06	21	21	15.8	57.8	4	7	8.5	19.5	81	67	46	63
08	28	27	18	71	13	15	6	34	54	44	67	52
09	18	26	14.5	58.5	2	7	1.3	10.3	94	73	91	84
13	20	23	14.5	57.5	10	14	8.3	32.3	50	39	43	44
Mean ± 1 SD	21.3 ± 3.8	21.7 ± 5.0	15.1 ± 1.6	57.8 ± 8.2	7.8 ± 4.3	9.0 ± 4.6	6.2 ± 3.8	23.0 ± 9.1	63.8 ± 20.5	60.0 ± 15.5	60.3 ± 28.9	59.5 ± 15.9

Mean postoperative follow-up 18.9 months, range 12–24 months. Breakdown into various aspects of evaluation and percentage changes are also displayed.
TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

TABLE 5. *AIMS evaluations of patients in miscellaneous group*

Patient no.	Preop AIMS	Postop AIMS	% Improvement
02	23	6	73.9
04	20	20	0.0
15	24	14	41.7
18	15	12	20
24	23	18	21.7
25	23	12	65.2
Mean ± 1 SD	21.3 ± 3.4	13.0 ± 5.5	37.1 ± 28.5

Preoperative and most recent postoperative (mean 11.0 months, range 4–24 months) scores are displayed.
AIMS, Abnormal Involuntary Movement Scale.

our cases and the effect of treatment duration, as patients appear to progressively improve over months to years. Alternatively DYT1-positive generalised dystonia may be the best indication for functional stereotactic intervention. The duration of disease onset to treatment may be an important factor influencing the efficacy of treatment. In this series, it was 12.75 years for the generalised dystonia group and perhaps explains why a mean improvement of less than 50% was achieved. Patient 20 illustrates this point, particularly as the comparatively minor improvements observed may have been limited by significant secondary cervical myelopathy, sustained over 30 years of severe truncocervical disease. Consequently, it may be important to treat this disease process at an early stage, before the establishment of any permanent neurological or musculoskeletal injury, to obtain maximum benefit from this technological advance.

The spasmodic torticollis group appeared to demonstrate a greater mean percentage improvement with less interpatient variability, which could be explained by the longer treatment duration and homogeneity of this group. Unfortunately direct comparison between this and the other groups was not possible due to the differing assessment scores used. One suggestion for addressing this problem would be the use of concurrent quality of life evaluations which, although not measuring disease severity directly, could provide a means of comparing the impact of treatment on differing subgroups of dystonia patients with widely varying disease presentation.[32] However, a quality-of-life scale is likely to be less responsive than a disease-specific impairment or disability scale.

The problem posed by Patient 10 questions the appropriateness of the patient-controlled hand-held programmers for patients with dystonia receiving chronic DBS. Although commonly supplied to patients with tremulous movement disorders[33] or neuropathic pain,[34] where varying stimulator settings are often desired or beneficial, this

incident suggests that the steady sustained improvements observed after this treatment are dependent on continuous, sustained chronic deep brain stimulation at constant settings. However, further assessment of this observation is required.

Widely differing results were observed in the miscellaneous group, with a range of improvement in AIMS score, varying from 0 to 73.9%. Heterogeneity of individual patient clinical presentation and underlying pathogenesis may account for much of this variation. Patient 4 with post-traumatic left hemidystonia improved only transiently before regressing to preoperative levels of disability. The initial short-lived relief of symptoms could be accounted for by either a placebo response or the transient "stun" (also known as the "microthalamotomy" effect) that is often observed[35] and is possibly due to localised oedema that later resolves. This finding is consistent with reports that post-traumatic hemidystonias with visible brain lesions on imaging respond at best only transiently to DBS,[36] although one patient exhibiting 4 years of sustained improvement after GPi DBS has been described in the literature.[7]

The potential problems related to hardware failure are underlined by events surrounding Patient 12, where sudden cessation of DBS led to a very acute severe relapse in the patients' condition. This "rebound" effect also occurred in Patients 3 and 5 and is a recognised but poorly understood phenomenon observed in dystonic patients who have had their stimulation turned off suddenly.[28,30] This finding emphasises the importance of patient education and the requirement for close patient follow-up to pre-empt the end of pulse generator battery life.

Although to date there do not appear to be any formal comparative studies of thalamic versus pallidal stimulation, there are several instances for which patients who have undergone both procedures, appear to have benefited more from pallidal rather than thalamic stimulation.[29,31] Blinded assessment of clinical outcome after pallidal stimulation, with the stimulator randomized to either on or off, will be essential for further validation of this treatment method. However, the marked deterioration in patients' dystonia when the stimulator fails suggests that it would be dangerous to enter patients into an *on→off* arm of a cross-over study. Furthermore, it is also important to note that a feature of these dystonic conditions is that the response is gradual, manifesting as a progressive improvement in the condition over months to years. Longer-term follow-up will be needed to confirm that these benefits are maintained. Although it is not yet established which patient groups would benefit most from this therapy, it is clear that GPi DBS offers effective treatment for a variety of dystonic conditions, with the exception of post-traumatic hemidystonia.

