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Clinical/Scientific Notes

Rivastigmine in the Treatment of Parkinsonian Psychosis and Cognitive Impairment: Preliminary Findings from an Open Trial

Paul J. Reading, PhD, MRCP,[1]* Anna K Luce, BSc,[2] and Ian G. McKeith, MD, FRCPsych[2]

[1]*Department of Neurology, Regional Neurosciences Centre, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom*
[2]*Institute for the Health of the Elderly, Wolfson Research Centre, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom*

Abstract: This open study assessed the ability of rivastigmine to treat the neuropsychiatric complications of advanced Parkinson's disease. In a group of 12 patients, hallucinations, sleep disturbance, and carer distress were all improved and cognitive performance significantly enhanced by the drug. © 2001 Movement Disorder Society.

A number of recent studies have documented the relatively high prevalence of psychotic symptoms in idiopathic Parkinson's disease (PD).[1–4] Hallucinations in particular affect approximately 30% of patients,[5–7] and are consistently associated with advanced age and the presence of significant cognitive impairment.[1–5] Severe sleep fragmentation, intrusive vivid nightmares, and disruption of rapid eye movement (REM) sleep patterns are also likely to be important factors.[8–11]

Attempts to treat psychosis and cognitive impairment in PD often present a considerable clinical problem. Atypical neuroleptic agents such as clozapine,[12] olanzapine,[13] and quetiapine[14] may be useful in alleviating hallucinosis but have no reported positive effects on cognitive function.[15] Agents such as olanzapine are also capable of worsening extrapyramidal symptoms at clinically effective doses.[16] It is also difficult to deduce the precise pharmacological mechanism of atypical neuroleptics, as this class of agents influences dopaminergic, serotinergic, and cholinergic systems.[17]

Regarding the pathogenesis of psychotic symptomology in PD, although dopaminergic agents may worsen or trigger hallucinations, several lines of evidence suggest that other factors may play a more primary role. In particular, the well-established cholinergic deficits in advanced PD may predispose to psychosis as well as producing many of the cognitive or attentional deficits seen in a significant proportion of cases.[18,19] Of potential relevance, cholinergic agents seem particularly effective at treating neuropsychiatric aspects of other neurodegenerative dementia syndromes, including dementia with Lewy bodies (DLB) and Alzheimer's disease.[20–25]

The potential use of cholinergic agents in PD may appear counterintuitive, given the modest efficacy of anticholinergic agents in relieving some of the physical symptoms (particularly tremor) when used early in the illness. However, a small open study using tacrine demonstrated significant improvement in cognitive status and psychotic symptoms in a group of advanced parkinsonian patients while actually improving their motor function.[23] An open exploratory study was therefore undertaken to investigate the tolerability and efficacy of the more recent pseudo-irreversible cholinesterase inhibitor rivastigmine in the treatment of psychotic symptoms and cognitive impairment in patients with established PD.

Patients and Methods

Fifteen consecutive patients from neurology outpatient departments in Newcastle upon Tyne and Sunderland, UK, who met the inclusion criteria for the study were screened for entry. Each patient had been initially diagnosed with idiopathic PD in the absence of overt cognitive or psychotic symptoms at least 2 years previously using the clinical criteria of the Parkinson Disease Society Brain Research Centre.[26] The key entry criterion for the study at screening was the presence of troublesome and recurrent hallucinations for at least the previous 3 months. The subjects were all required to be taking a stable medication regime that did not include neuroleptic nor anticholinergic agents. A reliable caregiver familiar with the patient's daily activities and night-time behaviour was also mandatory. Exclusion criteria were severe dementia, defined as Folstein Mini-Mental State Examination[27] (MMSE) scores of less than 10, the presence of significant urinary symptoms, and a history of cardiovascular disease or cardiac arrhythmia. The study was granted ethical approval and all patients and carers gave informed consent.

Throughout the study each patient was assessed thoroughly on five occasions including the screening session. Ten weeks following screening, rivastigmine at a dose of 1.5 mg twice daily was commenced (baseline session) and the dose titrated at 2-week intervals until either 6 mg twice daily or the highest tolerated dose was achieved. The patients were then assessed after 8 weeks of dose titration (high dose session) and once again when they had been taking the highest tolerated dose for 6 weeks (experimental session). At this point the drug was discontinued and a final fifth assessment undertaken 3 weeks later (withdrawal session).

At each assessment session the Folstein MMSE and the motor subscale of the Unified Parkinson's Disease Rating Scale[28] (UPDRS) were recorded as measures of overall cognitive ability and physical parkinsonian symptoms, respectively. Neuropsychiatric symptoms including hallucinations were measured using the Neuropsychiatric Inventory (NPI). The NPI is a vali-

*Correspondence to: Paul J. Reading PhD, MRCP, Department of Neurology, Regional Neurosciences Centre, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, NE4 6BE, UK.

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dated caregiver informant-rated measure of neuropsychiatric disturbance[29] that has been used in the assessment of a number of neurodegenerative conditions, including Alzheimer's disease[29] (AD), progressive supranuclear palsy,[30] corticobasal degeneration,[31] and Huntington's disease.[30] The NPI evaluates behaviours that have occurred in the 4 weeks preceding the evaluation by assessing in detail 12 separate symptom domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behaviours, sleep disturbance, and appetite changes. The presence of symptoms in each domain is initially assessed at interview by a summary screening question which, if answered by a positive response, invokes a more in-depth evaluation of specific behaviours within the domain. Items that have been identified are then collectively rated in terms of their frequency (1, less than once a week; 2, once a week; 3, several times a week; 4, every day) and severity (1, mild; 2, moderate; 3, severe). Severity ratings for each symptom domain are individualised with specific anchoring criteria. For each of the 12 domains rated on the NPI, the product of the frequency score (1–4) and the severity score (1–3) yields a symptom score (0 if absent; 1–12 if present). The total NPI score represents the sum of individual symptom scores (0 to a theoretical maximum of 144). In practice, total scores of around 20 or more correspond to highly significant neuropsychiatric disturbance.

The important aspect of carer distress was also recorded and scored for each neuropsychiatric symptom complex. The caregiver was asked to rate their own emotional or psychological distress caused by each symptom, if present (0, no distress; 1, minimal; 2, mild; 3, moderate; 4, moderately severe; 5, very severe). As with the total NPI score, a total carer distress score was obtained by summing the individual scores on the 12 items.

In view of the relatively small number of subjects and the non-normal distribution of the NPI data, nonparametric analysis was used throughout. For each measure, the key comparison between baseline and experimental sessions was assessed using the Wilcoxon signed ranks test (two-tailed).

