Decades of Delayed Diagnosis in 4 Levodopa-Responsive Young-Onset Monogenetic Parkinsonism Patients

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ABSTRACT

Background: We report 4 patients with young-onset monogenetic parkinsonism, each of whom was misdiagnosed with either a psychogenic movement disorder or chronic fatigue syndrome for 10 to 23 years after the onset of their first symptoms.

Results: Once the diagnosis was eventually made, they all had a rapid and excellent response to levodopa, albeit with the early appearance of interdose dyskinesias in 3.

Conclusions: We discuss possible reasons for the missed diagnosis despite the relentless progression of their motor handicap. DAT scanning supported the revised clinical diagnosis of parkinsonism.

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Key Words: parkin; monogenetic parkinsonism; psychogenic movement disorders; conversion disorder; chronic fatigue syndrome

Case reports

Patient 1

A British woman developed gait freezing at age 31 during her first pregnancy. She then became unsteady and clumsy and complained of jerky tremulous hands and curling of the toes. She also complained of profound fatigue and slowness of thinking. At age 37, she started to have urinary urgency and to fall over. Over 14 years, she was seen by 6 neurologists and had received diagnoses of motor conversion disorder (MCD), chronic fatigue syndrome (CFS), and depression. Her movements were described as distractible, variable, and deliberately slow. Her spontaneous movements were considered as strikingly normal in contrast with those found on formal neurological examination. At age 45, she was reviewed at the National Hospital for Neurology and Neurosurgery in Queen Square, London, where Parkinson’s disease was suspected.

In 2001, her brother committed suicide, which coincided with a marked deterioration in her physical symptoms at age 37. Three of her other 5 siblings had received psychiatric treatment for depression. Her mother had a longstanding history of severe depression.

On examination, she walked with 2 sticks and a narrow-based gait with stooped posture and postural instability (Video 1a). She had a melancholic, slightly anxious facial expression, an asymmetrical fast resting tremor that was also present on posture and action, and a fast synchronous rest tremor in both legs. Her movements were very slow. Finger tapping revealed progressive reduction in amplitude without motor arrests or fatigue. Tone was increased, which improved on distraction.

DAT-SPECT showed reduced tracer uptake in the basal ganglia (Fig. 1a). She was found to have heterozygous deletion of parkin exon 5 and a duplication of parkin exons 2, 3, and 4. After 3 weeks of l-dopa treatment of 300 mg/day, her motor UPDRS score improved from 56 to 7. She developed limb and trunk chorea within 7 weeks of starting treatment (Video 1b).

Patient 2

This Irish woman presented at age 19 with symptoms of fatigue, poor balance, difficulty walking, and quiet speech. She was reviewed by an immunologist and psychiatrist and was informed she had CFS and depression. Her symptoms gradually deteriorated and became

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much worse during pregnancy at age 38. She then developed right-hand tremor, limb dystonia, gait difficulty, and frequent falls. Over the next 5 years, she was followed up in a neurology clinic, but no organic cause was identified. Limb rigidity and brisk reflexes were noted but were considered inconsistent. She was described as being anxious and agitated during consultations. At age 42, she was admitted to the Royal Victoria Hospital in Belfast, where parkinsonism was suspected. During examination, she was very immobile with gait freezing and postural instability and had asymmetrical cogwheel rigidity, bradykinesia, right-foot dystonia, and stooped posture (Video 2). DAT-SPECT revealed reduced uptake in both basal ganglia (Fig. 1b). She was later confirmed to be a compound heterozygote with parkin mutations (ARG275TRP, GLN100X). She had an excellent response to pramipexole. Three years later, L-dopa was started, and peak dose dyskinesia developed within a few months.

**Patient 3**

At age 33, this Estonian nurse developed low mood, slowing of movements, and intermittent hand tremor a year after a minor car accident. She was diagnosed with posttraumatic stress disorder and considered to have an obsessional, rigid personality with severe depression by psychiatrists. She developed impairment of gait and speech 2 years later and began to require assistance to walk. She remained on antidepressants despite the relentless progression of her motor symptoms. She was twice admitted to the care of
neurologists, at ages 37 and 40. Examination showed generalized limb rigidity and slowness of movement, with examples of paradoxical kinesis such as normal reactions in catching a ball. Her gait was described as festinant but “atypical,” with knees flexed and short stride length, and she had never fallen. Her speech was slow and spoken in short sentences. The neurologists on both occasions diagnosed an MCD. At age 43, she became bedbound and developed dysphagia, resulting in severe weight loss. She was admitted to the University Hospital of Tartu in Estonia, where an organic cause of her symptoms was first suspected. Examination revealed postural instability, severe limb rigidity with contractions, and occasional limb and cervical dystonia (Video 3). She had facial masking and was almost anarthric. DAT-SPECT revealed severe reduced uptake in both basal ganglia and led to further investigation, which revealed exon duplication in the alpha-synuclein gene (PARK 1/4; Fig. 1c). She had excellent response to L-dopa but developed interdose dyskinesia within a week.