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Quantitative Rest Activity in Ambulatory Monitoring as a Physiological Marker of Restless Legs Syndrome: A Controlled Study

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Abstract: **An objective marker of restless legs syndrome (RLS) is needed for developing diagnostic tools and monitoring symptoms. Actometric ambulatory monitoring of 15 RLS patients and 15 healthy controls was undertaken in order to differentiate between RLS-related motor symptoms and normal motor activity. Nocturnal lower-limb activity per minute differentiated and discriminated between groups with no overlap, whereas the periodic limb movement index and the controlled rest activity during sitting showed less discriminative power. The naturalistic recording of nocturnal activity by actometry may prove useful for assessing the severity of RLS and for finding an objective marker to support the diagnosis of RLS.** © 2002 Movement Disorder Society

Key words: actometry; ambulatory monitoring; assessment; motor activity; quantification; restless legs syndrome

The severity of symptoms in restless legs syndrome (RLS) is difficult to quantify. As most RLS patients exhibit periodic leg movements (PLM) in electromyography (EMG), a PLM index is often used to support a diagnosis of RLS[1] and to monitor the severity of symptoms.[2] There is a high correlation between EMG recording of PLM and actometric ambulatory monitoring of PLM.[3]

Lower-limb motor activity has been used to monitor RLS symptom severity, and to define treatment response[4] and circadian rhythm.[5] Montplaisir and colleagues[1] quantified the motor restlessness of RLS patients during

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immobilization by EMG, which significantly discriminated RLS patients from healthy controls (with power similar to the PLM index). The movements while sitting seemed to consist of both involuntary PLM and voluntary movements to relieve discomfort. This method requires a laboratory setting and includes instructions for the subject, which imply conscious control of spontaneous behavior.[1]

Because the diagnostic criteria specify a desire to move with uncomfortable sensations and motor restlessness, but not necessarily PLM,[6] the voluntary motor restlessness response to subjective symptoms is an essential feature of RLS. We studied how general lower limb motor activity during sitting and during time spent in bed at night discriminates RLS patients from healthy controls. We also wanted to compare the discriminative powers of actometric parameters.

SUBJECTS AND METHODS

Subjects

Informed consent was obtained from all participants, and the study was approved by the Ethics Committee of Helsinki University Central Hospital. Fifteen RLS patients were recruited via advertisement in a health magazine, and the control group comprised 15 hospital employees. Inclusion criterion for both groups was an age of 18 to 65 years, and exclusion criteria were current medication or medication during past 2 weeks, long-term use of any psychoactive drugs, major somatic illnesses or traumas, secondary causes of RLS, any medical causes of insomnia other than RLS, and any past or present psychiatric axis 1 disorder. Clinical somatic examination of the subjects included laboratory tests (blood cell count, serum ferritine, serum glucose, serum creatinine, and serum glutamyl-transferase).

Psychiatric diagnoses were excluded by a structured diagnostic interview[7] in the RLS group. The controls were informed about exclusion criteria before recruitment, and their own report of mental health was accepted if no contradictory information emerged in the clinical interview. A diagnosis of RLS based on standard criteria[6] together with chronic (>1 year), frequent (>50% of the nights) and subjectively distressing or harmful symptoms of RLS was inclusion criterion for the RLS group. Any reported RLS symptoms or clinical sleep disturbances were exclusion criteria for the control group.

The mean age in the RLS group was 50.3 years (SD 11.2; range, 26–62 years) and 49.3 years (SD 6.46; range, 33–57 years) in the control group. Male to female ratio was 1:14 in both groups. The education level was equal in the groups, but 2 of the RLS patients were not working (1 unemployed, 1 retired). The profession of nurse, working in shifts, was over-represented in the control group compared to RLS group (8 vs. 1). There was slightly more tobacco use and alcohol consumption in the control group, although both groups represented healthy life styles. There were no significant differences in the hemoglobin ($t = 0.109$; $P = 0.914$) and serum ferritin levels ($t = 1.19$; $P = 0.246$) between the RLS (means: 138 and 60) and the control group (means: 138 and 41).

Experimental Procedure

All subjects carried ambulatory monitors at home for nocturnal three-channel actometric recording. They were asked to report accurately the time of going to bed and of waking up in the morning in sleep diaries to define the total time in bed, including the period of sleep latency and sleep. Also, they were asked to give an estimated time of falling asleep, and to report any periods of being awake for longer than 5 minutes and any getting up during the night.

In the evening preceding the sleep recording, the actometric recording was performed sitting in a 30-minute neutral interview between 5 and 7 P.M. To allow natural movement or voluntary movement aimed to relieve possible lower limb sensations and to avoid conscious control of movements, the subjects were not instructed to sit still. However, in this setting it is adequate and expected to stay seated. This method of measuring controlled rest activity has been described with akathisia patients.[8]

Measurements

We used actometric monitors containing piezoelectric sensors, which react to acceleration rates above 0.1 G. The recorded signal is sampled at a rate of 40 Hz, and the values for each sample are used to calculate the average activity level within each time span (the chosen time window). The movement index for a certain time period is the sum of all time span activity values within that period. We chose the shortest technically possible time span (0.1 second), to allow qualitative analysis of the movement patterns. Digital integration method[9] of the program used (*PAM-3*; IM-Systems, Baltimore, MD) allows the waveform of the movement to be reconstructed and the amplitude of the movements to be taken into account. The movement indices reported for controlled rest were divided by 1,000.