Results

Full data were obtained on 12 patients, because three were forced to withdraw. Of these three, one died from septicaemia, thought not related to the trial medication; another experienced side effects of severe nausea; and the third patient's caregiver became unable to participate further in the study due to ill health. Details of the 12 patients who completed the study are shown in Table 1. All patients had a clear sensorium and were able to cooperate fully with the assessments. Throughout the duration of the study (17 weeks from baseline to withdrawal phase), no changes were made in the patients' anti-parkinsonian therapy. All patients were established on a levodopa (L-dopa) preparation and three were also taking the dopamine agonist, pergolide. Following titration of the dose of rivastigmine, 3 of the 12 patients were able to tolerate the maximum daily dose of 12 mg (6 mg twice daily). Of the remaining patients, three reached 9 mg daily and five were maintained on 6 mg. One patient could not tolerate doses higher than 3 mg daily. The only significant side effect was nausea which limited the dose escalation in nine patients, as outlined above.

TABLE 1. *Baseline characteristics of 12 patients who completed the study*

Mean age, yr (range)	71 (64–77)
Sex (M/F)	10/2
Mean duration of illness, yr (range)	12 (3–24)
Mean daily dose of L-dopa, mg (range)	800 (400–1,600)
Additional Pergolide	3 patients, mean daily dose 1.5 mg
Nature of caregiver	10 spouses; 2 siblings

Comparisons of measures obtained at the experimental session with those at baseline revealed significantly lower scores on the total NPI scores (Fig. 1) ($Z = 2.85$; $P < 0.004$) and individual subscales relating to hallucinations (Fig. 2) ($Z = 2.24$; $P < 0.025$) and sleep disturbance (Fig. 2) ($Z = 2.43$; $P < 0.015$). Scores of carer distress at the experimental session were also significantly improved compared with baseline (Fig. 3) ($Z = 2.71$; $P < 0.007$).

Cognitive assessment using the Folstein MMSE revealed significant differences between experimental and baseline sessions, with a mean improvement of 5 points ($Z = 2.81$; $P < 0.005$; see Table 2). Motor symptoms of parkinsonism measured by the UPDRS showed a nonsignificant tendency to improve ($Z = 1.18$; $P > 0.2$; see Table 2). Within the UPDRS scores there were no changes in tremor ratings between the various assessment sessions.

At the assessment 3 weeks following withdrawal of rivastigmine, comparisons of total NPI and MMSE scores with corresponding values at the experimental session revealed significant deterioration ($Z = 2.81$, $P < 0.005$; $Z = 2.12$, $P < 0.034$, respectively).

Discussion

Rivastigmine significantly reduced neuropsychiatric disturbances in advanced parkinsonian patients suffering from troublesome hallucinations without worsening their extrapyramidal signs and symptoms. Improvements recorded by the NPI were particularly noticeable on the subsections measuring hallucinations and sleep disturbance. Carer distress consequent to the patients' neuropsychiatric or behavioural problems was also markedly ameliorated by the drug. In addition, overall cognitive performance was significantly enhanced, with a mean gain

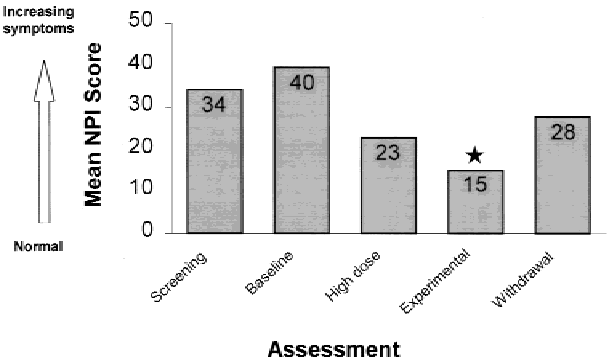

FIG. 1. Mean total NPI scores at each assessment session. Comparison of the experimental scores with those at baseline showed significant improvement; * $P < 0.004$.

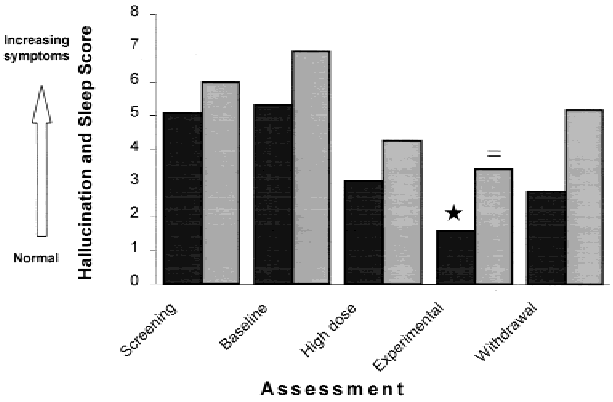

FIG. 2. NPI subscale scores for hallucinations and sleep disturbance at each assessment session. Black bars, hallucinations; grey bars, sleep. Significant improvements were seen when scores at the experimental session were compared with those at baseline for both hallucinations and sleep; ★ $P < 0.025$; † $P < 0.015$

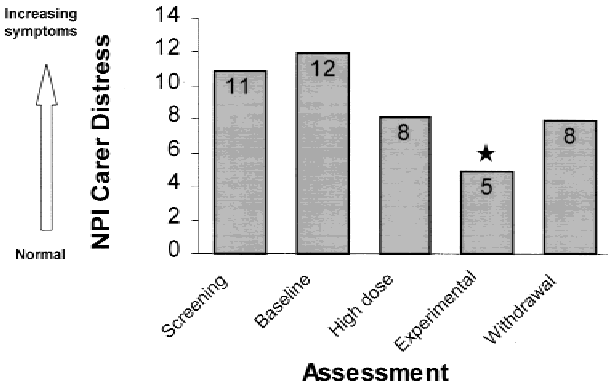

FIG. 3. Scores of overall carer distress at each assessment session. Comparison of score at experimental session with that at baseline revealed significant improvement; ★ $P < 0.007$.

of 5 points on the Folstein MMSE. All these indices of improvement were substantially reversed when recorded 3 weeks following withdrawal of rivastigmine.

The open nature of this exploratory study cannot exclude the possibility of placebo effects influencing patients and their carers. However, the degree of response seen in many of the patients and the nature of the improvements, such as those of severe sleep disturbance, would make this an unlikely full explanation. Furthermore, most of the patients were maintained on rivastigmine following the study and have not shown signs of significant deterioration after 70 weeks of subsequent detailed follow-up (data not shown).