**Patient 4**

At age 28, during an inpatient treatment for pneumonia, this Austrian pharmacist became agitated after a marital dispute and was given 20 mg of intramuscular triflupromazine for sedation. She developed an acute dystonic reaction with right laterocollis on the following day. Cervical dystonia resolved within 48 hours, but she subsequently developed an intermittent tremor in the left leg. She was diagnosed with reactive depression and was referred for psychotherapy. Subsequently, she developed gait difficulty and a stooped posture. Over 12 years, she was reviewed by 2 neurological teams and psychiatrists, all of whom agreed she had MCD. At age 40, she was referred to the Department of Neurology at Innsbruck Medical University, Austria, where parkinsonism was suspected for the first time. Examination revealed pill-rolling rest tremor in the left hand, asymmetrical rigidity, and bradykinesia. She walked independently with small steps and had marked postural instability. A dose of 300 mg/day of L-dopa led to complete resolution of her motor symptoms. She developed wearing-off symptoms a few years later and peak-dose dyskinesias 15 years after L-dopa treatment. At age 63, she continues to have a good response to L-dopa with mild motor fluctuations (Video 4). Her family history was negative at the time of diagnosis, but a maternal cousin has since developed Parkinson’s disease with dementia. Recent DAT-SPECT revealed reduced tracer uptake (Fig. 1d). She was found to carry digenic mutations for parkin and DJ-1.

### Discussion

We report 4 patients with young-onset parkinsonism with a delay to correct diagnosis of 10–23 years (Table 1). Once organic parkinsonism was suspected, the patients were investigated, and all were found to have a probable monogenetic cause. It was uncertain whether patient 4’s digenic mutations cause her parkinsonism, but her initial extrapyramidal symptoms were probably unmasked early by neuroleptic treatment. We believe their distinct constellation of psychiatric, behavioral, and
motor features, monogenetic cause, female sex, and young age of onset might have collectively contributed to the erroneous diagnosis of MCD. All patients had an excellent response to L-dopa treatment, and patients 1 and 3 developed dyskinesia within weeks of starting L-dopa therapy. Disability was so severe at diagnosis that L-dopa was considered as the most appropriate initial therapy despite the risk of early emergence of motor fluctuations.

Early instability, gait freezing, depression, and behavioral disturbances have been emphasised in some reports of parkin-related parkinsonism. Depression, anxiety, fatigue, and bradyphrenia overshadowed the motor symptoms in all our patients, and the patients' mental state had led to friction and disharmony in their marriages. These prominent neuropsychiatric features may have played a significant role in the failure to diagnose parkinsonism.

The early mislabeling of the movement disorder as psychogenic also seemed to have led to an uncritical acceptance of the diagnosis by subsequent specialists, despite progressive development of motor handicap. The fact that patient 1 had a strong family history of depression and patients 3 and 4 were health care workers may have compounded the initial error and led to an implicit but unspoken view that the patients were trying to deceive their physicians. A report on interviews with UK neurologists indicated that many did not clearly distinguish a conversion disorder from feigning. Neurologists also indicated that many did not clearly distinguish a psychogenic parkinsonism from PMD. The early mislabeling of the movement disorder as psychogenic also seemed to have led to an uncritical acceptance of the diagnosis by subsequent specialists, despite progressive development of motor handicap. The fact that patient 1 had a strong family history of depression and patients 3 and 4 were health care workers may have compounded the initial error and led to an implicit but unspoken view that the patients were trying to deceive their physicians. A report on interviews with UK neurologists indicated that many did not clearly distinguish a conversion disorder from feigning. Neurologists also tended to adopt an “agnostico” stance and assume it was no longer their problem to remedy the malady once a diagnosis of MCD had been made. Findings frequently cited in all 4 cases were distractibility, inconsistency in physical signs, florid symptoms, extreme slowness, and marriage disharmony, which led to the erroneous diagnoses of CFS, depression, and MCD (Table 1). In patients 1 and 3, the presence of kinesia paradoxica was mistakenly considered incompatible with neurological disease.

Psychogenic movement disorder (PMD) is a diagnosis made by neurologists with adequate expertise in movement disorders, and once the diagnosis of PMD is made, regular neurological follow-up is recommended for several years, even after psychiatric referrals. If relentless deterioration in motor function occurs, a critical appraisal of the diagnosis is warranted. Although tremor is the commonest PMD, a parkinsonian presentation is extremely uncommon, and therefore the diagnosis of psychogenic parkinsonism should be made with great caution. Other features that might potentially lead to the incorrect conclusion of psychogenic parkinsonism include sudden onset of symptoms after stress or trauma, prominent pain, brief response to placebo therapy, and coexisting functional features.

Parkinsonism can resemble the body language of retarded depression and CFS and was not suspected in our cases until the diagnosis was finally made. In patients who are chronically slow and tired, parkinsonism should always be considered. If tremor, dystonia, or signs of parkinsonism are present, a therapeutic trial of L-dopa is merited. Finger-tapping assessment can be an objective tool to differentiate organic parkinsonism from PMD. DAT scanning may also help in confirming the clinical suspicion of nigrostriatal dopamine denervation.

We have shared the lessons learned from 4 astonishing cases in the hope that the early suspicion of parkinsonism will lead to early correct diagnosis and effective therapy to maximize patients, of life.

**Video 1a.** Patient 1: Prior to treatment, moderate bradykinesia of the left hand was demonstrated on finger tapping along with right-sided resting tremor. Bilateral jerk postural tremor was observed. She was hypomimic. Her gait was extremely slow with small stride length, en bloc turning, stooped posture with arms held flexed at the elbow, absent arm swing, and intermittent resting hand tremor.

**Video 1b.** Patient 1: Seven weeks after treatment during “on” state, there was marked improvement in bradykinesia during finger-tapping task with evidence of choreiform dyskinesia of the right upper and lower limbs. Her gait was normal in speed with good arm swing. Mild right foot peak-dose dystonia was observed.