Two actometric monitors, one to each lower limb, were attached to the ankles of the subjects (Fig. 1). The third monitor was attached to the waist (Fig. 1) to serve as a reference monitor to control the time consistency of reported and measured gross movements and events dur-

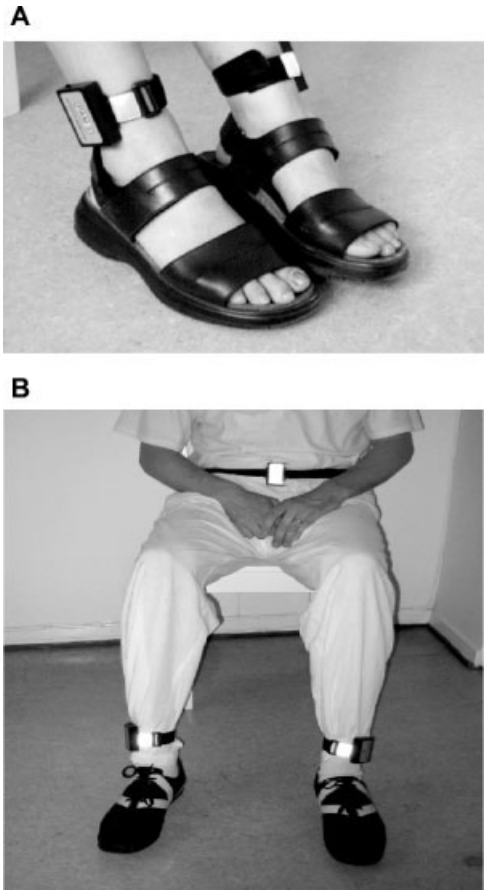

FIG. 1. Three-channel actometry: Two of the authors presenting the actometric monitors worn by the study subjects. Attachment around ankles (**A;** monitor on the lateral side) and waist (**B;** monitor on the anterior midline).

ing night, for example rising up and walking. Time periods out of bed were not included in the analysis, because we focused on the rest activity. The waist activity was also used to calculate the ankle/waist ratio of motor activity (lower limb activity divided by waist activity). Causing no more discomfort than wrist watches, the actometric monitors do not disturb the subject.

The main quantitative parameters of comparison were 1) nocturnal lower limb activity (the mean of right and left ankle activities) during time-in-bed, and 2) the lower limb activity during controlled rest. The nocturnal activity is the sum of all values for each 0.1-second time span for the varying time spent in bed divided by its duration in minutes, whereas the controlled rest activity is the sum of all the time span activities during the constant 30-minute period.

The qualitative analysis focused on the detected movement patterns. The recommended screening criteria of PLM,[10] later applied to actometry,[3,11] were used by an experienced rater, in a blind manner, to obtain quantitative data by calculating the PLM index. The discriminating qualities of the PLM index and the nocturnal activity were compared.

Data Analysis

Statistical analysis was performed using *SPSS v. 10.0* software (SPSS, Chicago, IL) using nonparametric Mann-Whitney *U* test for intergroup differences, Wilcoxon paired sample test for intragroup differences, and the Spearman correlation test, because the main variables were not normally distributed and the sample size was small. Accordingly, medians (M) and quartiles (Q) are reported. The analysis of sensitivity and specificity was based on χ^2 test.

RESULTS

Table 1 summarizes the central results concerning subjective and actometric data. Complete subjectively

Table 1. *Average actometric values of 15 patients with restless legs syndrome (RLS) and 15 healthy controls*

	RLS			Controls			Comparison	
	Median	Q1–Q3	Range	Median	Q1–Q3	Range	*U*	*P**
Controlled rest activity								
Left ankle activity	12	8.4–14	3.5–47	0.9	0.48–2.5	0.15–4.8	2.0	0.000
Right ankle activity	12	8.9–18	1.8–30.0	0.9	0.40–1.8	0.12–4.4	8.0	0.000
Lower limb activity[a]	11	8.4–20.3	2.8–30.0	1.1	0.43–2.8	0.21–3.5	4.0	0.000
Ankle: waist ratio[b]	1.3	0.62–2.2	0.41–6.1	0.60	0.37–1.6	0.29–6.8	70.0	0.078
Nocturnal activity								
Left ankle	720	340–910	140–2000	48	32–150	15–290	7.0	0.000
Right ankle	650	380–890	160–1300	80.4	23–180	13–220	5.0	0.000
Lower limb[a]	650	520–860	260–1500	58	27–140	13–220	0.00	0.000
PLM Index	1.4	0.00–7.4	0.0–46	0.00	0.00–0.00	0.00–1.5	47	0.002

*Statistical difference between RLS and control groups.
[a]Right and left ankle movement indices (mean).
[b]Movement index of the waist divided by the lower limb activity index.
Q1–Q3, interquartile range; *U*, Mann-Whitney *U* test; PLM, periodic limb movement.

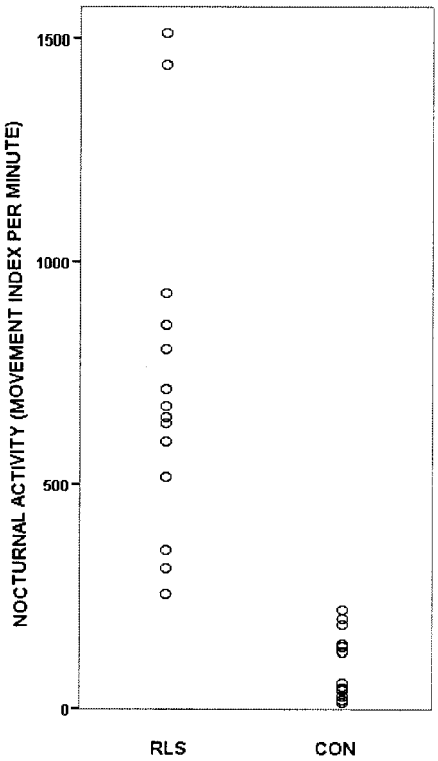

FIG. 2. Nocturnal lower-limb motor activity per minute in restless legs syndrome (RLS) and in healthy controls (CON) during time-in-bed.

reported data, including total time in bed, sleeping time, and sleep latency were obtained from both groups. Three of the RLS patients and 1 of the controls reported having been out of the bed during nocturnal recording.

