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Brief Reports

Myoclonus of Peripheral Origin: Two Case Reports

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Video 

Abstract: **The concept of peripheral myoclonus is not yet fully accepted by the medical community because of the difficulty in establishing a cause-and-effect relationship between trauma and subsequent movement disorders. Here, we report two cases of patients suffering from peripheral myoclonus after nerve injury. The first patient experienced myoclonus of the 4th dorsal interosseous muscle several days after trauma to the elbow. The second patient presented myoclonus of the arm stump (combined with phantom-limb pain) 1 year after amputation. In both cases, central nervous system function (spine and brain imaging, somesthetic evoked potentials, EEG back-averaging) was normal. For the second patient, local infiltration of xylocaine and botulinum toxin into the stump scar rapidly stopped myoclonus and pain. Nerve injury induces ephaptic transmission and ectopic excitation. The physiopathological mechanisms of this type of myoclonus involve a peripheral generator that induces central (spinal) generator activity.** © 2008 Movement Disorder Society

Key words: peripheral myoclonus; spinal myoclonus; phantom-limb pain; nerve injury

It is well established that brain trauma can cause movement disorders. However, the idea that peripheral trauma can trigger abnormal movements is not yet universally accepted.[1] Muscle twitching with a peripheral etiology is referred to as fasciculation, but few reports have attributed myoclonus-like movements to peripheral nerve damage.[2–9]

Here, we describe two cases of patients who experienced myoclonus after a peripheral nerve injury (trauma or amputation).

CASE REPORT NO. 1

A 15-year-old female had presented movement disorders of the right hand for 3 months. Involuntary movements of the right 4th and 5th fingers appeared 3 days after elbow trauma (direct impact of the elbow on a hook) that had caused significant swelling at the time. During a neurological examination 3 months later, the patient described paresthesia sensations in the 5th and in the half of the 4th fingers and on the medial side of her right hand. She had trouble keeping her 5th finger's extended and separated from the 4th finger. The motricity of the abductor pollicis brevis and the lumbrical muscles appeared normal. These sensory and motor deficits suggested ulnar nerve injury. Moreover, a neurological examination revealed involuntary, brief, stereotypical, and pseudorhythmic movements of the said fingers. Somesthetic and other exteroceptive stimulations did not induce involuntary movement. No other abnormalities were found during the neurological examination.

The velocity and amplitude of motor and sensory conduction in the right cubital nerve were normal. During surface electromyography (EMG) recording at rest, we recorded the abductor digiti minimi, the 4th dorsal interosseous, the 1st dorsal interosseous, the extensor digitorum muscle, and the flexor digitorum muscle. We noted bursts only of muscle activity for the 4th dorsal interosseous muscle. The bursts lasted for about 100 ms and had an irregular, rhythmic activity at rest. When the arms were held out, muscle bursts were more regular and displayed a 3 Hz rhythmic activity. Abnormal muscle activity disappeared during ventral interosseous activity (e.g. the fingers held tight together). The needle EMG exploration of the same muscles excluded spontaneous activity at rest (fasciculation or myokymia) and confirmed discharges of several motor units in the 4th dorsal interosse-

Additional Supporting Information may be found in the online version of this article.

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ous muscle. Magnetic resonance imaging (MRI) and echography of the right elbow, as well as spinal and cerebral MRI, were normal.

Functional discomfort was moderate and the patient refused additional exploration and treatment. After 1 year of clinical follow-up, the symptoms had not changed.

CASE REPORT NO. 2

A 55-year-old male presented myoclonus of the arm stump. A train had crushed his left arm 16 years previously and amputation above the shoulder had been necessary. During the operation, it was observed that the brachial plexus branches had been sectioned. Two months later, phantom pain appeared and was characterized by permanent paresthesia of the amputated hand and forearm and paroxysmal pain (described as electrical shocks). The symptomatology was described as really diffuse and did not correspond clearly to one of the nerve territory of the arm. One year after the accident, a neurological examination revealed involuntary, rapid, and periodic rhythmic movements of the stump during painful fits. Given the extensive muscle loss, it was difficult to judge the extent of myoclonus. However, myoclonus appeared to be generated in the left pectoralis major and left latissimus dorsi muscles. Somesthetic stimulation of the scar's central zone (the trigger zone) induced myoclonus. Conversely, voluntary stump movement or forced immobilization of the phantom limb reduced movements. A neurological examination did not reveal any other abnormalities.

A spinal MRI showed a C6-C7 osteophytic protrusion in the absence of spinal injury. Only dermatomal sensory-evoked potentials could be investigated. With C4 dermatomal stimulation, the cortical response was normal on both sides, whereas C5 dermatomal stimulation failed to evoke a cortical response on the left side. Standard sensory- and motor-evoked potential studies and a nerve conduction EMG study were not performed because of the remaining limb tissue. A surface EMG study at rest showed rhythmic, short bursts of muscle activity (with a frequency range of 8 Hz) recorded synchronously in the left pectoralis major and latissimus dorsi muscles. Myoclonus lasted about 80 to 100 ms. A needle EMG exploration was also performed on the left pectoralis major and latissimus dorsi muscles and excluded myokymia and fasciculation. At rest, we recorded either no electrical signal or simultaneous rhythmic (8 Hz) bursts activity on the two muscles. These bursts were made up of several motor unit potentials, judging from the morphology of the high-frequency discharges. The rhythmic activity was decreased by voluntary movement of the stump and increased or triggered by somesthesic stimulations of the central part of the scar. No premyoclonus cortical spikes were observed using a back-averaging technique. Six milliliters of 1% xylocaine solution was injected on the trigger zone and all around this point; phantom pain immediately decreased and the phantom limb phenomena faded and then disappeared completely. Within minutes of injection, myoclonus had completely disappeared and remained absent for the next 3 hours. Phantom pain was the first phenomenon to reappear. An injection of 30 U of botulinum toxin A around the scar led to disappearance of the myoclonus 1 week after administration, with the effect lasting for 14 weeks. However, even reduced, pain was always present.

DISCUSSION

In both cases described here, the abnormal movements were in accordance with a clinical and electrophysiological diagnosis of myoclonus. Both patients had brief, rhythmic muscle jerks of sufficient intensity to induce movement. We saw no clinical or electrographic evidence for a diagnosis of myokymia or fasciculation. Moreover, surface EMG exploration clearly revealed, brief muscle jerks (lasting about 100 ms) with an irregular rhythmic activity. This activity concerned only the 4th dorsal interosseous muscle in the first patient and the pectoralis major and latissimus dorsi (synchronous activity) muscles for the second case.

Use of the term "myoclonus" is usually restricted to phenomena of central origin.[10] Myoclonus can be classified into three groups: cortical, spinal, and subcortical.[11,12]

The myoclonus in our cases showed the characteristics of spinal myoclonus. Indeed, in clinical terms, myoclonus was either spontaneous or reflex after sensory stimulation (case report No. 2). Equally, the myoclonus appeared to be rhythmic. In spinal myoclonus, a decrease in frequency during motor activation is also frequently noted. A number of other arguments were provided by the electrophysiological study: myoclonus was confined to a distinct muscle group (only one or two muscles were concerned), it was rhythmic (3 Hz for the first case and 8 Hz for the second) and bursts were short (lasting about 100 ms). Moreover, there were no arguments in favor of a cortical or subcortical origin; there was no history of brain injury in either case and there were no clinical and electrophysiological findings (especially absence of premyoclonic electroencephalographic activity) to suggest these types of myoclonus.

However, even though the myoclonus presented by our two patients had the characteristics of spinal myo-

clonus, there was no evidence for spinal injury (anamnesis, clinical examination, spine imaging). In view of the peripheral injury (focal trauma or amputation), we suggest that the myoclonus observed here could have a peripheral origin. The cause-and-effect relationship is very significant in the first case; firstly, the trauma was responsible for intense swelling and the myoclonus appeared just 3 days after the injury. Secondly, the symptoms were limited to a scenario of ulnar nerve injury and the trauma to the right elbow was located exactly in front of the ulnar nerve pathway. The normal ulnar conduction results could be explained by limited fascicular injury (on the surface EMG, only the 4th right dorsal interosseous muscle innervated by the ulnar nerve was affected by myoclonus). In the second case, it is difficult to distinguish between the respective responsibilities of the accident or the subsequent amputation. However, in both situations, the left brachial plexus was clearly injured in a proximal position. Clinically, the muscles involved in myoclonus depended on this plexus, from different cords (the posterior cord for the latissimus dorsi muscle and the medial cord for the pectoralis major muscle). The abnormal C5 dermatomal sensory-evoked potential provides a further argument for major injury of the brachial plexus. The most important argument in favor of a peripheral origin in this case was the myoclonus trigger zone. Sensory stimulation of the scar (central zone) induced myoclonic jerks. Furthermore, when local anesthesia was used to block the area's sensory afferences, the myoclonus (the clinical symptoms and the EMG bursts) disappeared—even during sensory stimulation.

The second patient's story strongly suggests the presence of ectopic activity generated by a neuroma. Neuroma is a common complication of amputation,[13] and the dramatic effect of subcutaneous local anesthesia on the scar in this case is totally in agreement with this scenario. Concerning the first case report, it is less clear but a similar etiology could be evoked. The first symptoms could be explained by inflammatory injury of the nerve and their persistence by the formation of a neuroma in the same location. Even if we did not have any pathological evidence, our hypothesis is well supported by previous articles reporting peripheral myoclonus related to a neuroma. The neuroma at the site of nerve injury induced an ectopic excitation. An alteration of the inputs could modify the spinal excitability and facilitate the generation of abnormal movements. Generally, myoclonus can be cured by local xylocaine or botulinum toxin infiltration[5,7] or scar excision.[5]

In the second case, we were surprised to notice that myoclonus was preceded by a sensation of pain. Pain and sympathetic nervous system (SNS) alterations are frequently reported with peripheral abnormal movement.[14] Indeed, these factors could have had an influence on the motor system. Substance P has a significant effect on motor neuronal function[15] and the SNS could trigger ephaptic transmission and have an effect on primary C fibers and muscle spindles.[16] Reducing peripheral sympathetic activation with local anesthesia could counter first pain and phantom-limb pain and then abnormal movement.[17] Even though the efficiency of the local anesthesia by xylocaïne could be well understood in terms of a reduction in aberrant somesthesic inputs (peripheral motor generator function remains normal, so no motor deficit is associated), the effect of the botulinum toxin is still unclear. The botulinum toxin was first known as a poison of the neuromuscular junction (decreasing the presynaptic release of acetylcholine) inducing a weakness of muscular fibers' contraction. But more recently, it has been shown that this toxin could also have an impact over the central nervous system. The excitability of the spinal cord can be altered indirectly by reduced muscle spindles activity or changes in recurrent inhibition or perhaps directly by retrograde axonal transport.[18,19] Most recently, the antinociceptive effect of the toxin was also reported. Indeed, a local infiltration could reduce the release of glutamate and neuropeptides of the primary afferents terminals and decrease the feeling of pain.[20] In the case of peripheral myoclonus, the mechanism of the toxin certainly mixes the reducing of the somesthesic inputs with the alteration of spinal excitability.