The association of hallucinosis with vivid dreams and sleep fragmentation in PD suggests that REM sleep disturbances may be central.[8–11] Hallucinations during wakefulness are known to occur in subjects with prolonged REM sleep deprivation and most likely represent the phenomenon of REM sleep intrusion or rebound.[32] In PD, brainstem areas involved in REM sleep processes such as the predominantly cholinergic pedunculopontine nucleus are known to degenerate[33] and might be expected to produce a primary sleep disturbance.[9] The added presence of dopaminergic drugs could further worsen the quality of REM sleep.[34] Of note, hallucinating parkinsonian patients have been found to have severely impaired REM sleep indices when compared with matched nonhallucinating parkinsonian controls.[35] The success of rivastigmine in relieving hallucinosis may reflect its ability to enhance REM sleep, which is known to have a cholinergic basis.[36]

Rivastigmine was generally well tolerated in our patient group, although significant nausea was a dose-limiting side effect in most patients. The observation that tremor did not worsen and that overall motor function even showed a nonsignificant improvement on the UPDRS was not predictable a priori, although this mirrors the findings of Hutchinson and Fazzini.[23] Current established therapies for parkinsonian hallucinosis include the atypical neuroleptic agents clozapine[12] and olanzapine.[13] Although reasonably effective at reducing psychotic symptoms, these drugs are generally poorly tolerated in PD and even less so in the related condition DLB,[37] with significant side effects seen even at low doses.[16,37] Few studies have addressed their ability to improve cognitive performance but no change in MMSE scores (23.8 both pre- and posttreatment) was observed in a recent randomised trial of clozapine in PD.[12]

The cholinesterase inhibitor rivastigmine is now an established licensed treatment primarily for the amnestic aspects of mild or moderate AD, but accumulating evidence suggests that dementia syndromes with prominent neuropsychiatric symptomology may be even more responsive to the agent.[21,22,24,25,38,39] Our results are very similar to those found in studies using comparable assessments of patients diagnosed with DLB.[24,25] This is perhaps not surprising, given the degree of phenotypic similarity between DLB patients and our patient group, even though our subjects presented with motor symptoms of idiopathic PD many years before the onset of neuropsychiatric problems. The use of cholinesterase inhibitors provides a new approach to a difficult clinical problem and emphasises the potential importance of cholinergic mechanisms in the pathogenesis of the neuropsychiatric complications of neu-

TABLE 2. *MMSE and UPDRS (motor subscale) scores across five assessment sessions (n = 12)*

	Screening	Baseline	High dose	Experimental	Withdrawal
MMSE (mean ± S.D.)	20.8 ± 5.4	20.4 ± 5.7	24.2 ± 3.5	25.4* ± 3.5	21.2 ± 5.1
UPDRS (mean ± S.D.)	29.8 ± 9.5	32.3 ± 10.4	31.4 ± 14.5	29.8[a] ± 11.5	34.8 ± 12.2

Higher MMSE values imply improved cognitive ability, whereas higher UPDRS scores indicate worse motor function.

*Experimental compared with baseline, $P < 0.005$.

[a]Experimental compared with baseline, $P > 0.2$.

rodegenerative diseases. Further randomised trials in parkinsonian patients are warranted.

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Poetic Talent Unmasked by Treatment of Parkinson's Disease

Anette Schrag, MD, PhD, and Michael Trimble, MD*

Raymond Way Neuropsychiatry Research Group, Institute of Neurology, University College London, London, United Kingdom

Abstract: Parkinson's disease is typically characterised by loss of function and previous abilities, often accompanied by complications of treatment in later stages of the disease. We report on a patient who newly developed an artistic skill after starting treatment for Parkinson's disease. This case offers insight into the neurology of the artistic process as well as into the pathophysiology of psychiatric adverse reactions to the treatment of PD. © 2001 Movement Disorder Society.

Case Report

A 55-year-old patient had developed Parkinson's disease (PD) at age 40 years with tremor of the left hand, dragging of the left leg, and dystonia of the left foot. This gradually progressed, and treatment was started with a combination of the dopamine agonist lisuride and levodopa at age 44 years. His symptoms markedly improved and he had no initial side effects except an increase in libido. Within the first month of starting treatment, he began writing poetry for the first time in his life and went on to write 10 poems in the first year of treatment. He continued writing with success; winning a prize in the annual contest of the International Association of Poets and publishing several poems in newspapers and magazines.

He had never written poetry in his life before or felt the desire to do so, rather, on the contrary, described himself as the black sheep in the family due to lower intellectual achievements than his siblings. However, his maternal grandfather had written poetry and he was related to a well-known Irish poet.

As his PD progressed, he developed fluctuations in motor response to treatment and dyskinesias. Approximately 12 years after onset, taking 2,000 mg Levodopa (plus decarboxylase inhibitor) and 2,000 μg lisuride daily, he developed problems with depression, aggression, and volatile behaviour, which put considerable strain on his family. A year later, he also developed grandiose ideas, paranoid delusions, irritability, extreme circumstantiality, overtalkativeness, and pressure of speech. Discontinuation of lisuride and treatment with olanzapine improved these symptoms but led to deterioration of his parkinsonian symptoms. In the following year, taking 1,900 mg levodopa per day, he developed another episode of impulsivity, grandiose ideas, agitation, hostility, overactivity, pressure of speech, and flight of ideas. This was most likely to be due to self-overmedication and he was hospitalised to readjust his drug regime.

Neuropsychological testing revealed an I.Q. of 97 on the verbal subscores of the Wechsler Adult Intelligence test with high-average to low-average performances, and average and low-average scores in the two tests of the Performance scale, which he could complete (Picture Completion and Picture Arrangement, respectively). Abstract reasoning, reading performance, and memory were within the average range, and visual perceptual function was satisfactory. This represented no cognitive decline over 9 years, but a mild underfunctioning compared with his estimated premorbid ability. However, there was some impairment on frontal lobe tests, with impairment on the Wisconsin card sorting test, where he was only able to obtain three categories and made many errors. However, word fluency was satisfactory, producing 25 words starting with the letter S in 60 seconds and normal performance on Cognitive Estimates and the Stroop test.

There was no clear relationship between changes in treatment and his poetic activity, and his claims of poetic success were confirmed by his family and friends, and were seen in print.

Discussion

Enhanced artistic ability has been described in patients with frontotemporal dementia,[1] and was postulated to be caused by a loss of inhibition of the posterior visual cortex, thus intensifying visual experiences. In patients with PD, however, artistic productivity has been reported as either decreased[2] or unchanged,[3] and the development of a new artistic talent in PD has not been described previously.

There are several possible explanations for the development of this patient's new literary creativity. (1) Increased writing activity may be seen as hypergraphia in a number of neurological conditions, particularly when they affect the right hemisphere, and it is interesting to note that our patient's symptoms started on the left side. However, hypergraphia usually has little or no meaningful content, whereas the production of poetry requires creative, organized, complex and unique thoughts and associations; (2) In a psychodynamic model, the new or enhanced artistic activity may be explained by the concept of sublimation. The socially unacceptable increase in libido would thus have been transformed to artistic productivity in order to neutralise this instinctual energy and to render it conflict-free and socially acceptable. However, the increase in libido did not result in a subjective conflict or cause social problems for this patient; (3) The patient's artistic ability may have been previously impaired by a premorbid parkinsonian personality resulting from reduced dopaminergic input in the basal ganglia or other dopamine systems. Restoration of this balance by treatment with dopaminergic drugs may have revealed the underlying artistic ability. However, the existence and pathophysiological basis of a "parkinsonian personality" is controversial[4,5] and, even if present, it is unlikely to have suppressed the development of an artistic ability for the duration of the patient's entire previous life. There are a number of important artists in this century (e.g., Salvador Dali) who are known to have suffered from PD, making it unlikely that a premorbid parkinsonian personality prevents artistic activity many years before the onset of symptoms; (4) This patient's newly developed literary productivity, which first appeared on dopaminer-