Quantitative Data

Nocturnal activity differentiated between the RLS and controls significantly (Table 1, Fig. 2). In a between-group comparison of right- and left-ankle activities, the differences were significant (U = 5.0; $P < 0.0005$ and $U = 7.0$; $P < 0.0005$; respectively). The small laterality differences were nonsignificant in both RLS group ($Z = -0.227$; $P = 0.820$) and the control group ($Z = -0.341$; $P = 0.733$). Although being aware of the uncertainty related to subjective reports of the time of falling asleep, we further analysed the motor activity during sleep latency and activity during sleep, which both differentiated the RLS group from the controls significantly ($U = 4.0$; $P < 0.0005$; and $U < 0.0005$; $P < 0.0005$).

Controlled rest activity differentiated between the groups significantly (Table 1; Fig. 3). The difference remained significant when analyzing right ankle activity ($U = 8.0$; $P < 0.0005$) and left-ankle activity ($U = 2.0$; $P < 0.0005$) separately. The median ankle/waist ratio was higher in the RLS group, but the difference was not significant (Table 1).

Qualitative Data

The typical PLM pattern (Fig. 4) fulfilling the screening criteria[3] was detected in 10 RLS patients and in 2 healthy controls during nighttime and in 5 RLS patients and in none of the healthy controls during the controlled rest. Irregular, random unspecific motor activity was predominant in both groups. Furthermore, a motor pattern resembling PLM, but not fulfilling the screening criteria, was quite common in RLS during nocturnal recording (Fig. 4). The duration of these movements were often longer than allowed by PLM criteria, probably caused by clustering of shorter movements into longer movement complexes. The considerable amount of random background activity may also have complicated the diagnosis of PLM patterns. PLM index results in Table 1 and Figure 5.

During the 30 minutes of the controlled rest, the RLS group typically showed many random, transient, short activity intrusions of 1 to 10 seconds related to changing of the pose and moving the legs. This was sometimes intermixed with a more continuous, fluctuating activity

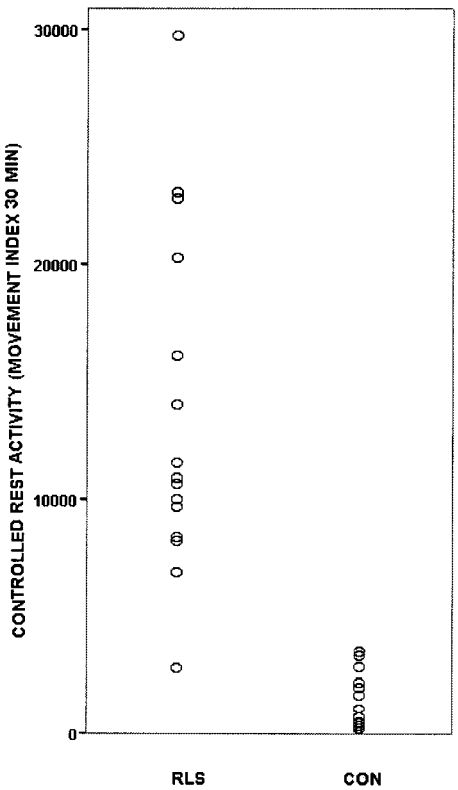

FIG. 3. Lower-limb motor activity during 30 minutes of controlled rest in restless legs syndrome (RLS) patients and in healthy controls (CON). Controlled rest means a standardized setting of sitting in an interview.

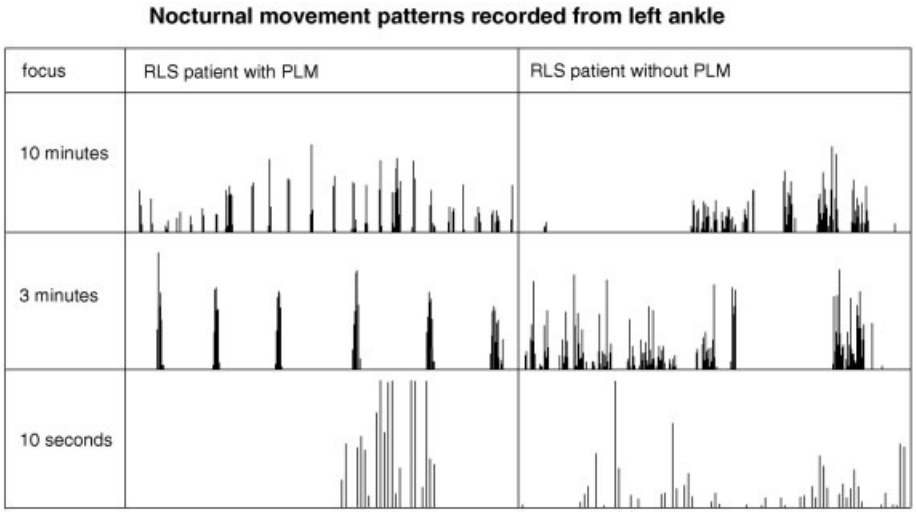

FIG. 4. Nocturnal actometric recording of an restless legs syndrome (RLS) patient who displayed several periodic leg movements (PLM) throughout the night and another RLS patient, whose movement patterns did not fulfil the criteria of PLM. Periods of 10 minutes are focused for both patients, in which a closer focus on 3 minutes and 10 seconds are presented.

of irregular or changing rhythm and amplitude obviously corresponding to the motor restlessness due to uncomfortable sensations during rest.