In conclusion, peripheral trauma with nerve injury may induce altered sensory inputs and disinhibition of anterior horn neurons (abnormal sensory inputs may modify the firing of anterior horn neurons via a local sensorimotor integration process). These two cases should arouse further interest in this type of peripheral myoclonus. Hence, patients presenting apparently spinal myoclonus must be carefully examined for a peripheral cause. Furthermore, local surgical treatment (scar or neuroma excision) or infiltration of local anesthetics or botulinum toxin can lead to a successful outcome on the movement disorder.

LEGENDS TO THE VIDEO

Segment 1. 1st part: irregular myoclonus of the last two right fingers was observed at rest and during activity of the right 4th dorsal interosseous muscle. The myoclonus persisted during an interferential cognitive task.

Segment 2. 1st part: spontaneous myoclonus of the stump was observed, together with right arm phantom pain. Myoclonus could be triggered by somesthetic stimulation of the scar (trigger zone). 2nd part: several minutes after infiltration of a local anesthetic into the scar, the phantom pain and myoclonus had both disappeared. Stimulation of the trigger zone no longer induced myoclonus.

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Atomoxetine for the Treatment of Executive Dysfunction in Parkinson's Disease: A Pilot Open-Label Study

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Abstract: **Executive dysfunction (ED) is a prominent and often disabling feature of cognitive impairment in Parkinson's disease (PD). Few studies have examined treatments. Given the role of noradrenergic pathology in ED, atomoxetine, a norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder (ADHD), may be a potential treatment for PD-related ED. Twelve patients with PD and disabling ED completed an 8-week pilot open-label, flexible dose (25–100 mg/day) trial of atomoxetine. On primary outcome measures, atomoxetine was associated with improved ED based on the Clinical Global Impression-Change Scale (75% positive response rate; 95% CI: 43–95%, $P < 05$) and behavioral measures of ED [Frontal Systems Behavior Scale (FrSBE) Executive Dysfunction and Connors Adult ADHD Rating Scale (CAARS) inattention/memory subscales]. Adverse effects included sleep and gastrointestinal disturbances and hypomania. Atomoxetine is tolerable in PD and may benefit clinical manifestations of ED, warranting further study in controlled trials.** © 2008 Movement Disorder Society

Key words: executive dysfunction; Parkinson's disease; cognition; norepinephrine reuptake inhibition; atomoxetine

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Cognitive impairment in Parkinson's disease (PD) is commonly characterized as a progressive dysexecutive syndrome involving deficits in sequencing, planning, set-shifting, response inhibition, working memory, and multitasking.[1] As these processes are essential for adaptive functioning, executive dysfunction (ED) is often disabling.[2] ED is also associated with transition to dementia,[3] but individuals with intact cognitive test performance are also affected negatively.[4]

Few studies have examined treatments for PD-related ED. Since dopaminergic and noradrenergic systems and prefrontal cortex are implicated in ED,[5] we conducted a pilot open-label trial on the effectiveness and tolerability of atomoxetine, a selective norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder (ADHD), as a treatment of patients with PD who have ED, but not dementia.

METHODS

Subjects were outpatients with idiopathic PD,[6] aged 21 to 65 years, recruited through community outreach and clinic sources. In the absence of established diagnostic criteria for ED, clinically significant ED was defined as problems with disorganization, distractibility, task completion, planning or problem solving of moderate severity that affected work or social function, represented a decline from pre-morbid (pre-PD) status, and were confirmed by an informant. Other inclusion criteria were: Mini-Mental State Exam[7] $\geq$26; absence of DSM-IV-TR Dementia due to PD; Clinical Dementia Rating Scale Global score[8] $<$1; Functional Assessment Staging score[9] $\leq$4; 21-item Hamilton Depression Rating Scale[10] score $<$10; stable medications for 3 months; and, absence of contraindications to atomoxetine use (narrow angle glaucoma, use of monoamine oxidase inhibitor antidepressants), urinary hesitation or retention, hepatic dysfunction, hallucinations without insight, pregnancy, current illicit substance use or alcohol abuse or dependence; and use of concomitant potent CYP2D6 inhibitors, psychostimulants, or wakefulness therapy. Subjects and informants provided informed written consent. The Western Institutional Review Board approved the study.

Dosing for this 8-week open-label, uncontrolled, flexible dose trial consisted of atomoxetine 25 mg/day (Week 1), 50 mg/day (Weeks 2–4), 75 mg/day (Week 5), and 100 mg/day (Weeks 6–8). Dose reductions were allowed to a minimum of 2.5 mg/day for intolerance. Primary outcome measures were the Clinical Global Impression of Change-Clinician rated (CGI-C) score[11] and self-rated behavioral measures of ED: the Frontal Systems Behavior Scale (FrSBe)[12] Executive Functioning deficits subscore and the Connors Adult ADHD Rating Scale Long form (CAARS-L)[13] Inattention/Memory subscore, a primary outcome measure in atomoxetine trials for ADHD.[14] Secondary outcomes included a comprehensive neuropsychological and psychiatric battery (see Appendix). Safety assessments included vital signs, spontaneously reported adverse events (AEs), UKU AE checklist,[15] Unified Parkinson's Disease Rating Scale (UPDRS)-Activities of Daily Living, Motor, and Complications of Therapy subscales,[16] Hoehn and Yahr Stage,[17] changes from baseline laboratory tests, and cardiovascular effects using conventions from previous atomoxetine studies.[18]

Analyses used STATA Version-9 (StataCorp, College Station, Texas). Efficacy, based on change from Baseline (Day 0) to end of treatment (Day 56), used Wilcoxon signed rank test for continuous variables and chi-square or Fisher exact test for categorical variables. A P-value $<$ 0.05 defined significance. There were no corrections for multiple comparisons.

TABLE 1. *Subject characteristics (n = 12) at baseline*

Variable	Mean (SD, Range) or *N* (percent)
Age (yrs)	57.3 (7.2, 40–65)
Gender (Male/Female)	5M/7F
Education (yrs)	18.2 (2.7, 13–24)
Age onset PD (yrs)	44.5 (9.2) (24–56)
Age diagnosis PD (yrs)	47.9 (8.2, 32–57)
Duration PD (yrs)	12.8 (8.4, 3–34)
Hoehn & Yahr Stage	2.1 (0.3)
	No. of subjects per stage $I^1/_2$ = 1, II = 8, $II^1/_2$ = 3
UPDRS ADL Subscore	14.9 (12.1)
UPDRS Motor Subscore	23.2 (12.7)
Concomitant Medications	
Antiparkinsonian Medications	
Dopamine agonists only	2 (17%)
L-dopa only	4 (33%)
L-dopa + Dopamine agonists	6 (50%)
Apomorphine	1 (8%)
COMT inhibitor	3 (25%)
Anticholinergics	1 (8%)
Selegiline	1 (8%)
Amantadine	2 (17%)
Psychiatric Medications	
Antidepressants	7 (58%)
Atypical Antipsychotics	3 (25%)
Benzodiazepine/hypnotics	2 (17%)

RESULTS

All 12 subjects (Table 1) completed the trial. The mean (SD, range) atomoxetine dose at the final visit was 89.6 (24.9, 25–100) mg/day. CGI-C ratings in nine

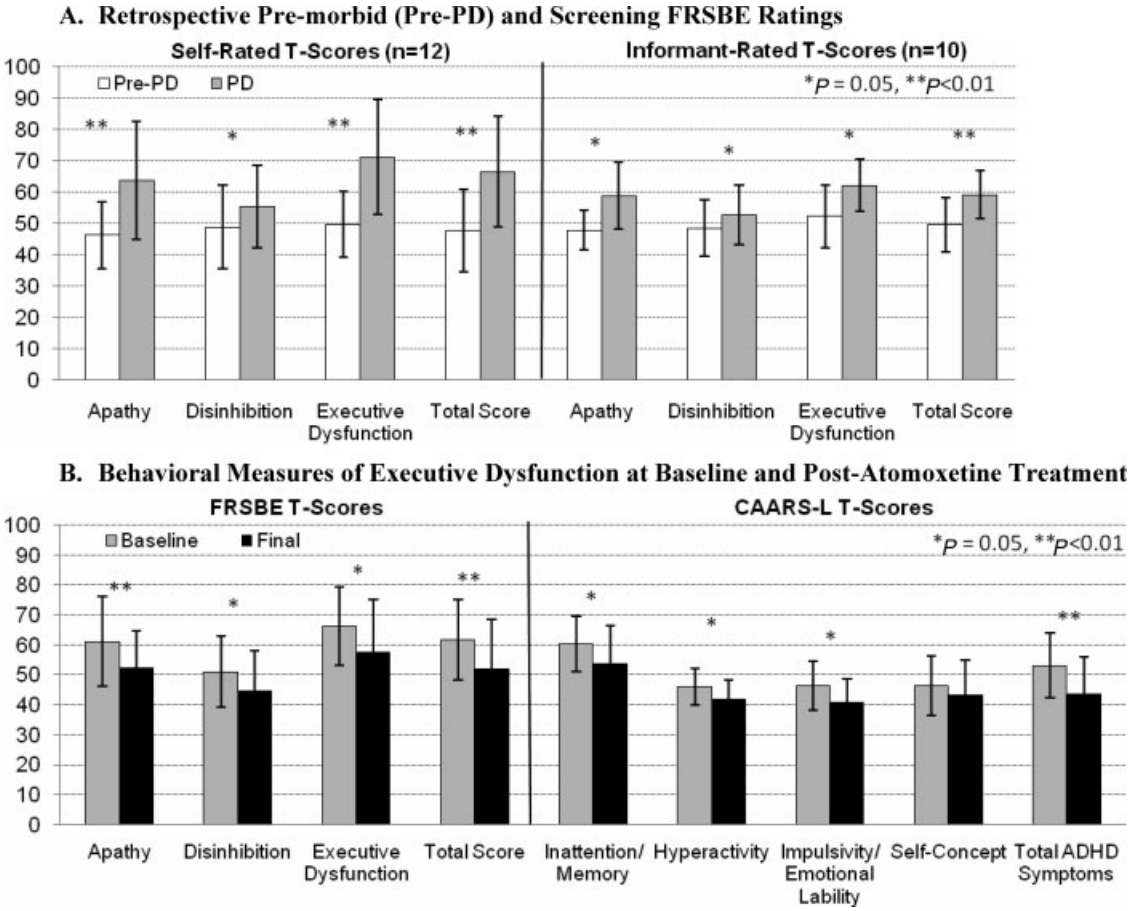

FIG. 1. The Frontal Systems Behavioral Scale (FrSBe), developed for neurological populations, includes current plus retrospective ratings of behaviors pre-illness. The Connors Adult ADHD Rating Scale-Long Form (CAARS-L) rates current symptoms.[24] The primary self-rated outcome measures, the FrSBE Executive Dysfunction and CAARS-L Inattention/Memory subscales, measure frequency of behaviors such as task incompletion, disorganization, distractibility, and difficulty planning, multi-tasking, and initiating tasks. **A.** Change in self- and informant-rated FrSBE scores based on behaviors endorsed retrospectively as present before onset of PD compared to behaviors endorsed at screening evaluation. Individual T-scores are based on ratings in a normative sample in which the distribution of T-scores has a mean of 50 and a SD of 10. Group mean (SD) T-scores are presented to allow comparability across gender, age range, and education level within the sample; higher scores indicate greater symptom severity. For all FrSBe scales, T-scores ≥65 are considered clinically significant and scores of 60 to 64 represent likely borderline impairment. **B.** FrSBe Subscale and Total scores and CAARS-L Subscales and Total Scores at baseline and final visits. CAARS-L scores are also depicted as group Mean (SD) T-scores, derived from comparison to CAARS norms based on gender and age in a normative sample. Similar to the FrSBE, higher T-scores are associated with greater symptom severity and T-scores above 65 represent symptoms of clinical significance.