**Video 2.** Patient 2: During “on” state, she could rise easily from sitting position with her arms folded. While she was walking, start hesitation, frequent gait freezing, en bloc turning, poor postural stability, and bilateral hand tremor were observed.

**Video 3.** Patient 3: Prior to treatment, she required assistance to rise from a chair and walked very slowly, dragging her right foot with elbow and fingers held constantly in a flexed posture. Postural instability was evident with striking retrogression.

**Video 4.** Patient 4: During the “off” state, there was bilateral leg tremor at rest on distraction. There was left-sided bradykinesia during finger tapping. Retrogression was demonstrated on pull test.

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**References**

Osteopontin Polymorphic Susceptibility Factor for Parkinson’s Disease Among Patients with Gaucher Disease

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ABSTRACT

Background: There is an increased incidence of Parkinson’s disease among obligate carriers of the common glucocerebrosidase mutations, and among patients with Parkinson disease there is an increased number who are carriers of glucocerebrosidase mutations. A Gaucher mutation is considered a susceptibility factor for Parkinson’s disease. Osteopontin single-nucleotide polymorphism–66 is associated with Lewy body disease and considered a susceptibility factor. The aim of this study was to ascertain whether Gaucher patients with parkinsonism carry the osteopontin single-nucleotide polymorphism–66 polymorphic genotype TT to a greater extent than other Gaucher patients.

Methods: Seventy adult patients with at least 1 allele having the common N370S Gaucher mutation including 10 patients with Parkinson disease were included.

Results: There was no statistically significant difference in incidence of the TT genotype in patients with clinically symptomatic Parkinson’s disease (88.9%) and other Gaucher patients (72.1%).

Conclusions: This may partly explain the increased incidence of Parkinson’s disease associated with Gaucher mutations. © 2011 Movement Disorder Society

Key Words: osteopontin; Parkinson’s disease; Gaucher disease; polymorphic variants

Gaucher disease, the most common autosomal recessive lysosomal storage disorder, is caused by mutations in the β-glucocerebrosidase gene, with consequent accumulation of glucocerebroside-engorged cells causing a multisystem disorder. Although there are neuronopathic forms, there is a predilection among Ashkenazi Jews for type 1, which has classically been termed non-neuronopathic. The hallmarks of symptomatic type 1 Gaucher disease are visceral: hepatosplenomegaly, anemia and thrombocytopenia, bone involvement, and, sometimes, pulmonary infiltration.

In 1996 we reported 6 patients with type 1 Gaucher disease who had developed early-onset, aggressive Parkinson’s disease (PD) that was refractory to standard Parkinson’s therapy: all had mild symptoms of Gaucher disease. This was among the earliest documented reports of putative neurological findings in patients with Gaucher genotypes including the N370S (1226G) mutation that had heretofore been considered protective of neuronopathic disease.

More recently, evidence has accumulated showing an increased incidence of PD among obligate carriers of the 6 common glucocerebrosidase mutations, as well as evidence that among patients with PD, there is an increased number who are carriers of a glucocerebrosidase mutation. The presence of a Gaucher mutation is now considered a susceptibility factor for PD.

This association was also evaluated on molecular and clinical/pathological levels. Based on autopsy findings in patients with type 1 Gaucher disease where unaltered brain glucosylsphingosine levels were noted but Lewy bodies were seen, it has been suggested that glucocerebrosidase deficiency may contribute to a vulnerability to parkinsonism.

There are few recognized susceptibility factors for Lewy body disease associated with parkinsonism (as distinct from that associated with dementia), the earliest report being for a mitochondrial mutation and the most recent for increased levels of osteopontin (OPN) in various body fluids. This would also make intuitive sense to explain a biochemical connection between Gaucher mutations and Lewy body disease because in both these disorders, inflammation is involved in the pathophysiological cascade, including in the neuronopathic Gaucher brain, and OPN is a multifunctional molecule expressed by activated T cells, dendritic cells, and macrophages that is up-regulated during inflammation. Specifically, OPN single-nucleotide polymorphism (SNP)–66 was associated with the occurrence of Lewy body disease and considered a susceptibility factor.

Therefore, the aim of this study was to ascertain whether Gaucher patients with symptoms of parkinsonism carry the OPN SNP–66 polymorphic genotype to a greater extent do than other patients with Gaucher disease.

Patients and Methods

A total of 70 adult patients with type 1 Gaucher disease, that is, with at least 1 allele having the N370S
mutation, of whom 10 patients had been diagnosed with PD but not dementia, were included in the study.

Zimran’s Severity Score Index (SSI) with a point scale of 0–30 points based on Gaucher-specific parameters was applied to each patient at presentation to the clinic and is used as an indication of disease severity, with <11 points considered mild disease and >20 points considered severe disease.

In addition to the SNP at 66, 2 other OPN SNPs, at 795 and at 1284, were analyzed. The OPN gene contains several common polymorphisms, distributed in 2 main haplotypes, which may modulate OPN production and/or activity, and to date these latter polymorphisms have been included as part of the major haplotype.

For OPN genotyping for SNP-66, the following primers were used: sense, CCCATCCCGTAAATGAAA; antisense, CCAAGCCCTCCCAAGATTTA. The PCR product was digested with the restriction enzyme FNU4HI (New England Biolabs, Ipswich, MA).

The SNP 795 was diagnosed by amplifying the DNA with the following primers: sense, CCGTGGGAGGACAGTTATG; antisense, TTGGGGTCTACAA. The restriction enzyme used was AluI (New England Biolabs, Ipswich, MA).