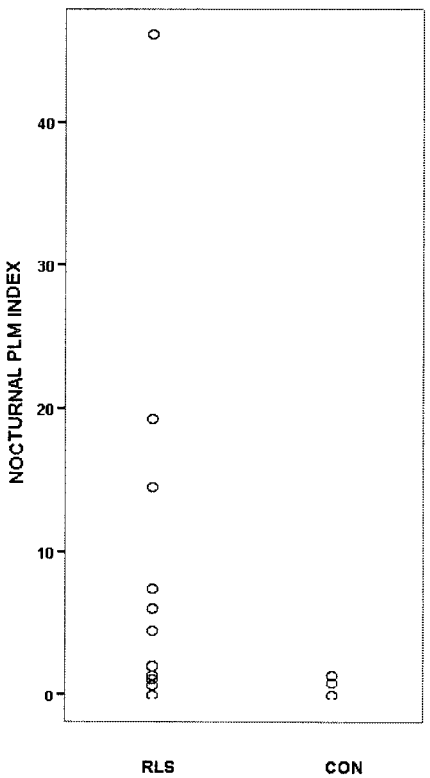

FIG. 5. The index of nocturnal periodic leg movements (PLM) in restless legs syndrome (RLS) patients and in healthy controls (CON). The PLM index is the number of PLM per hour during time-in-bed.

Discriminative Analysis

The nocturnal rest activity discriminated the RLS patients (range, 256–1510) from healthy controls (range, 13.1–221) with a sensitivity of 100% and specificity of 100% when using a threshold value of 250. There was some overlap between the controlled rest activity of the RLS patients (range, 2.79–29.8) and the healthy controls (range, 0.214–3.47). The best discriminative sensitivity was 93%, and the specificity was 100% with the threshold value of 5.00.

The best discriminative power for the PLM index, with a sensitivity of 67% and a specificity of 87% was obtained with a threshold value of 0.5. The ranges of the two groups overlapped (0.00–1.45 and 0.00–46.10).

Subgroup of an Equal Sleep Latency Range

The healthy controls (n = 6) with a sleep latency of 30 minutes or more (range, 30–90 minutes, M = 40) were compared to the RLS patients (n = 9) within the same range (M = 30). The nocturnal activity was again significantly ($U < 0.0005$; $P = 0.001$) higher in the RLS patients (M = 715) compared with the controls (M = 99.0), and the nocturnal activity still discriminated the RLS patients (range, 313–1510) from the healthy controls (range, 26.6–221) with no overlap. Also the controlled rest activity was significantly ($U = 2.0$; $P = 0.002$) higher in the RLS patients (M = 9.66) than in the healthy controls (M = 0.863) within this subgroup.

Subgroup of RLS Patients Without PLM

To exclude the possibility, that PLM activity would explain the increased general nocturnal activity in RLS patients, two subgroups of RLS patients were compared:

those 10 exhibiting PLM had even lower median nocturnal activity (644) than those without PLM (715), although the difference was not significant ($U = 18$; $P = 0.391$). When comparing the 5 RLS patients without PLM to all 15 control subjects, the significant difference in nocturnal activity ($U < 0.0005$; $P < 0.0005$) was again detected.

Intercorrelations

Because no validated symptom-severity scale was available, we chose the reported length of sleep latency as a nonactometric, indirect variable of symptom-severity or symptom-distress level, to look for intercorrelations with the actometric data. The length of sleep latency was positively and significantly ($r = 0.386$; $P = 0.035$) correlated to the nocturnal activity. There was a trend to positive intercorrelation between sleep latency and controlled rest-activity, but it was not significant ($r = 0.289$; $P = 0.122$). The nocturnal activity was significantly correlated ($r = 0.744$; $P < 0.0005$) to the controlled rest activity.

The PLM index was positively and significantly correlated to nocturnal activity ($r = 0.520$; $P = 0.003$) and to controlled rest activity ($r = 0.621$; $P < 0.0005$). There was also a positive, but nonsignificant ($r = 0.341$; $P = 0.065$) correlation to the length of sleep latency.

Multivariate Analysis

The demographic factors age ($P = 0.784$), sex ($P = 0.712$), and working status ($P = 0.923$) did not have a significant effect on nocturnal activity, neither was any significant association to other actometric parametres.

DISCUSSION

The average nocturnal activity and the average controlled rest-activity of the RLS group were 10-fold compared to controls, differentiating between the groups significantly. Nocturnal motor rest-activity was the best actometric measure to discriminate RLS symptoms from normal nocturnal motor activity. The RLS patients were carefully examined to exclude any somatic or psychiatric causes for motor symptoms and sleep disturbances. Thus, we can expect any actometric difference in comparison with the control group to be due to RLS, or RLS secondary effects, like insomnia.