subjects indicated clinically significant improvement in ED (75% positive response rate, 95% CI:43–95%) [Three subjects "very much improved" (95% CI:5–57%); six "much improved" (CI:21–79%), one "minimally improved" (CI:0–38%), and two with "no change" (CI:2–48%)] Atomoxetine was associated with improved scores on the FrSBe Executive Dysfunction and CAARS-L Inattention/Memory subscale and the remaining FrSBe and CAARS-L subscale and total scores, except the CAARS-L Self-Concept subscale (Fig. 1).

Baseline cognitive test performance was within published norms for most subjects. Except for an improved Hopkins Verbal Learning Test-Revised Recognition Discrimination score [10.8 (1.7) to 11.9 (0.3), change = 1.2 (1.8), $P < .05$], there were no changes in neuropsychological performance. The only changes on psychiatric rating scales were increased Neuropsychiatric Inventory[19] sleep difficulties [0.8 (1.5) to 1.8 (2.4), change = 1.0 (2.2), $P < .05$], and improved PDQL Emotional Symptoms Total[20] [33.7 (6.0) to 36.9 (5.5), change = 3.3 (2.9), $P < .01$].

Treatment-emergent AEs were mildly to moderately severe. Most common were reduced sleep (n = 6, 50%), constipation (n = 5, 42%), and nausea/vomiting, tension, confusion, slowed movements, and diaphoresis (each n = 3, 25%). AEs endorsed by 2 subjects (17%) were fatigability, depression, agitation, increased dream activity, rigidity, hyperkinetic movements, paresthesias, headaches, dry mouth, tachycardia, rash, weight gain, and dysmenorrhea. Eighteen other AEs were reported in one subject each. Because of AEs, two subjects delayed dose increases and two required dose reductions. One subject developed hypomania on atomoxetine 75 mg/day that remitted with reduction to 25 mg/day. There were no significant motor, vital sign, laboratory test, or EKG changes.

DISCUSSION

This pilot study supports the importance of exploring efficacy of atomoxetine for PD-related ED in future studies, using controlled designs. In 75% of subjects, we observed clinically significant improvement that corresponded to a decline in behavioral symptoms of ED. The majority tolerated atomoxetine and motor function was unaffected, but gastrointestinal effects and hypomania were notable AEs.

Two other studies describe treatment of PD-related ED in non-demented patients. A cognitive training program focusing on working memory showed improved performance on executive tasks, but did not assess ED in daily functioning.[21] Consistent with our results, a 16-week open-label study (n = 10) of donepezil, an acetylcholinesterase inhibitor, showed improved CGI ratings in the absence of changes in cognitive measures of ED.[22]

The focus on behavioral aspects of ED is a unique aspect of this study that ensured its clinical relevance. Given the diverse processes involved in ED and heterogeneous neuropsychological deficits of PD, there is no current basis for a single primary cognitive outcome measure.[23] Thus, cognitive complaints and behavioral evidence for acquired ED provided a standardized approach for defining appropriate study candidates, a potentially useful strategy for future trials. The CAARS-L Inattention/Memory Problems subscale captures many behaviors described by our subjects, but have not been studied in PD. We also used the FrSBe, a validated measure of behavioral changes associated with frontal systems damage.[12]

Whereas the CAARS-L, FrSBE, and CGI-C were sensitive tools for evaluating ED severity and treatment response in this study, our subjects were generally unimpaired on psychometric tests. This is not uncommon when evaluating individuals with ED in structured test settings.[12] High premorbid function in our sample may also limit detection of deficits relative to published norms. Nonetheless, evidence for changes from pre-PD FrSBE ratings (Fig. 1) reflected previously intact executive abilities. The utility of the FrSBe for identifying PD subgroups with ED or predicting cognitive decline needs further investigation; in the future, behavioral changes might serve as a basis for interventions, instead of delaying treatments until declines in cognitive performance are evident.[4]

The mechanism by which atomoxetine may improve ED is unknown; previous studies emphasize effects on inhibitory control. Atomoxetine acts primarily via presynaptic norepinephrine transporter blockade. It also elevates dopamine in selective cortical regions and has procholinergic effects.[24,25] In rats, atomoxetine improved performance on learning, memory consolidation, retrieval, and inhibitory control tasks.[25,26] In adult control and ADHD subjects, single atomoxetine doses produced selective effects on response inhibition in the absence of effects on attention or working memory.[27,28] Longer-term atomoxetine trials in adults with ADHD also showed improved measures of inhibitory control.[29,30]

An advantage of atomoxetine is that its long duration of action sustains elevations of prefrontal norepinephrine and dopamine, which may also account for its lack of abuse potential when compared to transient changes seen with psychostimulants.[24] In other studies of PD patients, manipulation of the noradrenergic system influences executive functions that rely on attentional resources and subcortical dopaminergic effects.[31–33] Methylphenidate, a psychostimulant, benefited attention, but only in non-demented patients taking L-dopa, supporting its primary dopaminergic effects.[34,35] Furthermore, dopaminergic drugs mainly improve motor function and only minimally benefit or possibly aggravate cognitive deficits, including ED.[34,36]

Atomoxetine was generally well-tolerated. AEs, especially gastrointestinal symptoms, were consistent with other reports[14] and there were no clinically significant motor effects. Although pre-existing psychiatric conditions were controlled at baseline, one patient developed hypomania. A previous report describes onset of mania in an adult treated with atomoxetine for depression.[37]

This study has several limitations. As an open-labeled study, placebo effects cannot be excluded; a blinded, placebo-controlled study with a larger sample is necessary to assess effectiveness and tolerability of atomoxetine for PD-related ED. The small sample-size, intersubject variability, possible inclusion bias, ceiling,

and practice effects limit interpretations of neuropsychological data. We did not correct for multiple comparisons and the sample size precludes evaluation of differential effects of atomoxetine relative to baseline cognitive performance. Finally, our sample was restricted to subjects younger than age 65 years.

In this study, atomoxetine was generally tolerable and reduced severity of behavioral symptoms associated with ED. Diagnosis of ED based on clinical symptoms may allow inclusion of patients in trials with disease-related behavioral changes before progression to the point of cognitive deficits on formal testing. Future trials should take into account heterogeneity of ED and cognitive impairment in PD, with deficits and variable progression across multiple domains and involvement of multiple neurotransmitter systems. The noradrenergic system may be an important target, with a favorable role for atomoxetine suggested by the present results, but requiring further study.

APPENDIX

All subjects completed a comprehensive neuropsychological and psychiatric Assessment battery. The cognitive battery assessed the following domains: global function: MMSE, Mattis Dementia Rating Scale; verbal and non-verbal learning and memory: Hopkins Verbal Learning Test-Revised (HVLT-R) and Brief Visuospatial Memory Test (BVMT); visual scanning and set-shifting: Trails A & B; reaction time, attention, and vigilance: Continuous Performance Test-II (CPT-II); planning, sequencing, and problem solving: CANTAB Stockings of Cambridge; generativity: verbal fluency; working memory: Paced Auditory Serial Addition Test (PASAT), letter-number sequencing, and digit span; and inhibition: Stroop. To limit the bias of practice effects on performance at the final visit, the battery was administered at screening and baseline and alternate test forms were used for the HVLT-R, BVMT, and MMSE. Psychiatric assessments included the Neuropsychiatric Inventory (NPI), 21-item Hamilton Depression Rating Scale, the Young Mania Scale, and self-rated measures of depression, anxiety, and quality of life [Beck Depression Inventory, State-Trait Anxiety Inventory, and PD Quality of Life (PDQL) scale.]

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Allied Health Care in Parkinson's Disease: Referral, Consultation, and Professional Expertise

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Abstract: **There is evidence for the efficacy of allied health care in Parkinson's disease (PD). However, barriers exist that hamper implementation of evidence into daily practice. We conducted a survey to investigate: (1) to what extent PD patients currently utilize allied health care for relevant problems in the core areas of allied health care and (2) the level of PD-specific expertise among allied health professionals. Questionnaires were sent to 260 patients and 297 allied health professionals. Referral rates were 63% for physical therapy, 9% for occupational therapy, and 14% for speech therapy. PD patients with problems that can potentially be alleviated by input from allied health professionals are often not being referred. Furthermore, most patients were treated by allied health professionals who lacked PD-specific expertise. Current referral to and delivery of allied health care in PD are suboptimal. Evidence-based guidelines for allied health care in PD and active implementation of these guidelines are needed.** © 2008 Movement Disorder Society

Key words: Parkinson's disease; allied health occupations; referral and consultation; physiotherapy; physical therapy

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Allied health care in Parkinson's disease (PD) provides a distinct therapeutic approach that may complement standard medical treatment such as medication or neurosurgery.[1] The evidence for the benefits of allied health care in PD is still limited, but increasing rapidly.[2–4] In order to provide optimal allied health care in daily clinical practice, not only evidence is crucial. Obviously, evidence needs to be translated into clinical guidelines and subsequently be implemented into daily practice.

However, there are barriers that hamper translation of evidence into daily practice. For example, the referral process to allied health care and the PD-specific expertise of allied health professionals may be suboptimal, e.g., patients needing allied health care are not always referred.[5–7] We therefore conducted a survey among both PD patients and allied health providers to investigate: (1) to what extent PD patients utilize allied health care for relevant problems in the core areas of allied health care and (2) the level of PD-specific expertise among allied health professionals. We focused on the "core specialties" of allied health care for PD: physical therapists, occupational therapists, and speech therapists.