For the SNP 1284, the following primers and restriction enzyme were used: sense, CATGGAAACTCCCTGTAAAC; antisense, ACACCACAAAAAGATAATCACA. The restriction enzyme used was AccI (New England Biolabs, Ipswich, MA).

Institutional Helsinki Committee (Shaare Zedek Medical Center) approved this study. Specific informed consent from the patients for the use of anonymized DNA (and blood) samples for the purpose of clinical research was received previous to advent of this study.

Statistical Analysis

Comparisons between the PD group and the non-PD group with regard to categorical variables (age, SSI) were analyzed using the Student t test and Levene’s test for equality of variance. Pearson’s chi-test and Fisher’s exact test were applied to compare Gaucher genotypes as well as OPN genotypes between groups. Cross-tabulations were also performed to compare all non-mutant OPN genotypes as a set between the PD group and the non-PD group. ANOVA was applied to compare within groups and between groups for the polymorphic genotypes. All tests applied were 2 tailed, and a $P \leq 5\%$ was considered statistically significant.

Results

The 10 patients in the group with PD represent all patients with PD in our clinic other than 1 patient who died more than a decade ago (and for whom there was no DNA sample).

The control group was chosen to include at least 1 patient age- and sex- and Gaucher genotype–matched to a PD patient but otherwise was a random collection of adult patients who appeared for routine clinic visits during the study period.

The -66 SNP could not be determined for 1 patient in each group; the 795 SNP could not be determined in 3 non-PD patients; and the 1284 SNP could not be determined in 1 non-PD patient.

Table 1 presents all the demographic findings and polymorphic variable comparisons.

The patients with PD had a high prevalence (88.9%) of the TT genotype of the -66 SNP as did the non-PD group (72.1%).

There were no statistically significant differences between the groups: not in sex, mean age, SSI, Gaucher genotype, or in the percentage of OPN polymorphic genotypes. Mean age and mean SSI compared with OPN genotypes between and within groups did not differ for all the OPN polymorphic genotypes (data not shown).

Discussion

It was shown by Maetzler et al. that increased OPN levels in serum and CSF are associated with Lewy body disease. In a subsequent study, this group also showed there were a higher number of T alleles at the -66 SNP site in the Lewy body disease group, so the TT genotype was significantly associated with systemic disease. Finally, these researchers have suggested that there may be a correlation between age and serum OPN levels.

The initial hypothesis was that this subset of patients would carry the TT genotype of the -66 SNP to a greater extent than would other patients with Gaucher disease, thereby explaining their risk for PD as an independently sorting factor. The other 2 polymorphic genotypes, at 795 SNP and 1284 SNP, are not associated with any risk of Lewy body disease but have been linked variously with immune disorders. Thus, these latter polymorphic genotypes

| Table 1. Results of demographic and OPN polymorphic findings among patients with Gaucher disease diagnosed with Parkinson disease and those not diagnosed with Parkinson disease |
|---------------------------|---------------------------|
|                          | Parkinson (n = 10) | Nonparkinson (n = 60) |
| Age (y), mean ± SD       | 62 ± 12.0           | 55.7 ± 16.8           |
| SSI (points), mean ± SD  | 8.6 ± 6.4           | 10.3 ± 6.3            |
| N370S/N370S              | 4 (40.0%)           | 35 (58.3%)            |
| N370S/other              | 6 (60.0%)           | 25 (41.7%)            |
| -66TT                    | 8/9 (88.9%)         | 42/59 (71.2%)         |
| -66GT                    | 1/9 (11.1%)         | 13/59 (22%)           |
| -66GG                    | 0                   | 4/59 (6.8%)           |
| 795TT                    | 0                   | 6/57 (10.5%)          |
| 795CT                    | 6 (60.0%)           | 27/57 (47.4%)         |
| 795CC                    | 4 (40.0%)           | 24/57 (42.1%)         |
| 1284AA                   | 4 (40.0%)           | 28/59 (47.5%)         |
| 1284CA                   | 6 (60.0%)           | 27/59 (45.8%)         |
| 1284CC                   | 0                   | 4/59 (6.8%)           |
were examined to highlight the index polymorphic genotype at the -66 SNP because it has been posited that ethnicity may be a factor.25

The current cohort of Gaucher patients with PD is small but includes all diagnosed patients in a Gaucher clinic with more than 500 adult patients. A very recent survey of 444 patients with type 1 Gaucher disease revealed 11 patients over a 12-year period,27 approximately comparable to the percentage in our single-center cohort with the same approximate number of adult patients. In addition, they estimated the risk of PD in patients with type 1 Gaucher disease to be 21.4 (95% confidence interval [95% CI], 10.7–38.3), higher among men (which is also true in the general population). The obverse situation was also shown in a study of 420 Israeli Ashkenazi Jewish patients with PD,28 where the carrier frequency of a glucocerebrosidase gene mutation was 17.9% relative to 4.2% in elderly controls and 6.35% in young controls. The proportion of carriers of a severe glucocerebrosidase gene mutation among the PD patients was 29%, increasing the risk of developing PD by 13.6-fold versus an increased risk of 2.2-fold among carriers of a milder mutation.28 Interestingly, this estimated risk is approximately that predicted among first-degree relatives of patients with PD29 who carry a copy of the mutated parkin gene (odds ratio compared with noncarriers, 2.8; 95% CI, 1.5–5.3; P = .002), a well-characterized risk factor for PD.