*Correspondence to: Prof. M Trimble, Raymond Way Neuropsychiatry Research Group, Institute of Neurology, Queen Square, London WC 1N 3BG. E-mail: m.trimble@ion.ucl.ac.uk

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gic treatment, may have been a manifestation of drug-induced hypomania, which has been suggested to be due to chronic overstimulation of dopamine receptors in specific brain areas, such as the limbic system.[6] Although no alterations of his mental state except an increase of libido were present at the time when poetic activity developed, a hypomanic syndrome developed on dopaminergic treatment later on, and a protracted course of mental state changes on dopaminergic treatment in PD is not unusual. Links between poetic creativity and a predisposition to hypomania are recognised[7] but hypomania typically results in subjective overestimation of the patient's own abilities without a realistic correlate (grandiosity) rather than objective ability of the quality seen in our patient. This makes it unlikely that drug-induced hypomania is the sole explanation for his newly developed literary talent; (5) Dopaminergic treatment in patients with PD[8] has also been shown to result in improvement of cognitive function, particularly of frontal tasks. It is thus possible that enhancement of cognitive abilities due to dopaminergic treatment resulted in the creative activity seen in this patient. However, improvement of cognitive function in patients with PD treated with dopaminergic agents normally does not exceed premorbid levels of cognitive function, and deficits of cognitive function usually remain. Moreover, newly acquired skills have not been reported; (6) Treatment was initiated and maintained over many years with a combination of levodopa and the dopamine agonist lisuride, which is also a potent serotonin agonist and has been associated with higher rates of behavioural problems and more psychotic behaviour than other dopamine agonists. Serotonergic stimulation has also been linked to artistic performance, and was used by many artists in the 1960s and 1970s in order to enhance their artistic perceptions. Prolonged treatment with this serotonergic drug may therefore have contributed to the unmasking of the patient's poetic talent; and (7) in analogy to the emergence of creativity in patients with frontotemporal dementia, the deficits in frontal lobe function, which were already present at the first testing 5 years after onset, may have led to a loss of inhibition of cortical function and an increase of creativity. The mild impairment on frontal lobe tasks may not have been sufficient to produce this new creative activity. However, dopaminergic treatment, through chronic overstimulation of specific dopamine receptors, and serotonergic stimulation may have unmasked specific functions such as a previously inhibited poetic talent in a patient with concomitant loss of inhibitory frontocortical function. We therefore speculate that the effect of dopaminergic and serotonergic drugs, either through cognitive enhancement, increased perception or a hypomanic syndrome, in addition to selective frontocortical dysfunction, led to the release of previously inhibited creative power in this patient.

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Macrogol 3350/Electrolyte Improves Constipation in Parkinson's Disease and Multiple System Atrophy

Tobias E. Eichhorn, MD, and Wolfgang H. Oertel, MD*

Department of Neurology, Philipps University Marburg, Marburg, Germany

Abstract: We describe an open study of macrogol 3350 in 10 cases of constipated patients with Parkinson's disease or multiple system atrophy. The agent produced a marked improvement in symptoms in all cases. © 2001 Movement Disorder Society.

Constipation is a frequent symptom in patients diagnosed with Parkinson's disease (PD) and multiple system atrophy (MSA). Besides physical measures (e.g., exercise, high fluid and fiber intake), lactulose and stimulant laxatives (sodiumpicosulfate, bisacodyl) and drugs which accelerate the gastrointestinal, especially colonic, transit (e.g., domperidone and cisapride) have been shown to alleviate constipation associated with PD.[1] Psyllium was also demonstrated to increase stool frequency and stool weight in patients with PD without altering colonic transit or anorectal function. In many cases, however, these treatments provide only a transient relief[3] or fail to work. We present an open label study on a new effective and reliable means to treat constipation in PD and MSA patients.

Macrogol 3350 is a polyethylene glycol with a molecular weight of 3350. For use as a laxative, it is combined with electrolytes ($NaHCO_3$, NaCl, and KCl). The galenic formulation is a white powder dispersed in water to a plasma–isotonic solution (Movicol, 13 g/bag; registered in Germany). Macrogol 3350 acts solely via osmotic action. Through its high water binding capacity, it increases the water content of the stool and its volume, thereby loosening its consistency. A solution of polyethylene glycol 3350/electrolyte has been shown to be more effective than lactulose in the treatment of opiate-induced constipation.[4] Similar positive effects have been observed in the treatment of puerperal constipation.[5]

*Correspondence to: Wolfgang H. Oertel, MD, Neurologische Klinik der Philips-Universität Marburg, Rudolf Bultmann strasse 8, D-35033 Marburg, Germany. E-mail: oertelw@mailer.uni-marburg.de

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TABLE 1. *Clinical data of PD and MSA patients before and after macrogol treatment*

Patient no.	Age (yr)	Gender	Stool freq. before macrogol 3350	Treatment before macrogol	Duration of treatment (wk)	Maintenance macrogol dose	Stool freq. (per wk)	Softening of stool change*	Effect on ease of defecation change*	Global impression change*
PD										
1	75	F	1 per 2 wks	Lactulose, senna, domperidone	21	2 × 1 bag/day	4	3	3	3
2	76	M	1 per wk	Lactulose, domperidone, picosulfate, senna, clyster	9	1 × 1 bag/day	4	3	3	3
3	66	M	2 per wk	Lactulose, cisapride	15	2 × 1 bag/day	3	2	3	3
4	70	F	<1 per wk; coprostasis	Lactulose	11	1 × 1 bag/2nd day	3	3	3	3
5	74	F	1 per wk		15	1 × 1 bag/2nd day	7	3	3	3
6	57	M	<1 per wk	Lactulose	9	2 × 1 bag/day	3	3	3	3
7	60	M	1 per wk	Lactulose	13	1 × 1 bag/day	4	3	3	3
8	67	M	1 per wk	Lactulose	11	1 × 1 bag/3rd. day	4	3	3	3
MSA										
1	62	F	1 per wk or less	Cisapride, lactulose	10	2 × 1 bag/day	4	3	3	3
2	51	F	1 per wk or less	Cisapride, lactulose	10	2 × 1 bag/day	4	3	3	3

*Change: 0, no difference; 1, slight improvement; 2, moderate improvement; 3, marked improvement.
Freq, frequency.

Eight patients clinically diagnosed with advanced PD (three women, five men; mean age, 68 years; mean duration of disease, 9.5 years; mean Hoehn and Yahr stage during *on* phase, 3.3; mean daily levodopa dose, 522 mg) and two patients diagnosed with probable MSA (both women; age 51 and 62 years, both wheelchairbound after 4 years duration of disease) were treated with a solution of macrogol 3350. All patients had suffered for at least 1 year from severe constipation. Patients were given a simple questionnaire to self-report on stool frequency, stool consistency, ease of defecation, and global impression. All patients gave written informed consent to participate in the study.