METHODS

Study Design

We performed a questionnaire survey that focused on referral to and consultation by allied health professionals in a representative cohort of PD patients, and on the level of PD-specific expertise among a representative group of allied health professionals. The questionnaires were first field tested and optimized among 5 PD patients and 10 professionals. Final questionnaires were sent by mail and reminders were sent within 4 weeks. The local medical ethics committee approved the study.

Referral and Consultation

Subjects

All patient records of two large medical centers that jointly cover the entire catchment area of Nijmegen (±230.000 citizens; ±225 km^2)[8] were screened. We approached all patients with idiopathic PD according to the Gelb et al.[9] criteria with Hoehn and Yahr[10] stage I–IV, living independently in the community. Questionnaires were sent to 260 eligible patients, and 217 (83.1%) questionnaires were returned. Of the participants, 66% were men, the mean age (±SD) was 66 (±10.2) years and mean disease duration was 7 years (±6.1).

Questionnaire

The questionnaire contained 40 items concerning limitations in the performance of daily activities and participation, arranged into 12 domains (Table 1). These domains cover the core areas for physical therapy[11], occupational therapy,[6] and speech therapy[12,13] in PD. Furthermore, patients were asked to report the number of falls in the preceding year and whether they utilized allied health care to prevent falls.

Analysis

For each domain, patients rated: (1) whether they perceived problems in performance of an activity on a five-point scale (from 0 = "no problems" to 4 = "severe problems"); (2) whether they wanted to improve this symptom on a five-point scale (0 = "not willing to improve" to 4 = "very much willing to improve"); and (3) whether allied health care was used to improve the problems on these specific domains. The perceived problems were defined as a "patient-relevant problem" if rated "2", "3," or "4" on both "problem in the performance of an activity" and on "willing to improve the problem" for a specific domain. Frequencies were calculated for patient-relevant problems. We calculated the proportion of patients with a patient-relevant problem that consulted allied health care.

Professional Expertise

Subjects

All physical therapy (n = 197), occupational therapy (n = 22), and speech therapy (n = 79) practices located in the catchment area of Nijmegen were approached. Questionnaires were returned by 198 (66%) allied health care professionals. Eighty-three professionals were excluded from the analyses, because they had not treated any PD patients during the previous year. A total of 115 questionnaires (86 physical therapy, 12 occupational therapy, and 17 speech therapy) were used for final analyses.

Questionnaire

Questionnaires contained items concerning work setting, work experience in years, the number of PD patients treated yearly, PD-specific education, perception of expertise in treating PD patients, and familiarity with treatment options for PD by other professionals.

TABLE 1. *Patient-perceived relevant problems and the consultation of allied health care to counteract these problems*

Domain	Patient relevant problems* (n = 216)	Allied health care utilized for relevant problems**			
		% PT	% OT	% ST	% No AHC
Arm/hand activities[a]	118 (54.6%)	23.7	1.7	1.7	72.9
Gait	116 (53.7%)	66.4	2.6	–	35.3
Transfers	115 (53.2%)	56.6	2.7	–	45.1
Balance	103 (47.7%)	56.4	2.0	–	44.6
Posture	98 (45.4%)	61.9	2.1	–	39.2
Leisure activities	89 (41.2%)	21.3	–	–	78.6
Speech	80 (36.9%)	–	–	20.0	80.0
Personal care	79 (36.6%)	–	2.6	–	97.5
Domestic activities	78 (36.0%)	–	1.3	–	98.7
Work activities	70 (32.4%)	20.0	1.4	2.9	75.8
Drooling	66 (30.6%)	–	–	6.1	95.4
Eating	43 (19.9%)	–	–	9.3	90.7

*Patient relevant problem, problem in both the performance of an activity and willing to improve this activity.
**Percentage of number of patients with relevant problems.
[a]Including reaching and grasping.
PT, physical therapy; OT, occupational therapy; ST, speech therapy; AHC, allied health care.

Analysis

The perception of PD-specific expertise and familiarity with treatment options by other professionals were rated using a five-point scale (0 = "insufficient" to 4 = "very good"). Allied health professionals were categorized into "specific expertise" if rated "3" or "4" on PD-specific expertise, and defined as "familiar" if they rated "3" or "4" on familiarity with the treatment options of other professionals. Descriptive statistics were then performed for those with and without PD-specific expertise.

RESULTS

Referral and Consultation

At the time of the questionnaire, 62.5% of the patients used physical therapy, 8.5% occupational therapy, and 14.4% speech therapy. The patient-relevant problems and any utilization of allied health professionals for these specific problems are presented in Table 1.

Physical therapy was mostly aimed at relevant problems in the domains of gait, posture, transfers, and balance (range, 66.4–56.4%). Only about 3% of the patients utilized occupational therapy for relevant problems concerning arm and hand activities, gait, transfers, balance, posture, leisure activities, personal care, domestic activities, or work activities. Speech therapy was utilized mostly for speech and voicing problems (20.1%) and less often for problems concerning eating and drooling (range, 9.3–6.1%).

Nearly 60% of patients reported at least one fall in the preceding year, but only 33% of these patients received physical therapy or occupational therapy to prevent future falls.

Fifteen patients used physical therapy without having a patient-relevant problem. This was not the case for speech or occupational therapy.

Professional Expertise

The expertise of allied health professionals is presented in Table 2. More than 75% of the allied health professionals reported a lack of PD-specific expertise, even though these professionals were treating most of the PD patients. Allied health professionals with sufficient PD-specific expertise treated more patients in the previous year, than those without (physical therapy 7.0 versus 3.3, occupational therapy 9.3 versus 3.2, and speech therapy 4 versus 3.1). No differences were found for professional setting or number of years of working experience between professionals with and without PD-specific expertise. More than 50% of the allied health professionals were unfamiliar with the treatment options of other professionals and had not followed educational programs concerning PD.

DISCUSSION

This study demonstrates that PD patients often do not utilize allied health care, despite having relevant problems that are potentially amenable to therapeutic intervention. Furthermore, if patients are being referred to allied health care, they are typically treated by professionals without sufficient PD-specific expertise.

TABLE 2. *Characteristics of allied health care professionals categorized into specific PD expertise (experts) and no specific PD expertise (non-experts)*

	Physical therapists (n = 86)*		Occupational therapists (n = 12)		Speech therapists (n = 17)	
Professional characteristics	Experts	Non-experts	Experts	Non-experts	Experts	Non-experts
N (%)	17 (19.8)	66 (80.2)	3 (25.0)	9 (75.0)	3 (17.6)	14 (82.4)
PD patients treated, number (%)	119 (35.4)	217 (64.6)	28 (49.1)	29 (51.9)	12 (21.8)	43 (88.2)
Work setting[a]						
Primary care (%)	100	100	33.3	0	66.7	50.0
Institutional care (%)	17.6	6.1	100	100	66.7	50.0
Work experience in years, mean (±SD)	21.2 ± 7.0	18.6 ± 8.1	9.7 ± 2.5	10.8 ± 11.4	17.7 ± 5.7	16.5 ± 9.8
PD patients treated yearly, mean (±SD)	7 ± 7.4	3.3 ± 2.7	9.3 ± 6.0	3.2 ± 1.0	4 ± 1.7	3.1 ± 2.7
% Education on PD	35.3	10.6	0	22.2	66.7	14.3
Familiarity with other treatment options						
Familiar with speech therapy (%)	35.3	6.1	33.3	0	66.7	7.1
Familiar with occupational therapy (%)	47.1	4.5	33.3	0	33.3	7.1
Familiar with neurological treatment (%)	35.3	19.7	66.7	0	66.7	0
Familiar with PD nurse specialist (%)	17.6	1.5	33.3	0	33.3	0

*Three missing cases.
[a]Professionals can work in both settings.

Referral and Consultation

In line with previous studies, we found that patient-relevant problems of PD patients were often not treated by allied health professionals.[7,14,15] This may be relevant, as there is increasing evidence for the benefit of allied health care; e.g., to introduce compensatory strategies to improve gait or transfers.[4,16] When patients were referred, it was most often to a physical therapist. It may be that the most frequent patient-relevant problems fall within the domains that "traditionally" belong to physical therapy. Furthermore, most evidence is currently available for interventions within physical therapy.[1]

The low frequency of allied health consultations may be explained by a lack of referrals, or problems after referral. In Netherlands, neurologists are responsible for most of the allied health referrals,[5] and it is possible that neurologists are insufficiently aware of the indications for allied health care or lack time to screen for these indications. It is also possible that patients themselves decline referral to allied health professionals. In Netherlands, allied health care is compensated by the health insurance, so financial concerns are not a likely explanation. Our study was limited in the fact that we did not include neurologists or nurse specialists to inquire about the above issues.

Professional Expertise

In our survey, the professionals that perceived themselves as "PD-experts" did treat more patients per year than the nonexperts. However, the number of PD patients treated yearly by the experts was still low (<10 patients/yr per therapist) and this may explain why educational programs are scarce, why only a small number of professionals is participating in these programs and why only a small number of professionals is aware of the possibilities of other disciplines involved in the care of PD patients.

Conclusion

We recommend the development and implementation of evidence-based guidelines for speech therapy and occupational therapy, as was recently done for physical therapy.[11] This implementation may be facilitated by PD-specific health care networks, in which physicians and allied health professionals participate.[17] Feasibility studies for this concept have been performed for rheumatoid arthritis.[18] In the past 5 years, we have set up such PD-specific networks in large part of Netherlands. Within these networks, a selected number of professionals are specifically trained to use evidence-based guidelines, and patients are specifically referred to these dedicated professionals according to explicit protocols. This concept is currently being evaluated in a controlled, cluster-randomized trial for health benefits, cost-effectiveness, and guideline adherence.[17]

Contributor Roles: Research project: (1) Conception (SHJK, RABO, WM, BRB, MM), (2) Organization (SHJK, RABO, WM, BRB, MM), (3) Execution (SHJK, MM); Statistical Analysis: (1) Design (MM), (2) Execution (MM), (3) Review and Critique (SHJK, RABO, SO, BRB, MM); Manuscript: (1) Writing of the first draft (SHJK, RABO, SO, MM), (2) Review and Critique (RABO, SO, WM, BRB, MM).