The unexpected finding in the current study was that in the control cohort of Gaucher patients there was no statistically significant difference in the incidence of the TT genotype of the -66 OPN polymorphism relative to that found in patients with clinically symptomatic PD. This should be considered in the context of the hypothesis that patients with Gaucher disease (and carriers) are at risk for PD.7–14 If indeed—and in contradistinction to possible other genetic and epigenetic factors that impact Gaucher symptoms and signs such as thrombocytopenia and bone density—the OPN genotype is an unique risk factor for PD and if indeed many patients (and carriers potentially) with Gaucher disease have the at-risk polymorphic genotype, this may be a possible link underlying the increased incidence of PD in Gaucher disease.

References
Pupillary Unrest Correlates With Arousal Symptoms and Motor Signs in Parkinson Disease

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ABSTRACT

Background: Arousal symptoms (e.g., sleepiness) are common in Parkinson’s disease, and pupillary unrest (spontaneous changes in pupil diameter) is positively associated with sleepiness. We explored pupillary unrest in Parkinson’s disease.

Methods: Arousal symptoms (Epworth sleepiness scale and sleep/fatigue domain of the nonmotor symptoms scale for Parkinson’s disease) and pupillary unrest were assessed in 31 participants (14 patients with Parkinson’s disease, 17 controls). Effect sizes and f tests compared patients with Parkinson’s disease with control participants. Correlation coefficients were calculated among arousal symptoms, pupillary unrest, and Unified Parkinson Disease Rating Scale Part III. Linear regression was performed with arousal symptoms or pupillary unrest as outcome.

Results: Participants with Parkinson’s disease reported more arousal symptoms than controls. Pupillary unrest, arousal symptoms, and Unified Parkinson Disease Rating Scale Part III were positively correlated. The association between nonmotor symptoms scale-sleep score and pupillary unrest was higher in participants with Parkinson’s disease than controls and higher in those with more Parkinsonian motor signs. Unified Parkinson Disease Rating Scale Part III was positively associated with pupillary unrest.

Conclusions: Pupillary unrest correlates with motor and nonmotor features associated with Lewy-related pathology, suggesting it may be a nonmotor marker of progression in Parkinson’s disease. © 2011 Movement Disorder Society

Key Words: nonmotor features; Parkinson’s disease; pupil; sleep disorders; autonomic dysfunction

There is a great need for earlier recognition of Parkinson’s disease (PD) and nonmotor markers of disease progression so that agents that alleviate motor symptoms may be evaluated for neuroprotective effects. Nonmotor features have a prevalence of 90% in PD.1 They may predate motor signs and include dysautonomia and disorders of arousal such as daytime sleepiness and sleep disorders.2

Pupillary unrest refers to the extent of spontaneous changes in pupil diameter in darkness that reflect spontaneous fluctuations in autonomic tone. In middle-aged healthy adults, pupillary unrest is positively associated with sleepiness.3 Consequently, the application of pupillary unrest in PD may address the need for nonmotor markers of PD progression, as it may measure dysautonomia and disorders of arousal. The objectives of this exploratory study were to determine whether pupillary unrest can be measured in PD, to characterize differences in pupillary unrest between PD and control groups, and to investigate the extent to which pupillary unrest correlates with sleepiness or parkinsonism in an elderly population.

Participants and Methods

Participants were recruited from the University of Pittsburgh Medical Center. PD participants fulfilled the UK PD Society Brain Bank Clinical Criteria, scoring Hoehn and Yahr stage (HY) < 5, taking either no antiparkinsonian medication, carbidopa/levodopa, or dopamine agonists. Controls were age- and sex matched to PD participants. Exclusion criteria included pyramidal and/or cerebellar signs, any other organic brain disorder, prior intracranial surgery, uncorrectable eyesight, bilateral cata‐ ract surgery, diabetes, uncontrolled hypertension, inability to participate due to motor disability (HY = 5), taking medications affecting autonomic measures that could not be safely withheld, and history of polynuropathy or failure to pass a toxicology screen for substances that could influence results (alcohol, opiates, cocaine, cannabis, benzodiazipines, and amphetamines).

Design and Measures

Baseline measures included age, sex, HY stage, and Unified Parkinson Disease Rating Scale Part II—Motor

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signs (UPDRS-III). Arousal measures were the Epworth Sleepiness Scale and the sleep/fatigue domain of the nonmotor symptoms scale for PD (NMS-Sleep). Both scales have established validity and reliability. The Epworth is an index of sleepiness (0–3) in 8 situations (range, 0–24).4 The NMS-Sleep has 4 items: daytime sleepiness, fatigue, restless legs, and insomnia. Severity (0–3) and frequency (1–4) are scored and then multiplied, and items are summed (range, 0–48).5 In both measures, higher scores indicate more symptoms.

Testing sessions began at 9:00 AM. Pupillary unrest was assessed as in the Pupillary Sleepiness Test,6 using infrared video pupillography, which digitized measurement of the horizontal pupil diameter of 1 eye (ISCAN RK726 sampling at 60 Hz with a resolution of 0.04 mm). Participants were seated in front of a computer monitor in darkness (illumination = 0.027 foot candles with monitor on) resting comfortably on a head-and-chin rest. They were instructed to stare at a dim red fixation point (intensity < 0.03 candelas/m²) at eye level at a distance of 28.75" subtending a visual angle of 0.25° for 11 minutes. Because of concerns about whether PD participants could remain adequately still off antiparkinsonian medication, the first 5 PD participants were tested without antiparkinsonian medications being withheld. Once feasibility was established, antiparkinsonian medications were withheld for at least 12 hours prior to testing.