At baseline, the self-reported stool frequencies ranged from two per week to one every second week. In all but one of the selected cases, other laxatives had been ineffective (see Table 1). Macrogol 3350/electrolyte at a daily dose of 1–3 bags (13–39 g) was effective in every patient treated. Relief of constipation was reported by patients with a latency of 2–10 days. Improvement was characterized by an increase in the self-reported stool frequency (ranging from two to four per week), softening of stool, and increased ease of defecation. After 2 weeks of successful treatment, the macrogol dose could be reduced in seven patients (ranging from one bag/day to one bag every third day). After treatment with macrogol 3350, all patients stopped all concomitant laxatives. To date, none of the patients has reported any adverse effects. The period observed so far ranges from 9 weeks to 21 weeks (mean 13 weeks) without any loss of efficacy.

Based on this preliminary data, macrogol 3350 seems to be a potent and safe option for the treatment of chronic constipation in patients with PD, MSA and possibly other hypokinetic syndromes. Macrogol 3350 increases the rate of transit of gut contents along the bowel without net electrolyte loss.[6,7] As cisapride has short-term but not long-term efficacy,[3] studies are needed to assess long-term efficacy and safety of macrogol 3350.

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Irresistible Onset of Sleep During Acute Levodopa Challenge in a Patient with Multiple System Atrophy: Placebo-Controlled, Polysomnographic Case Report

Birgit Högl, MD, Klaus Seppi, MD, Elisabeth Brandauer, MD, Gregor Wenning, PhD, and Werner Poewe, MD*

[1]*Universitätsklinik für Neurologie, Innsbruck Austria*

Abstract: A 67-year-old male patient with clinically probable multiple system atrophy developed severe reproducible sleepiness and irresistible onset of sleep during an acute levodopa (L-dopa) challenge. In a placebo-controlled, double-blind study of acute L-dopa challenge, videopolysomnography revealed multiple episodes of non-rapid eye movement sleep 60 minutes after L-dopa and none following placebo. These observations suggest the irresistible sleep can also be induced by L-dopa and also in patients with atypical parkinsonism. © 2001 Movement Disorder Society.

"Sleep attacks," defined as sudden onset of irresistible sleep, have been reported as a side effect of pramipexole and ropinirole.[1] Subsequent reports have highlighted the potential of other dopamine agonists[2,4] and even levodopa (L-dopa)[5,6] to induce similar episodes. We report on a patient with multiple system atrophy (MSA) in whom L-dopa-induced irresistible sleep onset could be observed in a placebo-controlled manner under sleep laboratory conditions.

Case Report

A 67-year-old man with a 5-year history of clinically probable MSA-P (the parkinsonian variant of MSA) according to current criteria[7] was assessed for L-dopa responsiveness using a single dose challenge (200 mg soluble L-dopa plus 50 mg benzerazide). The session had to be interrupted after approximately 60 minutes because of severe sleepiness and irresistible sleep intrusions precluding meaningful motor assessments. The patient subsequently agreed to undergo a double-blind, placebo-controlled L-dopa test with simultaneous polysomnographic recording in order to evaluate the sleep-inducing effects of L-dopa. A soluble preparation of 200 mg L-dopa plus 50 mg benzerazide versus matching placebo was administered on two consecutive mornings after an overnight drug-free period of 12 hours (day 1, placebo; day 2, L-dopa). Prior to each challenge, the patient had about 7 hours of night sleep.

Standard polysomnographic recording[8] was performed beginning immediately before intake of L-dopa/placebo and for a period of 2 hours postdosing. In addition to standard montage, vertical eye movements and digital video were recorded (Schwartzer Brainlab, Munich, Germany). Sleep stage scoring was performed according to standard criteria.[8] Sleep onset was defined as three epochs of stage 1, or one epoch of stage 2 sleep. During polygraphic registration, the patient was seated in a comfortable chair, provided a book for reading, and instructed to remain awake. Unified Parksinson's Disease Rating Scale (UPDRS) motor examinations[9] were performed at baseline, and 1 and 2 hours after drug challenge. Blood pressure was measured at the time of motor testing or when subjective or clinical signs of sleepiness occurred. Previous drug treatment with ropinirole 6 mg/day and L-dopa/benzerazide 150/37.5 mg/day was withheld for 3 days.

Results

Following the placebo challenge, the patient remained behaviorally wakeful throughout the observation period. Polysomnography showed continued wakefulness throughout the recording time according to standard criteria.[8] Leftward saccades were present during reading.

Following 200 mg of oral L-dopa, the patient remained awake for the first hour, but fell asleep during UPDRS motor assessments performed 60 minutes after L-dopa administration. During the second hour of recording, he had to be awakened 16 times by acoustic stimuli or verbal commands, and reminded to remain awake each time. Sleep occurred despite these instructions and the patient's apparent attempts to remain awake, and in some instances even despite manipulations such as electrode repositioning, or blood pressure measurements. Each time, the patient could be easily aroused, but quickly went back to sleep. He was fully aware of his increased sleepiness, and after awakenings acknowledged to have been almost or fully asleep.

Polysomnography showed three episodes containing stage 1 sleep and 16 episodes of stage 1 and 2 sleep. No rapid eye movement (REM) sleep episodes were oberserved during the entire registration periods. After awakenings, reading saccades occurred briefly in instances when the patient resumed reading, but were soon replaced by slow rolling eye movements. Immediately before sleep onset, repeated blinking occurred in some instances. Figure 1 shows sleep architecture following the L-dopa challenge.

UPDRS motor scores did not significantly change after either placebo or L-dopa. Results at baseline/1 hour/2 hours were:

*Correspondence to: Werner Poewe, MD, Universitätsklinik für Neurologie, Anichstr. 35, A-6020 Innsbruck Austria. E-mail: werner.poewe@uibk.ac.at

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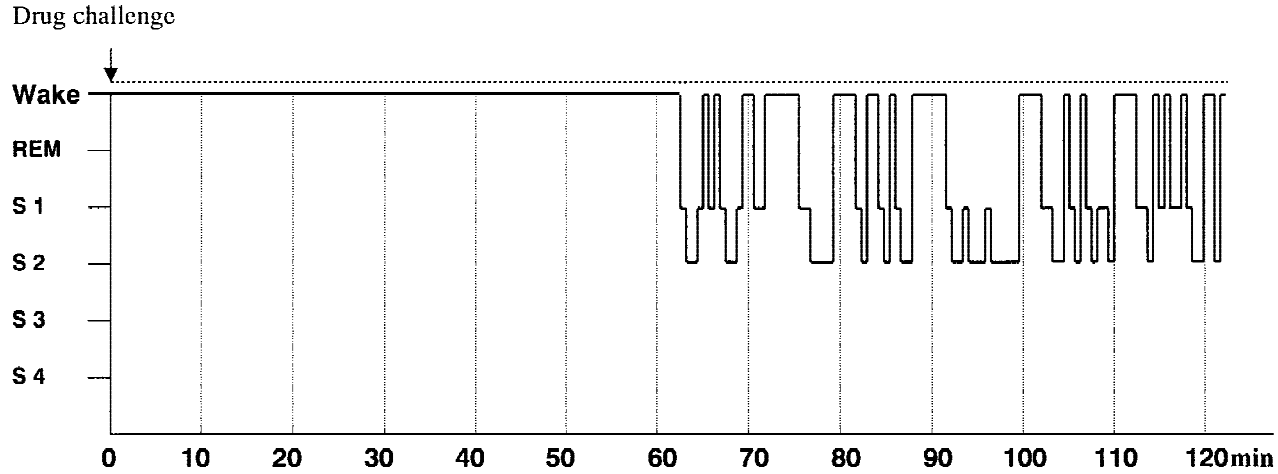