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Microsubthalamotomy Effect at Day 3: Screening for Determinants

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Abstract: **A microsubthalamotomy (mSTN) effect has been frequently reported after implantation that improves Parkinson's motor disability. It is usually believed that mSTN effect reflects the post-traumatic tissue reaction within the STN. However, it has never, to our knowledge, been reported whether pre and intraoperative factors could predict this mSTN effect. Preoperative clinical characteristics, that is, age, disease duration, Mattis Dementia Rating Scale score, levodopa responsiveness, severity of motor fluctuations and dyskinesia, and intraoperative parameters, that is, the number of tracks, distance of typical STN neuronal activity recorded along all microelectrodes, and along the definitive electrodes, were assessed in 40 consecutive PD patients submitted for STN stimulation. Multiple stepwise regression analysis showed that only the number of tracks used for microelectrodes recordings was predictor of the contralateral mSTN effect ($F_{(4,73)} = 1.83$, $P = 0.02$). This result suggests that the contralateral mSTN depends on the tissue changes along the entirety of surgical trajectories affecting both STN and its adjacent structures.** © 2008 Movement Disorder Society

Key words: microsubthalamotomy; subthalamic nucleus; deep brain stimulation; Parkinson's disease

A microsubthalamotomy (mSTN) effect is often observed after implantation that improves transiently parkinsonian motor sign and symptoms.[1] Some authors have suggested that the presence of mSTN effect may predict the long-term efficacy of STN stimulation

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itself.[1,2] It is usually believed that the level of clinical motor changes due to mSTN depend mainly on the post-traumatic tissue reaction: (1) consecutive to the number of tracks affecting STN during the electrophysiological recordings; (2) along and in the vicinity of definitive electrodes. However, the parameters reflecting this post-traumatic reaction have not yet been accurately determined. Moreover, to our knowledge, it has never been reported whether preoperative clinical characteristics could influence the mSTN effect.

Then, the aim of this study was to determine whether preoperative clinical characteristics and intraoperative parameters correlate with the mSTN effect.

PATIENTS AND METHODS

Patients

Forty consecutive PD patients (24 men and 16 women), who were selected for bilateral implant of electrodes within the STN for high frequency stimulation in our centre between February 2004 and March 2008 were assessed. All patients were diagnosed with advanced levodopa-responsive form of the disease (Hoehn and Yahr score ≥ 3) with severe L-dopa-related complications despite optimal adjustment of antiparkinsonian medication. The mean disease duration was 11.6 (SD 3.8) years and age ranged from 37 to 71 years, with a mean age of 58.8 (SD 8.2) years.

Surgical Procedure

The radiological procedure started the day before surgery by mounting the stereotactic ring with local anaesthesia. Merging between stereotactic CT scan and T1 gadolinium, T2 spin echo and CISS sequences of the MRI were performed with the Stealth Station and the Framelink software. STN coordinates were derived from direct visualization of the structures in the T2-MRI sequence. The trajectory was determined in the contrast enhanced T1 sequence. The next morning, the surgery started in a patient free of medications, by focusing on the STN contralateral to the most affected side. Simultaneous microrecordings were performed starting 10 mm above the predefined target until the substantia nigra pars reticulata. The definitive quadripolar electrode was positioned to locate at least two contacts within the STN according to the best perioperative motor improvement and the fewest side effects. The whole procedure was repeated to implant the contralateral STN. The programmable pulse generator was implanted under general anaesthesia in the subclavicular region. Postoperative imaging (MRI, n = 25 or CT-scan, n = 15) was performed within 48–72 hours postoperatively.

Clinical Evaluation

A baseline clinical evaluation was performed based on the CAPIT protocol.[3] Preoperative clinical characteristics considered to be predictive of postoperative clinical improvement after STN stimulation were recorded.[4–6] The motor state was assessed by the Unified Parkinson's Disease Rating Scale motor disability score (UPDRS part III).[7] The scores for tremor (items 20-21), rigidity (item 22), bradykinesia (items 23, 24, 25, 26, and 31), axial motor features (items 18, 28, 29, and 30) were assessed separately using the corresponding UPDRS III sub-scores. The severity of the preoperative motor fluctuations (items 36–39) and dyskinesia (items 32–35) was assessed by the UPDRS IV.

The global mSTN effect was defined by the percentage improvement of UPDRS III baseline score assessed the third day morning following STN implantation, after at least a 12 hour withdrawal of dopaminergic treatment and before the programmable pulse generator was switched on (*off*-drug/*off*- stimulation).[2]

The contralateral mSTN effect was defined by the percentage improvement of composite unilateral sub-score, that is, sum of items for tremor, rigidity, and bradykinesia assessed on the contralateral limbs, using the UPDRS III.

Anatomical Extent of the mSTN: Intraoperative Parameters

Intra-operative parameters were related to: (1) the brain tissue affected by electrophysiological recordings: mean $\pm$ SD number of tracks used for microelectrode recording; (2) the anatomical extent of the STN affected by tracks during the microelectrode recording: mean $\pm$ SD number of trajectories over which typical STN neuronal activity was recorded; and the mean $\pm$ SD distance (expressed in μm) over which typical STN neuronal activity was recorded along all microelectrodes; (3) the anatomical extent of the STN affected by the definitive electrode: mean $\pm$ SD distance (expressed in μm) over which typical STN neuronal activity was recorded along the trajectory selected to implant the definitive electrode of stimulation.[8]

To assess the correlation between intraoperative parameters and global mSTN effect, we added the parameters of the both hemispheres for each patient.

Statistical Analysis

The different changes of score were expressed as mean value. Statistical analysis was performed with the *STATISTICA version 7.1, StatSoft*®, France.

Firstly, the preoperative clinical characteristics, that is, age, disease duration, Mattis Dementia Rating Scale

TABLE 1. *Improvement of Parkinsonian features after microsubthalamotomy (n = 40 patients)*

Parkinsonian motor disability	Baseline	After mSTN
UPDRS part III	40.5 ± 10.8	30.5 ± 13.6
Tremor	4.8 ± 4.1	2.8 ± 3.8
Rigidity	8.8 ± 3.5	5.7 ± 3.6
Bradykinesia	18.5 ± 6.4	14.3 ± 6.8
Axial motor features	6.1 ± 2.5	5 ± 2.7

Values are expressed as mean ± SD.

The scores for tremor (items 20-21), rigidity (item 22), bradykinesia (items 23, 24, 25, 26, and 31), axial motor features (items 2, 28, 29, and 30) were assessed separately using the corresponding UPDRS III sub-scores.

score, L-dopa responsiveness, severity of motor fluctuations and dyskinesia, and the intraoperative parameters (sum for both hemispheres, n = 40 patients) were included in stepwise multiple regression with the threshold of 0.05 to determine which were predictive of the global mSTN effect.

Secondly, the different unilateral intraoperative parameters were included in stepwise multiple regression with the threshold of 0.05 to determine which were predictive of the contralateral mSTN effect (n = 80 hemispheres).

RESULTS

Improvement of Parkinsonian Features after Microsubthalamotomy

All the postoperative cerebral images were normal. The global mSTN effect improved the total preoperative *off*-period motor score (UPDRS part III) by 19% (range, 3–90%). When compared with baseline (*off*-state), the sub-score for tremor improved by 47% (range, 11–100%), rigidity by 34% (range, 10–100%), and bradykinesia by 17% (range, 8–95%). The preoperative *off*-state axial motor features remained almost unchanged (Table 1).

No Correlation between Global mSTN Effect, Preoperative Clinical Characteristics, and Intraoperative Parameters (N = 40 patients)

Microelectrodes recordings were performed on 9.4 ± 1.4 (range, 6–10) tracks. Typical STN neuronal activity was recorded: along 5.6 ± 1.4 (range, 2–8) trajectories of the microelectrodes; over a total distance of 2,3615 μm ± 8,897 μm (range, 3,500–3,8000) along all microelectrodes. The mean distance over which typical STN neuronal activity was recorded along the trajectory of the definitive electrodes was 7,936 μm ± 2,014 μm (range, 3,500–11,500). The multiple regression analysis (F (11,25) = 0.56, $P = 0.84$) failed to select preoperative clinical characteristics and intra-operative parameters significantly associated with the global mSTN effect.

Correlation between Unilateral Intraoperative Parameters and Contralateral mSTN Effect (N = 80 hemispheres)

Microelectrodes recordings were performed on 4.7 ± 0.7 (range, 3–5) tracks. Typical STN neuronal activity was recorded: along 2.8 ± 0.8 (range, 1–5) trajectories of the microelectrodes; over a total distance of 11,808 μm ± 5,861 μm (range, 1,000–23,000) along all microelectrodes. The mean distance over which typical STN neuronal activity was recorded along the trajectory of the definitive electrode was 3,968 μm ± 1,234 μm (range, 1,000–6,000). Multiple stepwise regression analysis showed that only the number of tracks correlated significantly with the contralateral mSTN effect [F (4,73) = 1.83, $P = 0.02$].

DISCUSSION

It is commonly believed that the mSTN effect reflects the microlesion following intraoperative electrophysiological recordings and oedema spreading within the subthalamic area.[1,2] Because it improves parkinsonian motor disability, it is also considered to be an obvious sign of good placement of the definitive quadripolar electrode within the sensorimotor portion of the STN.[1] We hypothesized that mSTN effect could be influenced both by intraoperative parameters reflecting the microlesion effect and by preoperative clinical characteristics.

Inclusion criteria for the PD patient submitted to surgery in our centre followed recommendations based on previous studies demonstrating that age, disease duration, L-dopa responsiveness, and cognitive performance were the optimal predictive factors of STN stimulation.[4] Therefore, our population of PD was biased toward younger patients with good L-dopa responsiveness and preserved cognitive performance. Thus, it may be the first explanation for the lack of correlation between clinical characteristics and global mSTN effect. Then, one may consider that mechanisms underlying STN stimulation differ in part from those involved by mSTN effect. In fact, STN stimulation may result not only in direct inhibition of STN neurons but also to excitation of myelinated fibres passing in the vicinity of the subthalamic area.[9–13] On the contrary, the mSTN effect is essentially related to inhibition of subthalamic neurons.[13]

While we found no correlation between intraoperative parameters and global mSTN effect, the number of tracks used for unilateral recordings predicts the contralateral mSTN effect. These results are in keeping with previous studies reporting no correlation between intraoperative electrophysiological recordings and STN stimulation efficacy.[8] In addition, our results suggest that the unilateral mSTN effect depends on the tissue changes along the entirety of surgical trajectories affecting both STN and its adjacent structures.

Few histopathological studies, concerning PD patients treated by high frequency stimulation of the STN, have been reported.[14–16] The track of the definitive electrode usually affected the white matter of the middle frontal gyrus, passing laterally to the ventricles, through the centrum semi-ovale, via the thalamus and the tip of the internal pallidum before reaching the dorsolateral sensorimotor region of the STN. Therefore, we hypothesized that the unilateral mSTN effect could be related to: (1) the direct inhibition of hyperactive neurons of the dorsolateral area of the STN; (2) the disruption of pallidal outflow coursing through the lenticular fasciculus and ansa lenticularis, dorsally to the STN, mimicking a micro-pallidotomy. These hypotheses are in accordance with previous studies demonstrating that unilateral subthalamotomy and pallidotomy improved contralateral parkinsonian features in advanced PD.[17–19] Further investigations considering both volumetric and anatomical definition of the microlesion are nonetheless required to identify the exact mechanisms involved in the mSTN effect.