In theory, the insomnia may have a direct effect on nocturnal activity, but not on the controlled rest-activity. Moreover, it seems that the nocturnal actometric between-group differences are rather due to RLS itself than due to secondary insomnia as they remain significant when controls with sleep initiation difficulties are compared to RLS patients with similar sleep latencies. Our control sample, consisting mainly of nurses working in shifts, did not represent ideal sleepers, although they did not report any clinical sleep disturbances at admission to the study.

Difficulty in falling asleep is a common feature and consequence of RLS[12] reflecting the distress caused by the symptoms. We found a positive correlation between nocturnal activity and the length of sleep latency, both obviously reflecting the RLS symptom severity. The nocturnal rest activity and the controlled rest activity are strongly intercorrelated. Both these measures are significantly correlated to PLM index, which is a widely used symptom severity measure, although not as good as sleep morbidity.[13] In our study, the discriminative qualities of general nocturnal rest activity and controlled rest activity seem to be better than those of PLM index in RLS; the specificity (67%) and sensitivity (87%) of PLM index being closer to those reported previously (68–81% and 73–81%).[1]

Despite some clinical,[14] diagnostic,[6,15] polysomnographic,[16] and pathophysiological[17,18] similarities, there are several actometric differences between akathisia and RLS; the RLS patients do not demonstrate a significantly increased ankle-waist ratio typical of akathisia patients[8] and their movement pattern during controlled rest is qualitatively different from an akathisia pattern consisting of irregular, transient, or fluctuating motor activity and sometimes PLM, in contrast to the clearly episodic, regularly rhythmic bursts of activity in akathisia patients.[8,19]

The recruitment channel of RLS patients may have skewed the male/female ratio 1:14 of this study sample. It does not match the reported ratio in epidemiological studies, which ranges from equal prevalences to slightly higher prevalences in women.[20] The generalization of our results is also limited by the selection of severely affected RLS patients with no comorbid disorders.

The most common objective outcome measures in treatment trials[21] require a laboratory setting, unlike actometric measures.[4] The RLS assessment methods, including actometry, should be further developed to provide more reliable evidence of effective treatments in RLS.[21] In the absence of reliable objective methods, the actometric recording of nocturnal lower-limb rest-activity may offer an option to support the diagnosis of RLS and to monitor the severity of motor symptoms. Preliminary results indicate that the actometric measures used in our study are able to show a clear treatment response at least in severe RLS, which was detected as a 81% decrease of nocturnal activity and a 68% decrease of controlled rest activity.[22]

The benefits of this method are 1) simple home recording with minimal disturbance of the subject and cost-effectiveness[3]; 2) good discriminative qualities; 3) an objective, quantitative measure of motor activity; and 4) inclusion of the restless movements responsive to subjective, sensory symptoms essential of diagnosis.

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Basal Ganglia Injury as a Complication of the Ketogenic Diet

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Abstract: **Movement disorders or basal ganglia injury have not been reported as complications of the ketogenic diet, an alternative treatment for intractable epilepsy. We report on a novel complication of the ketogenic diet manifesting as a severe extrapyramidal movement disorder and bilateral putaminal lesions. A single case is described. A video demonstrating the movement disorder is included. A 5-year-old girl with a cryptogenic epileptic encephalopathy developed focal dystonia, diffuse chorea, and ataxia after starting the ketogenic diet. Cranial magnetic resonance imaging (MRI) demonstrated bilateral putaminal lesions that were not present before starting the diet. MR spectroscopy showed a lactate peak in the basal ganglia, suggesting a failure of mitochondrial energy metabolism as the mechanism of cerebral injury. The radiographic abnormalities resolved after stopping the diet, although the movement disorder persisted. Basal ganglia injury and extrapyramidal movement**

A videotape accompanies this article.

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abnormalities are potential complications of the ketogenic diet. Concomitant use of valproate or a latent inborn error of metabolism may be risk factors for these rare complications.

Key words: ketogenic diet; chorea; dystonia; mitochondrial metabolism

The ketogenic diet is a low-carbohydrate, high-fat diet that is an effective treatment for refractory childhood epilepsy.[1] Minor side effects of the diet are common and include constipation, fatigue, hyperlipidemia, and anorexia.[1,2] More serious complications may affect up to 10% of patients and include severe acidosis, hypoproteinemia, nephrolithiasis, cardiomyopathy, cardiac conduction abnormalities, and pancreatitis.[1–4] Focal brain lesions or movement disorders have not been reported as adverse outcomes of the ketogenic diet. We describe a patient who developed a severe movement disorder and bilateral lesions of the basal ganglia shortly after starting the ketogenic diet.

CASE REPORT

A 5-year-old girl with sensorineural hearing loss, developmental delay, and refractory cryptogenic epilepsy was treated with the ketogenic diet. She was the only child of non-consanguineous parents and was born at term without complications. Early development was normal, but at age 8 months she was diagnosed with deafness associated with global language and cognitive delay. At age 2.5 years she developed epilepsy manifested by atypical absence seizures, generalized convulsive seizures, and frequent episodes of status epilepticus. Interictal EEGs showed frequent multifocal, bilateral, asynchronous epileptiform discharges and a diffusely slow background rhythm. Cranial magnetic resonance imaging (MRI) at 2, 3, and 4.5 years of age were normal, including a study carried out 3 months before starting the ketogenic diet. Numerous anticonvulsants were ineffective or poorly tolerated. A combination of valproate and ethosuximide eliminated the convulsive seizures but atypical absence seizures persisted.