FIG. 1. Sleep architecture after placebo (dotted line) and L-DOPA (solid line) challenge. One hour after intake of 200 mg L-DOPA, the patient falls asleep. Despite 16 provoked awakenings, he returns quickly to stage 1 and 2 sleep during the second hour of recording. No rapid eye movement sleep occurs.

40/37/39 after placebo, and 41/–/38 after L-dopa. Testing 1 hour post L-dopa was not possible due to overwhelming sleepiness and intrusion of sleep interfering with motor evaluations. Blood pressure measurements revealed drops in systolic and diastolic pressure from 110/70 at baseline to 80/50 2 hours postplacebo and from 100/50 to 80/40 2 hours post L-dopa.

Conclusions

Recently, a number of case reports have highlighted "sleep attacks" caused by dopamine agonists, occasionally in delicate situations such as car driving.[1–4,10,11]

This case supports the concept of direct involvement of dopamine in sleep wakefulness regulation, which is increasingly recognized as a major issue in Parkinson's disease:[12,13] Yawning and somnolence after L-dopa ingestion have been recognized earlier,[14,15] and sedative effects of L-dopa have been demonstrated in healthy volunteers.[16] The site of action of dopaminergic somnolence is unknown.

The term "sleep attacks," used by Frucht and colleagues[1] in their description of dopaminergic somnolence, has been rejected by sleep specialists[4,17] and does not represent a recognized syndrome in the International Classification of Sleep Disorders (1997 revised).[18] Sleep onset is invariably preceded by electrophysiological signs of sleepiness even in subjects not aware of this,[5,19] possibly due to sleep onset-associated amnesia.[5] Poor subjective perception of sleepiness is well recognized in patients with chronic daytime somnolence due to sleep disordered breathing or other causes.[19,20]

Previous reports addressing sleep related topics in patients with MSA have focused on REM sleep behavior disorder[21–25] and sleep disordered breathing.[26–28] To our knowledge, L-dopa-induced excessive somnolence and sleep onset have not been reported in this disorder. Sleep induction occurred in the absence of an obvious motor benefit following L-dopa. This case suggests that neuronal networks mediating dopaminergic sleepiness in idiopathic Parkinson's disease are also responsive in MSA.

Further prospective studies in larger series of patients are required to establish the prevalence of L-dopa-induced sleep onset in MSA as well as underlying mechanisms.

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Unilateral Periodic Limb Movements During Sleep in Corticobasal Degeneration

Jorge Iriarte, MD,[1]* Manuel Alegre, MD,[1]
Javier Arbizu, MD,[2] and Purificación de Castro, MD[1]

[1]Department of Neurology, Clínica Universitaria, University of Navarra, Pamplona, Navarra, Spain; [2]Department of Nuclear Medicine, Clínica Universitaria de Navarra, University of Navarra School of Medicine, Pamplona, Navarra, Spain

Abstract: Periodic limb movements in sleep (PLM) have been associated with several degenerative disorders and other focal or diffuse diseases. We present a patient with clinical diagnosis of corticobasal degeneration and sleep complaints, in whom video recording and polygraphic study confirmed the presence of right PLM. The unilaterality of the movements and the positron emission tomography findings (hypometabolism in the left frontoparietal, basal ganglia, and thalamic areas) suggest that the loss of inhibitory descending central pathways, with origin in the cortex or basal ganglia, may be involved in the pathogenesis of PLM. © 2001 Movement Disorder Society.

Periodic limb movement disorder (PLM) is characterized by periodic episodes of repetitive limb movements that occur during sleep.[1] Typically, they consist of extension of the big toe combined with flexion of the ankle, knee, and, less frequently, the hip. They are usually bilateral, although unilateral or asymmetric involvement is possible. Its pathogenesis remains unclear; both central and peripheral mechanisms have been proposed.[2] It is associated with a variety of medical conditions: metabolic disorders, anemia, myelopathies, antidepressants, antiepileptic drug intake, and withdrawal from hypnotics have been related to PLM.[3,4]

Corticobasal degeneration (CBD) is a rare neurodegenerative disorder with a distinctive clinical picture, including features referable to both cortical and basal ganglia dysfunction; some of its most characteristic signs are dystonia, cognitive deficits, myoclonus, and an asymmetric akinetic–rigid syndrome.[5,6] Sleep abnormalities in CBD have only recently been reported; PLM has not been associated with this disease so far.[7]

We present a patient diagnosed as having CBD with noticeable sleep complaints. We confirmed the diagnosis of unilateral PLM, involving the contralateral side to the brain abnormality. This association is a new finding and it raises questions about the pathophysiology of PLM.

Methods

Patient

The patient is a 65-year-old man who presented with a 5-year history of right-hand clumsiness with increasing tendency to adopt an abnormal posture during writing, and a slowly progressive language disturbance consisting of loss of verbal fluency, monotone speech, phonemic paraphasias, palilalia, and echolalia. The patient's wife also noticed sleep problems described as insomnia and frequent kicking movements while sleeping. At the time of the admission, he was not receiving any medication. Neurological examination showed a predominantly motor dysphasia, ideomotor apraxia, a right upper limb dystonia, right hyperreflexia, and right limb rigidity with some degree of bradykinesia. There was no dysmetria. The patient did not have diurnal somnolence, fatigue, hypertension, or other symptoms or signs suggestive of sleep apnea. The wife did not refer to breathing arrests.

Sleep Study

An in-patient sleep study was performed using an 8-channel Medilog-Oxford device. Four electroencephalograms (EEG) channels (1-F3-C3, 2-C3-O1, 3-F4-C4, 4-C4-O2), 5-EOG, 6-channel EMG, 7 left tibial EMG and 8 right tibial EMG were recorded. The system is an analogic device. A video recording was made with a fixed commercial black-and-white camera in the room for 12 hours; during the night there was light enough to permit the correct visualization of the bed and the patient. Written permission was obtained from the patient and his family.