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Mitochondrial DNA Haplogroups J and K are not Protective for Parkinson's Disease in the Australian Community

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Abstract: **MtDNA haplogroups J and K have been associated with a decreased risk of developing Parkinson's disease (PD). To confirm this finding, we compared the distribution of mtDNA haplogroups J and K in a large sample of Australian patients with PD (n = 890) to population-based controls (n = 3,491). We assigned subjects to haplogroups J or K using standard PCR/RFLP techniques. Of the 890 subjects with PD, 10.6% were haplogroup J (95% CI 8.6–12.8, n = 94) and 7.1% were haplogroup K (95% CI 5.5–8.9, n = 63). In our controls, 10.2% belonged to haplogroup J (95% CI 9.2–11.2, n = 356), and 7.8% were in haplogroup K (95% CI 6.9–8.7, n = 272). There was no significant difference in the prevalence of mtDNA haplogroup J or K in PD patients compared to population-based controls. Our findings indicate that mtDNA haplogroups J and K are not associated with a lower risk of PD.**

Key words: Parkinson's disease; mitochondrial DNA haplogroups; prevalence

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Mitochondrial DNA (mtDNA) is highly polymorphic in the general population and is transmitted almost exclusively through maternal lineages. Specific single nucleotide polymorphisms in mtDNA have accumulated and persisted along maternal lineages and as a consequence, the human population can be divided into different haplogroups.[1] Three ethnically distinct lineages of human mtDNA populations have been identified: European, characterized by nine haplogroups H, I, J, K, T, U, V, W, and X; African, characterized by superhaplogroup L; and Asian, characterized by superhaplogroup M. The mtDNA haplogroup analysis is now used world-wide for studying human history and population dynamics and for exploring mitochondrial and nuclear mutations. Certain mtDNA polymorphisms have been suggested to be protective against the development of Parkinson's disease (PD);[2,3] in particular, haplogroups J and K.[2,4] It has been proposed that genetic polymorphisms within the mitochondrial genome may act as susceptibility factors and contribute to the expression of PD either directly or through the interaction with nuclear encoded genes or environmental toxins.[2] Another explanation for the protective effect of haplogroups J and K in these earlier studies[2,4] was that a single polymorphism or group of polymorphisms may enhance respiratory chain function within the substantia nigra neurons conferring a reduced risk for PD.[4] This hypothesis is yet to be confirmed by functional studies. Confusingly, other mitochondrial haplogroups, such as the JT and JTIWX clusters have been reported to be associated with an increased risk of developing PD.[5,6]

In this study, we aimed to confirm the association between mtDNA haplogroups J and K with PD. We therefore determined the frequency of mtDNA haplogroups J and K in a large sample of patients with PD, and compared the frequency of mtDNA haplogroups in population-based age and sex-matched controls from the Australian community.

SUBJECTS AND METHODS

A total of 890 unrelated white patients with PD were included in this study. DNA samples were obtained from two established Australian PD DNA banks (125 cases from New South Wales and 765 cases from Queensland). There were 521 males and 362 females. Mean age was 70.5 (SD 10.7) years. To eliminate the possibility of including undiagnosed autosomal recessive genetic forms of PD, we included only

patients with PD onset over the age of 45 years. Experienced neurologists with clinical expertise in movement disorders examined all subjects (DB, PS, and CS). All patients with PD had at least two canonical signs of PD (tremor, bradykinesia, or rigidity) and no other clinical features to suggest any other parkinsonian syndrome.

For our control cohort, we studied a population-based sample of 3,491 whites aged 45–98 years that had been clinically studied in the Blue Mountains Eye Study[7] (BMES). There were 1,500 males and 1,991 females. We collected clinical information and performed clinical examinations on all NSW controls. Mean age of controls at entry of the study was 66.6 (SD 9.5) years. Human Research Ethics Committees for each institution approved the study.

Total DNA was extracted from blood or hair follicles[8] from all patients with PD and controls. MtDNA haplogroup analysis for the control population was performed as part of a previously published study[1] using standard PCR/RFLP-based techniques. The BMES controls were selected because they were representative of an older Australian population. In this study, assignment to mtDNA haplogroups J or K for the PD patients was performed using standard PCR/RFLP techniques as previously described.[1] The mtDNA haplogroup frequencies between patients and controls were compared using the chi-square test, and 95% confidence intervals (CI) were calculated.

RESULTS

We found no significant difference in the frequencies of mtDNA haplogroup J or K in PD patients compared to control subjects (Table 1). Of the 890 subjects with PD, 94 were identified as haplogroup J (10.6%, 95% CI 8.6–12.8) and 63 as haplogroup K (7.1%, 95% CI 5.5–8.9) (Table 1). This was comparable with that 356 of the 3,491 controls with haplogroup J (10.2% 95% CI 9.2–11.2) and 272 of control subjects with haplogroup K (7.8%, 95% CI 6.9–8.7). In addition, when we pooled the number of subjects in both haplogroup J and K together and compared PD and control subjects of these pooled groups, we also did not find any significant differences (PD—17.6% (CI 15.1–20.1), BMES controls—18.0% (CI 16.7–19.3). The power of our study using a case to control ratio of 1:3 was estimated to be between 85 and 90%.

TABLE 1. *Frequencies of mtDNA haplogroups J and K in PD patients and control subjects*

	Parkinson's disease (n = 890)			BMES controls (n = 3,491)		
Haplogroups	n	%	95% CI	n	%	95% CI
Haplogroup J	94	10.6	8.6–12.8	356	10.2	9.2–11.2
Haplogroup K	63	7.1	5.5–8.9	272	7.79	6.9–8.7

n, number; %, percentage; CI, 95% confidence interval.

DISCUSSION

MtDNA haplogroups J or K were not found to be associated with a reduced risk of developing PD in this large sample of Australian patients and population-based controls. Given the large number of cases and the use of population-based controls, our study has greater study power than most previous studies and should be able to detect small differences in the distribution of mtDNA haplogroups J or K between PD cases and controls. Our findings highlight the need for caution in interpreting results from genetic association studies with small sample sizes.

Mitochondrial haplogroups J and K belong to different mitochondrial clades. Haplogroup J is a clade within haplogroup T and haplogroup K within haplogroup U.[9] Individual haplogroups can differ from each other in the average number of nonsynonymous mutations.[5] Both higher[2,4] and lower[5,9] frequencies of haplogroup J and K have been reported in PD cohorts. However, all previous studies were conducted in either relatively small samples with small or disease-based rather than population-based controls,[2–6,9] and their final results have been inconsistent. Firstly, Van der Walt et al.[2] studied 609 PD cases and 340 control subjects, finding that the frequency of haplogroups J and K, relative to the most common haplogroup H, was significantly less common in PD cases. The reduced frequencies of haplogroup J and K in that study[2] only reached statistical significance when referencing to the frequency of haplogroup H. Furthermore, they also found that the 10398A>G polymorphism defining European haplogroups J, K, and I were associated with a reduced likelihood of PD.[2] However, an Italian study of 620 PD patients replicated the reduced frequency of haplogroup K in PD patients, but found no association between PD and haplogroup J or the10398A>G polymorphism.[9]

Moreover, a British study[4] investigating 455 PD patients was unable to confirm the protective effects of

haplogroup J and K when each haplogroup was considered separately. However, by comparing the frequency of the pooled haplogroups U, J, K, and T, they reported a statistically significant lower prevalence of mtDNA haplogroup cluster UJKT in patients with PD. We were unable to confirm this finding after pooling these haplogroups in our study.

Minor variations in different ethic backgrounds of the study samples may partly explain the discrepancy in our study findings, given that mtDNA sequence diversity may vary greatly between different ethnic populations.[5] However, while it is possible that there may be ethnic differences in our Australian cohort, the prevalence of mtDNA haplogroups within our population was similar to other Caucasian samples.[1] Discrepancies between the results of different studies may also in part be explained by potential selection bias of the control groups, given that some clinic-based controls suffered from neurodegenerative disorders rather than using a population-based sample, as was the case in our study.

In conclusion, our study found that mtDNA haplogroups J and K are not associated with a lower prevalence of PD. Our study highlights the importance of eliminating potential selection bias using large sample sizes and population-based controls, to ensure adequate study power and validity of comparisons between cases and controls. We believe that replication of study findings in different populations with appropriate controls is essential to confirm any genetic associations. Functional analysis of specific mitochondrial haplogroup subclades may not necessarily provide a better understanding of the contribution of mitochondrial dysfunction in subjects with PD given that this association has been brought into question.

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Atypical Dystonic Shoulder Movements Following Neuralgic Amyotrophy

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Video 

Abstract: **Peripherally induced movement disorders are relatively rare. Here, we present 3 patients who suffered a lesion of the brachial plexus because of neuralgic amyotrophy and developed involuntary movements of their shoulder muscles. The nature of the involuntary movements, which did not easily comply with classic descriptions of hyperkinetic movement disorders, is probably best referred to as dystonia.** © 2008 Movement Disorder Society

Key words: dystonia; dyskinesia; shoulder; neuralgic amyotrophy

Both hyperkinetic and hypokinetic movement disorders can be present in patients with a central nervous system lesion, particularly if the lesion involves the basal ganglia or their output tracts.[1] In contrast, movement disorders in the context of a peripheral nervous system lesion are less frequently encountered.[2–6] The mechanisms underlying such peripherally induced movement disorders are not fully understood and are under continuous debate.[7,8] Here, we present 3 patients who developed involuntary movements of their shoulder muscles following neuralgic amyotrophy (NA) (idiopathic brachial plexus neuropathy).

CASE HISTORIES

Case 1

A 40-year-old man, who had undergone back surgery (thoracic spondylodesis) because of scoliosis 22 years ago, visited us because of a painful right shoulder. Two years earlier, he had developed acute, severe pain in his right shoulder, which then spread to his left shoulder, without any weakness. In the following 2 years, he developed two new attacks of right-sided shoulder pains, which extended to his right upper arm and which were then accompanied by weakness and atrophy of that arm.

Neurological examination showed bilateral (yet mainly right-sided) atrophy and weakness of the following muscles: supraspinatus, infraspinatus, biceps brachii, triceps brachii, trapezius, and anterior serratus. Sensory examination and tendon reflexes were unremarkable.

Concentric needle EMG showed chronic neurogenic abnormalities without spontaneous activity in the affected muscles on the right side, compatible with a diagnosis of mainly upper brachial plexopathy because of NA. He underwent rehabilitation and was discharged from our outpatient clinic. Two years later, he was reevaluated because he had developed involuntary movements of his shoulder muscles a few months after another NA attack of his left arm. In the resting position, we only observed a marked midline skin fold between the shoulder blades. Upon or following arm movements, involuntary slow, painful contractions of the rhomboid and teres major muscles emerged causing adduction of the shoulder blades (right more than left) (video 1) accompanied by a retrocollis. Tactile stimuli provoked similar but more brisk movements. A diagnosis of peripherally induced dystonia was made. The patient recently received his first treatment with botulinum toxin (Botox® 200 mouse units) injections in the rhomboid muscles on both sides, which resulted in a significant decrease of the pain and to a lesser extent of the dystonic movements.