**Signal Processing and Statistical Analyses**

As described by Lüdtke et al,6 pupillary unrest was quantified employing a fast Fourier transform and summing spectral power from 0 to 0.8 Hz for an 82-second segments of data. Because several participants were unable to stay awake and keep their eyes open for 11 minutes, pupillary unrest was quantified as the spectral power for the first 164 seconds of pupil signal collected.

Two-sided $t$ tests or Wilcoxon rank-sum tests compared PD versus controls group ($\alpha = 0.1$). Effect sizes (Cohen’s $d$) and their 95% confidence intervals were calculated. The Shapiro-Wilk normality test showed pupillary unrest was not normally distributed. This was normalized by logarithmic (base 10) transformation for correlations and regression analyses. Pearson correlation coefficients were used to determine linear associations among arousal measures (Epworth and NMS-Sleep), pupillary unrest, and Parkinsonian motor signs (UPDRS-III). A 1-sided $t$ test for the difference between 2 dependent correlations compared associations of arousal measures (Epworth or NMS-Sleep) with UPDRS-III. Linear regressions were performed to test if associations between arousal (outcome) and pupillary unrest were different for PD and controls based on a PD diagnosis (categorical) or UPDRS-III score (continuous); test for interaction, $\alpha = 0.1$. A univariate model with log(pupillary unrest) as outcome and UPDRS-III as the predictor was also tested. Given the sample size, regression models were limited to no more than 3 predictors. A secondary analysis compared those PD participants in whom antiparkinsonian medications were withheld with those in whom they were not. Analyses were performed with Stata (Stata-Corp LP, version 10) or R (version 2.11).7

**Results**

PD and control participants were of similar age (mean [SD]): 64.5 (3.2) versus 59.4 (3.3) years,
respectively (Table 1). The PD group had HY = 1.7 (0.6) and UPDRS-III = 10.1 (3.7). The PD group scored higher in measures of arousal-related symptoms (Epworth effect size [ES], 0.71; P = .05; NMS-Sleep ES, 1.07; P = .007) and pupillary unrest (ES, 0.90; P = .07). There were no significant differences in any outcome measure between the PD participants in whom antiparkinsonian medications were withheld and those in whom they were not.

Positive correlations were seen between arousal-related measures and pupillary unrest (Epworth: r = 0.39, P = .03; NMS-Sleep: r = 0.41, P = .02) as well as arousal-related measures and UPDRS-III (Epworth: r = 0.38, P = .04; NMS-Sleep: r = 0.66, P = .001). Correlation was higher with UPDRS-III for NMS-Sleep than for Epworth scores (r = 0.66 vs 0.38, P = .06). UPDRS-III was positively associated with pupillary unrest (r = 0.32, P = .08).

Epworth scores were positively associated with PD diagnosis (R² = 0.13, P = .05), log(pupillary unrest) (R² = 0.15, P = .03), and UPDRS-III (R² = 0.14, P = .04) in univariate models but not in a simultaneous regression. Multiple linear regression (Fig. 1) demonstrated that the association between pupillary unrest and NMS-Sleep score was higher for PD than for controls, with a difference in slope between the PD and control groups of 1.07 (P = .09). The association between NMS-Sleep score and pupillary unrest was higher with more severe Parkinsonian motor signs (difference in simple slopes of 0.85 [P = .10] for UPDRS-III one standard deviation above and below the mean).

**Discussion**

Pupillary unrest has not been previously evaluated in PD. Compared with controls, the PD group had more severe arousal symptoms, which were positively correlated with pupillary unrest. A positive interaction on NMS-Sleep scores was seen involving PD diagnosis (PD diagnosis x log[pupillary unrest]) and severity of Parkinsonian motor signs (UPDRS-III x log[pupillary unrest]).
Parkinsonian motor signs were also positively associated with pupillary unrest. This study found an association between pupillary unrest and arousal in older adults with PD. The pupil sympathetic pathway integrates input from frontal, limbic hippocampal-amygdaloid, and thalamic sources. The pupil parasympathetic pathway integrates information in the Edinger-Westphal nucleus (cranial nerve III) from ascending reticular fibers and descending fibers from cortical regions. Therefore, pupillary unrest is influenced by neural structures that underlie arousal. Although the possibility of processes peripheral to the Edinger-Westphal nucleus contributing to pupillary unrest has not been excluded (glaucoma may be associated with higher parasympathetic tone resulting in less pupillary unrest), this is unlikely given the exclusion criteria for participants. The correlation of pupillary unrest with Parkinsonian motor signs was higher for NMS-Sleep scores versus Epworth scores ($r = 0.66$ vs $0.41$, $P = .06$), possibly because the Epworth scale assesses only daytime sleepiness, whereas the NMS-Sleep scale captures additional symptoms that coexist in PD.

The positive correlation between arousal symptoms or pupillary unrest and parkinsonism suggests either that one contributes to the other or that both motor function and arousal are affected by the same underlying process in PD. Although it is possible that parkinsonism contributes to symptoms such as daytime sleepiness or that fatigue could lead to bradykinesia, this does not explain why arousal disorders (eg, REM sleep behavior disorder) predate motor signs. Furthermore, neuropathologic studies in PD have demonstrated Lewy-related pathology in the structures that influence the pupillary autonomic pathways detailed above. Thus, a possible explanation is that higher UPDRS-III scores and pupillary unrest are both measures that reflect impairments due to PD neuropathology. The UPDRS-III reflects motor impairment of the basal ganglia, whereas pupillary unrest may reflect disorders of arousal involving the reticular activating system. Because PD pathology also involves structures that influence pupillary unrest but not arousal, pupillary unrest may not only reflect disorders of arousal as seen in healthy adults, but additional PD pathology as well. This may explain the significant positive interactions observed between PD diagnosis or parkinsonian motor signs and pupillary unrest.