Other Paraclinical Tests

A brain magnetic resonance imaging (MRI), a positron emission tomography (PET) study using fluordeoxiglucose (FDG), and a cortical magnetic stimulation to the upper limbs (abductor digiti minimi; ADM), were obtained to confirm the extent of damage and to rule out other diseases. These tests were performed according to the standard procedures of our Center.

Results

Clinical diagnosis of corticobasal degeneration was established according to the criteria proposed by Kumar et al.[8] Brain MRI showed diffuse corticosubcortical atrophy. PET scan showed major left frontal, parietal, thalamic, and basal ganglia hypometabolism (Fig. 1). All of these findings are consistent with the diagnosis of corticobasal degeneration. The cortical magnetic stimulation evoked no motor response on the right limbs. The cervical response was symmetrical (Fig. 2).

The nocturnal video recording demonstrated typical frequent periodic movements of the right leg, which consisted of dorsal flexion of the toe, flexion of the knee, and flexion of the hip. These movements appeared every 20–30 seconds in runs of 20–30 minutes. All of the movements occurred on the right side regardless of the position of the patient. The polygraphic study confirmed the diagnosis of PLM of sleep and the asymmetry of the periodic movements (Fig. 3). PLM index was 30.

A videotape accompanies this article.

*Correspondence to: Jorge Iriarte, MD, Clínica Universitaria, University of Navarra, Avda Pío XII, 36, Pamplona 31008, Navarra, Spain. E-mail: jiriarte@unav.es

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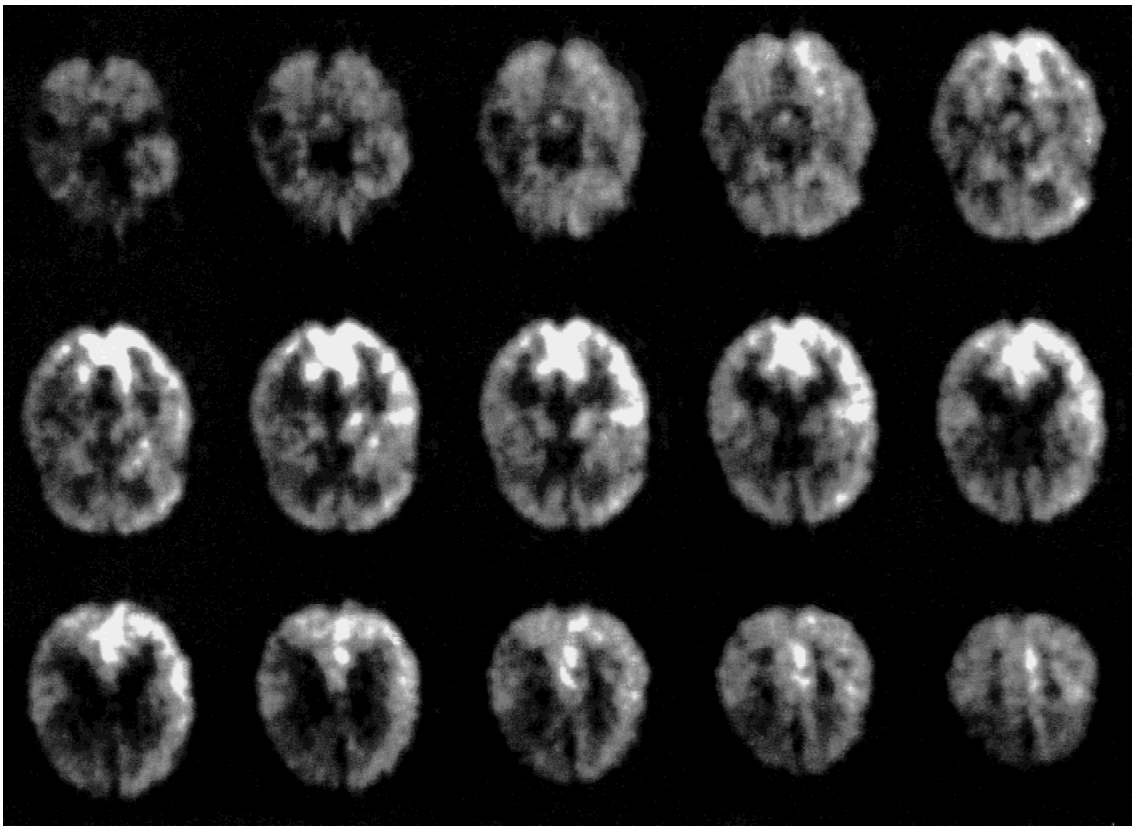

FIG. 1. The fluordeoxiglucose-positron emission tomography (FDG-PET) study showed a marked asymmetry with left frontoparietal and subcortical hypometabolism.

Discussion

Clinical diagnosis of CBD has a low sensitivity but a high specificity.[9,10] Most of the best predictor signs for the diagnosis were present in our patient: limb dystonia, ideomotor apraxia, asymmetric rigid–akinetic syndrome. Gait disturbance is usually a late finding in the disease. Even though a definite diagnosis is only possible by pathology, the combination of the clinical facts described (which meet the proposed clinical criteria) and the hypometabolism contralateral to the clinically affected side shown in the PET study support this diagnosis. PET and SPECT are used to confirm the diagnosis also in other series.[11,12] Lu and colleagues.[13] found an increase of the threshold in the cortical magnetic stimulation in the clinically affected side; we did not observe a response on the affected side, indicating an increase in the threshold, which probably represents a more severe involvement of the motor cortex.

Sleep disorders have rarely been quoted in CBD, although it is well known that other neurodegenerative diseases present frequent sleep problems including PLM (i.e., Parkinson's disease, strionigral degeneration, progressive supranuclear palsy, Shy-Drager syndrome, Parkinson-ALS dementia).[14–17] The reason for this could be the low incidence of CBD. Actually, rapid eye movement (REM) sleep behavior disorder has been signaled as associated with CBD.[7]

The pathogenesis of PLM is still under discussion. Both central and peripheral mechanisms have been postulated.[18] Among the central abnormalities, myelopathies, brainstem and thalamic lesions are quoted.[19] Polineuropathies have been related to PLM as well. Also, some diffuse diseases such as anemia or drug intake have related to the presence of PLM. PLM has also been described in a patient during epidural and spinal anesthesia. This wide range of diseases makes it difficult to establish a single mechanism. The description of unilateral PLM in a patient with CBD in whom central lesions have been demonstrated supports the hypothesis that PLM may be due to the loss of cortical or subcortical inhibition to a spinal or brainstem pacemaker. This inhibition could be mediated by the corticospinal tract, or by a different pathway running near it. The fact that PLM may improve in some patients with levodopa or dopamine agonists points to an involvement of dopaminergic pathways, probably in the brainstem and the basal ganglia.[20,21] The involvement of these pathways may also explain the changes in PLM between non-REM and REM stages, because of the different activity in the brainstem nuclei.[2,22]

Our case indicates that corticobasal degeneration must be included in the list of the neurodegenerative disorders associated with PLM. Our findings support the hypothesis that the loss of control of central descending pathways over a spinal or brainstem pacemaker could be the related to the mechanism of PLM. More patients with CDG and PLM must be studied to confirm these findings.