An extensive evaluation for inborn errors of metabolism was negative. Studies included serum lactate, pyruvate, carnitine, quantitative amino acids, biotinidase, ammonia, thyroid panel, creatine kinase, lysosomal panel, peroxisomal panel, high-resolution chromosome analysis, quantitative urine organic acids, and cerebrospinal fluid amino acid and lactate levels. Ophthalmologic examination and electromyography were normal. Muscle biopsy demonstrated normal morphology, normal enzyme-staining patterns, absence of ragged red fibers, and normal enzymatic activity of mitochondrial complexes I to IV, succinate dehydrogenase, and citrate synthetase. Mitochondrial DNA mutation analysis was negative for 12 common mutations.

The ketogenic diet was initiated using a commonly employed protocol.[5] Carnitine, vitamin supplements, and calcium were administered in addition to the patient's usual doses of valproate and ethosuximide. She tolerated the initial fasting period and induction of ketosis without difficulty.

Three weeks after diet initiation, intermittent dystonic posturing of the right arm appeared. A day later, she developed continuous, diffuse, truncal and appendicular chorea as well as truncal and appendicular ataxia (see Video, Segment 1). She was unable to sit or stand unsupported due to the severe, involuntary movements and ataxia. Motor strength and ocular motility were preserved, although muscle tone was mildly hypotonic. Deep tendon reflexes were normal with flexor plantar responses. There was no evidence of infection, volume depletion, or altered mental status. Laboratory studies demonstrated 3+ urine ketones, a normal finding on the ketogenic diet. Blood count, electrolytes, glucose, liver function, erythrocyte sedimentation rate, ceruloplasmin, anti-streptolysin-O titer, and blood lactate were normal. EEG and valproate levels were unchanged from baseline. Urine organic acids showed a small elevation of lactate but no other abnormalities. Cranial MRI demonstrated bilateral, symmetric hyperintensity in the putamina on T2 and FLAIR images (Fig. 1). No other signal abnormalities were observed. MR spectroscopy showed a focal lactate peak in the region of the putamen (Fig. 1). MR spectroscopy was normal in other brain regions.

The diet was immediately discontinued, glucose-containing intravenous fluids were administered, and high-dose vitamin therapy including selenium, coenzyme Q10, B-complex, biotin, C, and E were started. All of the movement abnormalities partially improved over the next month, allowing the patient to sit unsupported and manipulate objects with the arms. Since then, her neurological condition has not changed significantly over a period of 18 months. Three months after stopping the ketogenic diet, MRI demonstrated resolution of the putaminal signal abnormalities and MR spectroscopy showed no detectable lactate within the basal ganglia (Fig. 1).

DISCUSSION

Extrapyramidal movement abnormalities or basal ganglia lesions have not been previously associated with use