Case 2

This 65-year-old man came to us because of involuntary movements of his right shoulder. His medical

Additional Supporting Information may be found in the online version of this article.

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history revealed treatment for prostate cancer and a traumatic brain injury not leading to any objective permanent neurological damage.

He first had slowly progressive right shoulder pains and accompanying weakness 2 years earlier. He mentioned that the involuntary movements of his right shoulder occurred after five massage therapies for his NA-related pains, and by the time of his visit to our outpatient clinic, these movements were almost continuously present.

On neurological examination, there was winging of the right scapula and mild weakness in multiple shoulder and arm muscles. Arm elevation provoked involuntary, relatively slow nonjerky contractions of the right major teres and atissimus dorsi muscles (see video 2), but without movement or posturing of the right scapula or right arm. The movements were absent at rest and were not provoked by tactile or acoustic stimuli. Motor-evoked potential studies showed a normal central conduction. A MRI of the cervical spine showed spinal canal stenosis without any abnormalities to the myelum. Concentric needle EMG showed chronic neurogenic abnormalities in several shoulder muscles (most notably in the serratus anterior and trapezius muscles), indicative of a lesion of the upper part of the right brachial plexus (left side was not examined during needle examination). There were no abnormal contractions at rest. Voluntary arm motion produced concurrent involuntary movements in the right teres major and latissimus dorsi muscles with bursts lasting up to 500 milliseconds, without any neurogenic abnormalities. In addition, involuntary movements of his left teres major and latissimus dorsi muscles were noted. A surface EMG was also performed; entrainment was negative. A diagnosis of peripherally induced dystonia was made. The patient declined further treatment, as the impact on his daily activities was mild.

Case 3

A 56-year-old man was referred to our outpatient clinic because of chronic pain and involuntary movements of his right shoulder, which had been present for years. His medical history revealed surgery 3 years earlier because of benign prostate hypertrophy. In a period of physical exercise (as a bricklayer), patient had developed nightly pains in his right arm 20 years ago, which had disappeared spontaneously in the course of 2 weeks. Three months later, he developed a heavy feeling in his right upper arm and, subsequently, he noticed difficulties in raising this arm. An orthopedic surgeon, whom the patient visited 2 years after the onset of the pain attack, had noted a movement disorder of the shoulder and described it as an abnormal scapulocostal rhythm. The complaints slowly progressed and, a year after the onset, he slowly developed a painless weakness of his left upper arm. Patient explained that these movements had been more or less present since the onset of the first attack, although he found it difficult to recall it precisely. His family history revealed that his daughter and several other relatives had suffered from NA.

At our visit to our outpatient clinic, we found normal neurological examination of sensory modalities and tendon reflexes. Motor examination showed reduced ability to fully abduct and anteflex the arms as well as bilateral winging of the shoulder blades due to paresis of the serratus anterior muscles. There was normal strength in the other arm and leg muscles. A diagnosis of hereditary NA was made on the basis of typical clinical phenotype and the positive family history. An EMG of the left deltoid and trapezius muscles showed polyphasic motor units. Needle EMG of the serratus anterior muscle was not done.

Multichannel surface EMG was performed, which showed continuous bilateral contractions in the trapezius, supraspinatus, rhomboid, and infraspinatus muscles. The contractions in trapezius and supraspinatus were less apparent when the patient rested his arms on his legs. In the resting position, there were involuntary movements of the periscapular, back, and neck muscles, which resulted in sinuous movements of the back and anteflexion of the head and upper trunk. Active or passive forward and lateral movements of the upper arm and cutaneous stimulation of the periscapular region provoked similar movements (see video 3). A diagnosis of peripherally induced focal dystonia was established. Physiotherapy and a muscle relaxant (dantrolene sodium 75 mg tid) were prescribed. This resulted in a reduction of his head and neck pains. Although there seemed to be a decrease in the involuntary movements, it was only short-lived and was only slight after the first injections of botulinum toxin bilaterally in the trapezius, supraspinatus, and rhomboid muscles (Botox® 200 mouse units). However, at follow-up, the patient was pleased with the botulinum toxin injection because the pain had decreased significantly.

DISCUSSION

We present 3 patients who developed involuntary movements of the periscapular muscles after a lesion

of the brachial plexus due to NA. In all patients, these involuntary movements were atypical and did not fit the classical description of a movement disorder. Therefore, the term "focal shoulder dyskinesia" is perhaps the most suitable. Yet for several reasons, we feel that these involuntary movements are better classified as a form of dystonia. First, the movements were composed of slow and prolonged muscle contractions that lead to sinuous movements and, particularly in cases 1 and 3, abnormal posturing. Second, the involuntary movements were provoked or aggravated by action. Third, there were no additional features that would, for example, suggest tics. Fourth, not all dystonic muscles were involved in the primary neurogenic lesion suggesting overflow, compatible with dystonia. Marsden and coworkers have described 5 patients with slow sinuous movements of shoulder muscles that resembled the involuntary movements in our cases.[9] They also concluded that the observed movements were not fully compatible with any recognized movement disorder, yet they suggested these may in fact "represent further examples of focal dystonias."

The initial clinical diagnosis in patient 2 was myokymia, but EMG showed focal contractions with a duration up to 500 milliseconds not compatible with the diagnosis. Spinal myoclonus was considered as it can consist of jerks that last for several hundreds of milliseconds, but these jerks are usually more rhythmic and occur in the setting of a spinal cord lesion.[2,9] The contractions of the two muscles (teres major and dorsal latissimus) did not result in any abnormal posturing, which could cast doubt on the "dystonia" label. However, the contractions in the nonaffected shoulder (overflow-dystonia) and the slow nature of these contractions are most compatible with a diagnosis of dystonia.

The following criteria to diagnose peripheral-induced movement disorders have been proposed[3]; (1) the trauma is severe enough to cause local symptoms for at least 2 weeks or requires medical evaluation within 2 weeks after trauma; (2) the initial manifestation of the movement disorder is anatomically related to the site of injury; and (3) the onset of the movement disorder is within days or months (up to 1 year) after the injury. In patient 3, it was not clear when the involuntary movements first occurred, as the patient could not recall it precisely anymore. However, the orthopedic surgeon had noted them 2 years after the onset of the peripheral damage. If this date is used as the time of onset of involuntary movements, this patient does not fulfill the proposed criterion of temporal relationship, i.e., onset within 1 year of peripheral damage. Still, we have chosen to label his movements as a peripheral-induced movement disorder, for several reasons. First, the temporal relationship mentioned is arbitrary. Second, the peripheral trauma was severe enough to have caused peripheral damage, which was confirmed by EMG. Third, there was a strong anatomical relationship between the movement disorders and peripheral damage. Both the second and third points fulfill the proposed criteria.

Patient 1 and 3 had the classical phenotype of NA as described in a large series of 246 patients with NA.[10] Patient 2 had a "nontypical" onset and course of the NA attack, as is seen in a minority of the NA patients. The prevalence of such involuntary movements following NA remains unknown. NA is an idiopathic neuropathy involving the brachial plexus and is generally associated with extreme pain and wasting of shoulder and arm muscles commonly leading to immobility of the affected extremity. Recently, one of the authors (NvA) has published the largest case series of NA, which included 246 patients.[10] In the database that presently contains data of 545 NA patients, the 3 presented here are the only patients that developed involuntary movements following their NA attack. However, because a systematic follow-up on the occurrence of movement disorders has never been conducted, we cannot exclude that more subtle movement disorders are present or will eventually develop in more patients.

Movement disorders that evolve in the setting of peripheral nerve injury are rare. A few case series have been published, mainly describing dystonia or myoclonus.[2–6] Most patients in these series developed a segmental dystonia after a traumatic injury of the peripheral nervous system. In many patients with (post-traumatic) peripherally induced dystonia, the dystonia is often fixed and painful.[5] Our patients mostly had mobile involuntary movements and in only 2 patients dystonic movements were accompanied by pain. Furthermore, the mobile character of the movements, the activation by action, the presence of overflow (case 3), response to tactile stimuli and botulinum toxin, and the relative mild severity not requiring treatment (case 2) are all features atypical for fixed dystonia.

The pathophysiological mechanisms of movement disorders after a peripheral nervous lesion are not fully understood and are subject of intensive debate.[7,8] Pain and limb immobility appear to be the most consistent predisposing factors associated with peripherally induced movement disorders, particularly with dystonia.[7] It has also been suggested that peripherally induced movement disorders result from a maladaptive central process, and that—given the rarity of these movements

disorders—predisposing genetic and environmental factors that act on these central mechanisms could play a role.[7,11] In our patients, however, there was no family history of movement disorders or consanguinity, no premorbid movement disorder, and no prior use of dopamine receptor blocking agents. One patient had a positive family history for NA, but none of the affected family members has developed similar involuntary shoulder movements. The response to tactile stimuli and the overflow (case 2 and 3) do favor a central component as a result of central maladaptation. A surgical implant at the level of the thoracic vertebral column used for correction of the scoliosis in case 1 might have been a peripheral mechanical trigger of such a central maladaptation.

Although the movement disorders in our patients could have had a nonorganic origin, the patients had no relevant psychological history and we could not find any other signs that suggested a functional basis. Additionally, entrainment and distractibility were not present in any of the patients.

In conclusion, focal or segmental dyskinesias of the shoulder can be encountered in patients with a prior inflammatory lesion of the upper brachial plexus. These movements are probably best classified as dystonia, although some features remain atypical. The histories of our patients suggest a peripheral origin of the involuntary movements. Two-third of the patients with NA develop skeletal pain in the paretic or compensating muscles caused by scapular instability. This pain can be a sensory trigger and could contribute to the development or further spread of dystonia, but unknown central processes most likely play a modifying role.

LEGENDS TO THE VIDEO

Case 1. Segment 1: At rest there is a prominent midline skin fold. Segment 2: Dystonic movements with adduction of the medial borders of the scapula on both sides, which are more pronounced on the right side, are provoked by action. Segment 3: Tactile stimulation provokes similar dystonic movements.

Case 2. Segment 1: During multichannel surface EMG polymyographic recording, no abnormal movements are noted at rest. Segment 2: Slow contractions of the right teres major and dorsal latissimus muscles (and transient contractions on the left side) are noted during anteflexion of the arms. There is no clear abnormal posturing.

Case 3. Segment 1: At rest there are no abnormal movements. Segment 2: Passive abduction and exorotation of the shoulder and cutaneous stimulation of the periscapular region provoke sustained contractions of the periscapular, back, and neck muscles leading to sinuous movements and distortion of the posture.