Limitations of this study include its small sample size, limited range of PD severity ($HY = 1.7\ [0.6]$), limited range of arousal symptoms, and cross-sectional design. Nonetheless, results demonstrate the feasibility of measuring pupillary unrest in PD and suggest that pupillary unrest is a marker of disorders of arousal. As such disorders can occur prior to motor signs, pupillary unrest may increase in PD prior to parkinsonism becoming apparent. In later-stage PD, the correlation between pupillary unrest and motor signs may be higher as motor signs and arousal symptoms accumulate. Longitudinal investigation of pupillary unrest in a more heterogeneous PD population and in those at risk for PD (REM sleep behavior disorder) is needed to assess the potential of pupillary unrest as an objective nonmotor marker of PD progression.

References

Thalamic Neuronal and EMG Activity in Psychogenic Dystonia Compared with Organic Dystonia

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ABSTRACT

Background: This is a retrospective analysis of thalamic neuronal and electromyogram activities between subjects with organic dystonia and a subject with psychogenic dystonia in whom a thalamotomy was carried out before the diagnosis of psychogenic dystonia was made.

Results: The signal-to-noise ratio in the lowest frequency band (dystonia frequency < 0.76 Hz) in the electromyogram was not significantly different by diagnosis or muscle. The coherence at dystonia frequency for wrist flexors X biceps electromyograms was significantly higher in organic dystonia, whereas the phase was not apparently different from zero for either diagnosis. In a thalamic pallidal relay nucleus (ventral oral posterior), neuronal firing rates were not apparently different between psychogenic and organic dystonia. The neuronal signal-to-noise ratio in ventral oral posterior was significantly higher in organic dystonia than in psychogenic dystonia, whereas both were greater than in controls with chronic pain. Spike X electromyogram coherence apparently was not different between psychogenic and organic dystonia. The proportion of thalamic cells responding to joint movements was higher in the cerebellar relay nucleus (ventral intermediate) of psychogenic dystonia than in organic dystonia.

Conclusions: These results suggest that some features, such as firing rates and thalamic reorganization, are similar in psychogenic and organic dystonia. Other features differ, such as the coherence between the electromyograms from different muscles and the thalamic neuronal signal-to-noise ratio, which may reflect pathophysiological factors in organic dystonia. © 2011 Movement Disorder Society

Key Words: psychogenic dystonia; organic dystonia; human thalamus; neuronal activity; plasticity; dystonia-related activity

The pathophysiology of psychogenic dystonia (PsyD) is not well understood, and some of the same physiological abnormalities identified in organic dystonia have also been found in PsyD.1 It is possible that some physiological abnormalities do not cause the dystonic movements, but result either from the movements or from some other common pathophysiological factor. Reorganized forebrain sensory and motor maps have been suggested to result from repetitive movements both in patients with dystonia and in a monkey model of dystonia.2-4 This concept is consistent with studies demonstrating that repetitive motor activity can lead to reorganization of thalamocortical sensory and motor maps in monkeys.5,6 In addition, the activity of thalamic neurons often shows significant peaks of activity at the frequency of dystonic movements (dystonia frequency < 0.76 Hz).4

We have previously reported reorganized thalamic maps and altered dystonia frequency activity in patients undergoing thalamotomy for dystonia.4 Subsequent to surgery, 1 of these patients was diagnosed as having PsyD. This situation provided a unique opportunity to report descriptively how thalamic neuronal activity in PsyD differs from that recorded in patients with organic dystonia and in “controls” operated on for treatment of chronic pain.

Patients and Methods

Results of surgery in the patient with PsyD were included in a report of 9 patients with organic dystonia.4 At that time, our patient with PsyD was diagnosed with organic dystonia. Thalamic activity in the psychogenic patient could be analyzed only for the first operation because of the poor quality of recordings in the previously operated thalamic nuclei.4 The electromyogram (EMG) was sampled from myohyoid, deltoid, biceps, and wrist flexors in the psychogenic patient versus flexors and extensors of the elbow and wrist in the other 9 patients. Therefore, the thalamic spike X EMG cross-correlation was not previously compared with the other patients.4 These results were also compared with those in 3 patients with chronic pain secondary to thoracic spinal cord injury. None of these patients had pain or altered
motor function in the upper extremity; clinical details were reported in a previous publication.7

All the methods used in this study have been previously described in detail.8–10 Deep sensory cells responded reliably to rapid joint movements and/or squeezing of muscles or tendons but did not respond to stimulation of the skin deformed by these stimuli. Dystonic movements prevented the subclassification of deep sensory cells and the identification of cells responding during active movements.4 Therefore, cells responding to cutaneous stimuli provided our most reliable physiological landmark; putative nuclear location was estimated by moving the atlas maps along the anterior commissure–posterior commissure (AC–PC) line to align the anterior border of Vc with the most anterior cell in the region, where the majority of cells respond to cutaneous stimulation.4