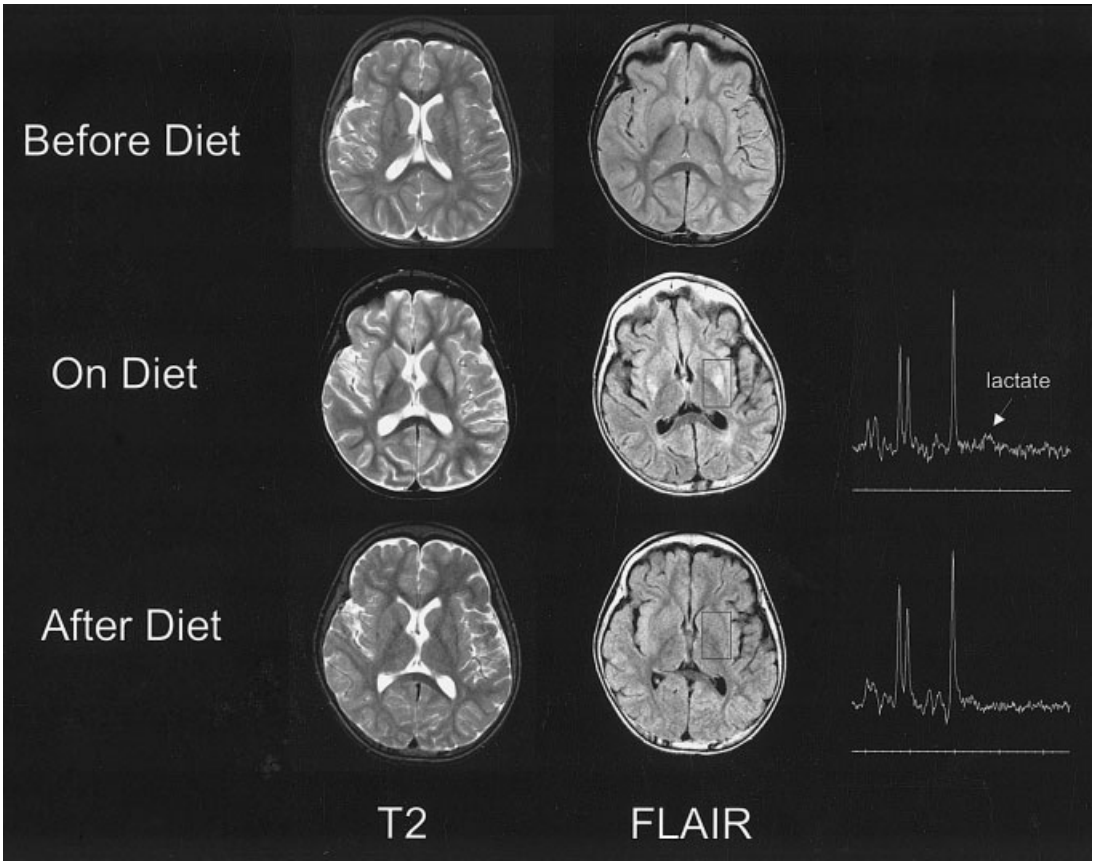

FIG. 1. T2 and fluid attenuated inversion recovery (FLAIR) MRI images of brain obtained 3 months before starting the ketogenic diet ("Before Diet"), 3 weeks after starting the diet ("On Diet"), and 3 months after stopping the diet ("After Diet"). Hyperintense signal abnormalities in bilateral putamina were present when the patient was on the ketogenic diet. These abnormalities were absent before diet initiation and after diet cessation. MR spectroscopy, obtained from the areas indicated by boxes, showed a lactate peak on the diet, an abnormality that resolved after diet cessation.

of the ketogenic diet. A causative role of the diet in the development of chorea, ataxia, and bilateral putaminal lesions in our patient is suggested by the onset of clinical and radiographic abnormalities within three weeks of diet initiation, and the improvement of radiographic abnormalities after diet discontinuation.

The bilaterally symmetric distribution of lesions and focal cerebral lactate elevation implicate a failure of aerobic energy metabolism as the mechanism of brain injury. Such a mechanism of injury is consistent with an etiologic role of the ketogenic diet. The diet induces a dramatic shift in energy metabolism, mimicking the biochemical changes of starvation, in which ketone bodies provide the chief source of cerebral metabolic fuel via oxidation of fatty acids.[5] The physiologic demands of the diet occasionally induce symptomatic hypoglycemia, acidosis, or dehydration. We suspect the metabolic stress of the diet triggered a failure of cerebral aerobic metabolism in our patient, causing lactate accumulation, edema, and neuronal death in the putamina that manifested clinically as dystonia and chorea. Cerebellar circuits were also presumably injured by a similar mechanism, accounting for the patient's ataxia, although no identifiable lesions of cerebellar circuitry were found on MRI.

The ketogenic diet has been extensively used since its development in the 1920s but no prior reports of basal ganglia injury exist, suggesting that factors unique to our patient may have predisposed her to this complication. A latent inborn error of mitochondrial metabolism is likely, and is supported by the history of sensorineural hearing loss, epilepsy, and mental retardation. No metabolic abnormalities were identified, however, despite extensive pre-diet investigations. Consistent with the possibility of an inborn error of energy metabolism, the radiographic and movement abnormalities that appeared in our patient after diet initiation resemble those of Leigh syndrome and familial striatal necrosis, disorders caused by genetic defects in mitochondrial metabolism.[7,8] Our patient corresponds best with a group of patients with familial striatal necrosis, described by Aicardi, who developed

neurological deterioration after an acute systemic illness or other metabolic stressor.[8]

This case also emphasizes the challenge of identifying patients at risk for a catastrophic outcome on the diet. Although most ketogenic diet protocols suggest screening for inborn errors of metabolism, only disorders of fatty acid oxidation or transport are considered absolute contraindications to the diet.[6] In fact, some disorders of energy metabolism such as pyruvate dehydrogenase deficiency and glucose transporter deficiency (Glut 1) may respond favorably to the diet.[6,9] Avoiding the diet in all patients suspected of having a metabolic disorder would deny many of them a potentially beneficial therapy. Further complicating the selection of candidates for the diet, metabolic disorders can elude detection despite thorough diagnostic testing, as was the case with our patient. Thus, the role of extensive pre-diet metabolic screening, beyond that necessary to exclude a fatty acid oxidation defect, remains unclear. MR spectroscopy, carried out before or shortly after diet initiation, could potentially assist in assessing the risk of cerebral metabolic decompensation on the diet, although such a screening method has not been investigated to date.

Concomitant use of valproate may have contributed to cerebral injury in our patient on the ketogenic diet. Valproate impairs mitochondrial oxidative phosphorylation as well as fatty acid oxidation, and its toxicity is exacerbated by carnitine deficiency, a cofactor in mitochondrial fatty acid transport.[9,10] Valproate has been associated with the development of chorea by an unknown mechanism, although it has also been used effectively in the treatment of some forms of chorea.[11,12] The use of valproate without adverse effects in our patient for many months before starting the diet, the unchanged serum valproate levels while on the diet compared to pre-diet levels, and the use of carnitine supplementation while on the diet all argue against valproate toxicity alone as the primary cause of cerebral injury in our patient. An adverse interaction between valproate and the ketogenic diet is a more likely possibility. Such a potential interaction is supported by the higher frequency of serious complications in patients on the ketogenic diet who take valproate.[2]

This first report of a disabling movement disorder and basal ganglia injury associated with use of the ketogenic diet expands the spectrum of serious complications that can occur on the diet. Patients suspected of harboring a latent inborn error of energy metabolism and those using valproate may be at increased risk for this rare, adverse outcome. This complication, and other serious effects of the diet, should be included in pre-diet counseling of candidate patients and their families.

LEGEND TO THE VIDEO

A 5-year-old girl with a cryptogenic epileptic encephalopathy, 3 weeks after starting the ketogenic diet and 24 hours after the onset of abnormal movements. Generalized appendicular and truncal chorea and ataxia are shown.

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