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Reverse Sensory Geste in Cervical Dystonia

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Video 

Abstract: **Sensory gestes (SG) are a pathognomonic sign of dystonia, which can be detected in up to two thirds of patients with cervical dystonia (CD). They reduce dystonia severity markedly but transiently. We report a patient whose CD substantially worsened with sensory input to the back of the head and neck in different body postures, a phenomomen recently termed "reverse" sensory geste (rSG) in craniocervical dystonia. In a cohort of CD outpatients, screening for "reverse" effects of SG on dystonia yielded a prevalence of 12.8% (n = 6/47). The most frequent rSG pattern was increased dystonic activity in a supine, resting position while trying to fall asleep. The response to rSG persisted throughout the course of the disease arguing for an impairment of central integration of neck proprioception. Assessment of rSG should be included in the routine examination of CD patients, since BTX treatment may have to be adjusted accordingly to be efficacious.** © 2008 Movement Disorder Society

Key words: Key words: cervical dystonia; reverse geste antagoniste; botulinum toxin A; sensory trick.

Cervical dystonia (CD) is characterized by involuntary tensioning of neck muscles, which leads to tonic or phasic head movements. Typically, CD is exacerbated by activities like walking, by stress or fatigue.[1,2] In more than two thirds of patients a reproducible but transient reduction of dystonia severity is accomplished by slightly touching face or neck, a manoeuvre called sensory geste (SG, "geste antagoniste").[3–5] If SGs are present, the spectrum of these manoeuvres is broad and not restricted to a single trick.[3,6,7] Even the imagination of a SG may decrease dystonic muscle activity.[6] SGs seem to be particularly prevalent among patients with age at onset below 32 and persist throughout the course of the disease.[8]

By EMG-polygraphy two types of geste-induced polymyographic patterns could be observed: either a decrease in recruitment density and amplitude in at least one dystonic muscle or an increased tonic muscle activation in phasic CD.[3] In severe forms of CD, SG can be ineffective and be replaced by forceful counterpressure, so called "forced tricks."[4] The exact pathophysiological correlate of SG in CD has yet not been detected.

Recently, a single patient with segmental craniocervical dystonia associated with Parkinson's disease was reported, in whom sensory input from a ribbon attached to the patient's glasses triggered dystonia.[9] The authors termed this phenomenon "reverse sensory geste" (rSG).

We report on a patient, who presented with marked worsening of her head torsion by different sensory gestes to the back of the head and the neck. The prevalence of similar rSG was assessed in a cohort of outpatients with CD.

PATIENTS AND METHODS

Patients with idiopathic CD from a dystonia outpatient clinic were offered to participate in this study. All patients gave their informed consent prior to participation. Patient characteristics are summarized in the Table 1. Patients were interviewed with a standardized questionnaire focussed on gestes and the influence of different body postures including a supine position on dystonia severity. All patients were on regular botulinum toxin treatment at the time of assessment and examinations were scheduled at least 3 months after their last botulinum toxin injection, including an assessment of CD severity in a recumbent position.

As reported previously,[3] patients were classified according to the complexity of head deviation and to the predominance of phasic or tonic head movements

Additional Supporting Information may be found in the online version of this article.

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TABLE 1. *Patient characteristics of 47 patients with cervical dystonia (CD)**

Characteristics	Number or median	Percentage or range
Female : male ratio	27/20	1.35 : 1
Age at onset (yr)	37	10–67
Age at examination	44.4	15–77
Disease duration	7.7	8–38
Reverse sensory geste (rSG)	6	12.8
rSG in supine position	5	10.7
Impact of rSG[a]	1.33	1–2
Spontaneous Tsui-score	9.7 ± 3.5	3–19
Clinical pattern		
Simple type	34	72.3
Complex type	13	27.7

Simple type: predominant head deviation in one plane with max 15° deviation in both other planes. Complex type: head deviation over 15° in two or more planes.

[a]Clinical features of this cohort have been in part reported by Muller et al.[3]

*0 = no worsening, 1 = mild to moderate, 2 = severe increase of dystonia.

similar to the scale published by Tsui.[10] The magnitude of the worsening of dystonia by reverse sensory tricks was subjectively assessed with a three-point scale (0 = no worsening, 1 = mild or moderate worsening, 2 = severe increase of dystonia).

Case Report

A 52-year-old woman was referred to our dystonia clinic 10 months after the onset of involuntary head torsion to the left and slight head tremor. From the start, she experienced substantial worsening of her head torsion while leaning her head on a backrest or when trying to fall asleep in a supine position. Over time, her attempts to doze off took up to 2 hours and she tried to sleep in an upright, almost sitting position. The patient's mother suffered from dystonic no-no head tremor since the age of 60 years. Tetrazepam (25–50 mg/day) and trihexyphenidyl (2–4 mg/day) showed mild but continued symptomatic relief. By cranial MRI and laboratory testing including urine copper, causes of secondary CD were excluded.

Examination at rest detected an irregular, horizontal dystonic head tremor but only mild torticollis to the left. Visual control but not sensory gestes like touching the face stabilized her head transiently in a near-neutral position. In contrast, several different manoeuvres markedly increased her torticollis, like closing her eyes, touching her neck by an examiner, leaning against a wall with the back of the head, lying on a couch (Tsui Score at baseline: 4, see the video). Correspondingly, surface EMG registration demonstrated immediate increase of activity of sternocleidomastoid muscle on the right and splenius capitis muscle on the left side.

Injections with BTX A (for details see Supp. Info. Table) including the trapezius muscles initially led to a paradoxical increase of head torsion and tremor starting immediately after injection and lasting up to 6 weeks.

Only the third BTX A injection of 460 MU (Dysport, Ipsen Pharmaceuticals) was successful and the patient was able to fall asleep supine only after a few minutes. After injection, rSG caused only mild involuntary head torsion to the left on rare occasions (Tsui score after injection: 2). On five follow-up injections using the same regimen of BTX A, therapeutic responses for 10 to 11weeks were observed.

Prevalence of Reverse Sensory Gestes in a Dystonia Clinic

Forty-seven of fifty consecutive primary CD outpatients with predominant rotatory CD were systematically assessed for clinical features of reverse sensory gestes.

Forty-one demonstrated improvement of head mobility and a reduction of dystonia severity of at least 30% measured on the Tsui score. Six patients (12.8%) reported a triggering of dystonic muscle activity by slightly touching the neck or the occipital region. On examination two of these patients had no head torsion during standing or unassisted sitting, but torticollis (up to 30–40°) started immediately after touching the back of the head or after contact of the head to a backrest. The remaining four patients showed mild retrocollis (~10°) after sensory input to the occiput during sitting.

Five of 47 patients (10.6%) showed a worsening of CD in a recumbent position, imitating falling asleep in bed. Two patients as during sitting displayed an increase of head torsion (up to 40°), whereas the three remaining patients showed phasic retrocollis with a constant urge to recline the head. Accordingly, all of these patients reported moderate to marked problems falling asleep due to an increase of dystonic head movements. Therefore, this subgroup of CD patients had a clinical presentation with rSG similar to the index patient presented.

DISCUSSION

Previous reports on factors influencing CD severity mostly focused on "classical" sensory gestes (SG).[1] Effective SGs are mainly located bilaterally in the facial region.[3,5] Touch to the back of the head is effective in less than 5% of CD patients,[3] suggesting impor-

tant differences between the integration of sensory input from different regions of the head and neck.[3] Aggravating factors of CD have been addressed only rarely[2,11]: unspecific activation of motor networks induced by running or writing worsens head torsion in up to 60% of patients.

Wider et al. have recently described a PD patient, who experienced worsening of her craniocervical dystonia triggered by a ribbon attached to her glasses touching her face. They have proposed to term this phenomenon "reverse SG" (rSG).

We propose to adopt this term for the aggravation of CD by sensory input observed in our present study for the following reasons: (1) Like classical sensory gestes, the area of input is topographically defined. In our study rSGs have only been observed in the occipital region or the back of the neck. (2) In sitting patients, the aggravation occurred without changes of the body posture and could therefore be separated from mere postural influences. (3) Surface EMG registrations showed increased activity in rotatory or reclinatory neck muscles.

These clinical observations underline the importance of surface EMG registration and of systematic assessments for CD patients during activities like sitting, walking, lying, or bending the head.

Compared to ameliorating SG, CD patients with rSG may show different malfunctions of sensory integration. Based on EMG patterns of CD patients during the execution of SG and on the results of a PET study on CNS correlates of SG,[12] Schramm et al.[5] proposed a two-phase model for SG in dystonia. In a first step, the head position should be normalized by counter pressure or volitional antagonistic muscle activity. In our patients with rSG, maintenance of an almost neutral head position was grossly dependent on visual control, which apparently overrode the baseline sensory information from the neck.

Unlike the second phase of the SG model by Schramm, additional sensory information destabilized head control and triggered a continuous increase in dystonic muscle activity.

In our index patient and in two additional patients, injections of the trapezius/semispinalis muscles with BTX A paradoxically increased head torsion in the first weeks after injection similarly to touch to the back of the head. Whereas many CD patients experience improved head mobility by intrafusal effects early after BTX injections[13] in CD patients with rSG parallel mechanisms might worsen CD. The efficacy of BTX injections in these patients might be therefore only dependent on the location and the extent of extrafusal muscle paresis.

Bove et al.[14] studied sensory integration in CD patients by applying lateral continuous vibration to the sternocleidomastoid muscle and simultaneously recording stepping and postural responses. Patients in this study had lost response to lateralized proprioceptive neck input or they responded with the same orientation pattern regardless of the side stimulated suggesting central adaptation to sensory input from the neck in CD.

In contrast, rSGs in our patients did not habituate over a follow-up period of 2 to 10 years, suggesting distinctive defects in central adaptation. Further studies will be necessary to address the underlying neurophysiological correlates of this maladaptation.

LEGENDS TO THE VIDEO

"Reverse" sensory gestes (rSG) in CD. Video segments show worsening of head torsion in two different body positions only when the back of the head has contact to a leather cushion placed on the wall or during rest in a supine position. Surface EMGs of sternocleidomastoid muscles are recorded simultaneously.

Segment 1. For the first 10 seconds the patients holds her head freely with additional visual control. Afterward, the back of her head contacts a leather cushion and head torsion to the left increases as seen on the surface recordings of both SCM muscles. This phenomenon is demonstrated twice.

Segment 2. The patient leans the back of her head on a small cushion in a supine position. As in an upright position, EMG surface recordings of both sternocleidomastoid (SCM) muscles shows predominant activation of the right SCM for head torsion to the right. Left SCM shows dystonic cocontraction and bilateral tremulous EMG activity. On voluntary head torsion to the right muscle, activity is reversed but dystonic cocontraction persists. Because of the constant head drive, the patient was unable to sleep supine before adjustment of BTX A therapy.

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