**Postoperative Analysis**

The action potentials of single neurons were discriminated and digitized at 10 kHz by a standard shape-fitting package (Explorer, Brainwave, Thornton, CO). The spike train was converted into an equivalent analog signal using the French-Holden algorithm, a standard technique that preserves the time resolution of the action potentials in the spike train.10–12 The EMG signals were high-pass-filtered (6 dB) at 20 Hz to eliminate low-frequency movement artifact while preserving the raw EMG signal. We had data epochs that were long enough to be analyzed by a standard spectral analysis technique rather than by a multitapper technique that would have been required for shorter epochs.13 Standard techniques were used to take, process, and interpret the spectral analysis of the neuron and EMG signals.4,10,12

**Patient with Psychogenic Dystonia**

The patient was a 33-year-old woman with a 2-year history of dystonia at the time of the first surgery. The dystonia involved the left oromandibular structures and the left upper and lower extremities. She had failed treatment with trihexyphenidyl (40 mg/day) and with levodopa/carbidopa. Marked postoperative improvement lasted only 2 months. Following a second, right-sided thalamotomy 18 months after the first, dystonia progressed to involve the other side of the body. Six months later, she was seen by a movement disorders neurologist (AEL). The diagnosis of PsyD was subsequently made based on: (1) inconsistencies on examination such as severe tongue involvement only when speech was formally assessed, extreme slowness in performing finger-to-nose testing, but normal speed of similar voluntary movements outside the context of the examination; and (2) incongruities with organic dystonia including marked acute exaggeration of generalized dystonic postures, such as severe axial extension triggered when she was asked to look upward, and the rapid progression to generalized involvement in an adult without other neurological abnormalities. At that time, she had severe generalized dystonia involving her face and all limbs and required assistance to walk.

The patient was informed that she might improve considerably with admission to hospital, physiotherapy, and withdrawal of the anticholinergic medication. Within days of hospitalization, the dystonia had almost...
completely resolved. At the time of discharge, she had only minimal posturing in the left hand, and that subsequently resolved. In view of the rapid and sustained remission, the diagnosis of PsyD was clear. She remained stable on further follow-up, and so psychiatric assessment and treatment was not actively pursued.
Results

Analysis of EMG was carried out and demonstrated no apparent difference in signal-to-noise ratio (SNR) between diagnoses of dystonia (Table 1). The EMG X EMG cross-correlation function could only be compared for wrist flexors × biceps (see Patients and Methods section). In patients with organic versus psychogenic dystonia, more synchronous EMG activity was observed between these muscles (Table 1).

Although RF maps were recorded for cells in the ventral intermediate nucleus (Vim), records of activity during involuntary movements were only available for neurons in the ventral oral posterior (Vop) in the patient with PsyD. Therefore, analysis of spike trains and spike X EMG functions was limited to Vop, whereas analysis of somatic sensory properties included neurons in both Vim and Vop. The Vop spike SNR at dystonia frequency was significantly higher in organic dystonia than in PsyD, and both were greater than in patients with chronic pain (Table 1). Neither firing rates nor ISIs appeared to be different between these diagnostic groups.

The proportion of neurons with spike X EMG coherence > 0.42 and maximum SNR at dystonia frequency did not appear to differ between PsyD and organic dystonia for either wrist flexors or biceps. The phase did not appear to differ between dystonia diagnoses.

Figure 1 shows the thalamic map of neuronal location and stimulation sites for the patient with PsyD. It is remarkable for the large number of cells with deep receptive fields, which was significantly greater than that in patients with chronic pain. The size of the representations of individual joints in Vim (see Fig. 1) did not appear differ between the dystonia diagnoses, although these lengths were less in chronic pain than in organic dystonia.

Discussion

The patient with PsyD has a secure diagnosis because her dystonia remitted with suggestion and physiotherapy, fulfilling Fahn and Williams’ criteria for documented psychogenic dystonia. We believe that it is unlikely that she had organic dystonia originally, followed by PsyD postsurgery, because the appearance of the dystonia was very similar throughout her clinical course and because the pattern of clinical remission was consistent with PsyD. The results reported in this article were obtained from this 1 patient, and the number of cells studied was limited, so the conclusions must be considered tentative until confirmed.

The physiological results suggest that Vop neuronal activity is characterized by higher SNR in organic than in psychogenic dystonia, whereas both are higher than that in patients with chronic pain (Table 1). This finding suggests that SNR is an abnormal feature in both types of dystonia, which differs in degree between the 2 diagnoses. The increased SNR in PsyD may be a consequence of dystonic movements, a risk factor that predisposes to the development of dystonia during repetitive movements, or both.2,15 The origin of this change could be related to grouped GPi neuronal discharges in dystonia patients,16,17 which increase with increasing duration and severity of dystonia.16,18 GPi projects to Vop and lesions of either of these structures may interrupt dystonia.4,19 Thalamic neuronal activity was often correlated with EMG activity in both diagnoses and so may drive movement for both, whether it is a consequence of dystonic movements or a risk factor for the development of these movements.

The large number of deep sensory cells in PsyD may also be a result of plastic change in the sensory representation resulting from dystonic movements. Specifically, cortical plasticity associated with sensory protocols including associative conditioning leads to greater cortical reorganization than do protocols in which sensory stimuli are not related to conditioning.20,21

The present study also points to differences between the 2 types of dystonia. EMG coherence between arm muscles has previously been described in organic dystonia,22,23 except for focal hand dystonia.24 EMG coherence was lower in PsyD (Table 1). This may be a useful measure to distinguish psychogenic from organic dystonia. Paired associative magnetic stimulation testing of cortical plasticity may also differentiate these conditions.25 Such noninvasive measures may be practical biomarkers for distinguishing psychogenic from organic dystonia, especially given the difficulty differentiating them on clinical grounds alone.

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References