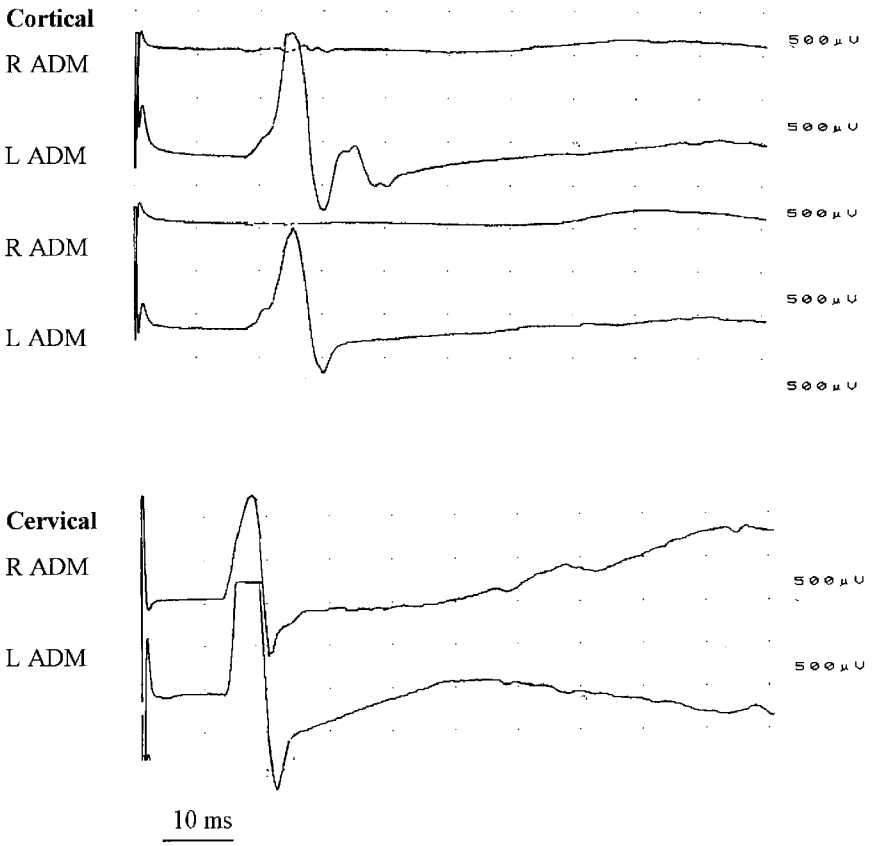

FIG. 2. Cortical magnetic stimulation. There was no response on the right abductor digiti minimi (ADM) to cortical stimulation, either using the A or B side of the stimulator. The response to the cervical stimulation was normal.

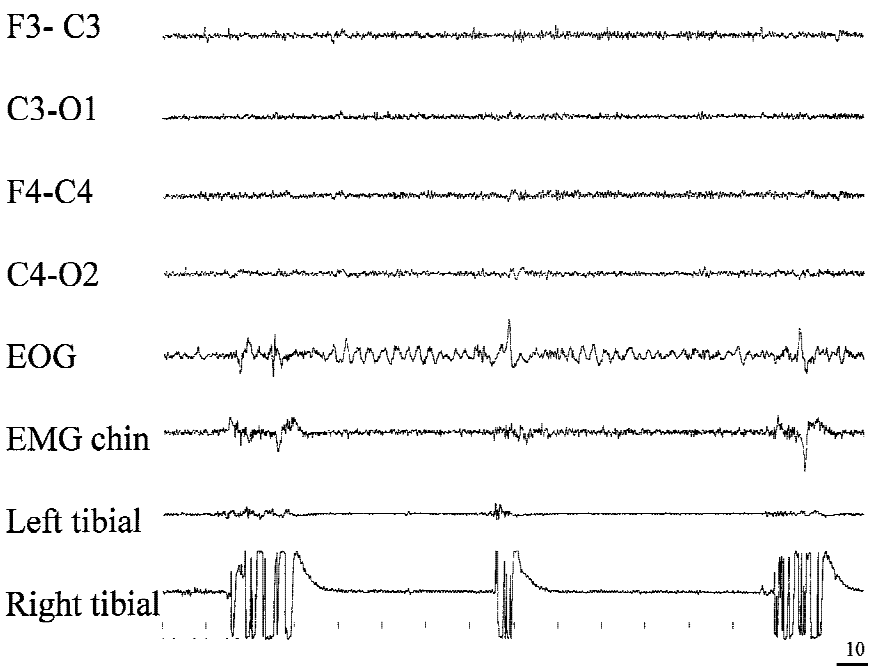

FIG. 3. Polygraphic study of periodic limb movements; right leg.

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Action Hand Dystonia After Cortical Parietal Infarction

J.A. Burguera, MD,* L. Bataller, MD, and C. Valero, MD

Neurology Service, Hospital Universitari La Fe, Valencia, Spain

Abstract: A 46-year-old patient with a pure left cortical infarct affecting mainly the gyrus postcentralis developed action dystonia in the right hand. Mechanisms involved in the genesis of focal secondary dystonia are discussed with emphasis on abnormal cortical sensory processing. © 2001 Movement Disorder Society.

Focal secondary dystonia may appear as a consequence of lesions in particular parts of the brain. When it occurs after a cerebral infarct, dystonia frequently arises as a delayed phenomena.[1,2] Reported cases emphasize the role of basal ganglia in the genesis of secondary dystonia,[3] but less attention has been drawn to cortical lesions. We report on a case of action hand dystonia evolving soon after a cortical parietal infarct.

Case Report

A 46-year-old, right-handed man was admitted to our hospital in November 1984 because of transient blurring of vision through the left eye followed by sudden weakness and numbness in the right arm and hand. Five days before, he had noticed clumsiness in his right hand that lasted for several minutes. He had a 10-year history of noninsulin-dependent diabetes mellitus and was a heavy cigarette smoker. On admission he had right arm monoparesis that severely affected the hand and anesthesia for all sensory modalities over the right wrist and hand. An emergency cerebral CT was unrevealing, as was a control CT 3 days later. Routine analysis only disclosed basal hyperglycemia. Detailed cardiovascular examinations, including echocardiography, were normal. On the fourth day a four-vessel cerebral arteriography was performed, showing a complete obstruction of the internal left carotid artery. Somatosensory-evoked potentials stimulating both median nerves showed a slight prolongation of latency of left N20. On the tenth day the patient was discharged. During the following weeks, as right-hand strength improved, abnormal sustained flexion of the right fingers occurred on attempting to manipulate objects. Examina-

*Correspondence to: Juan A. Burguera, Servicio de Neurología, Hospital Universitari La Fe, Avenida de Campanar 21, 46009 Valencia, Spain.

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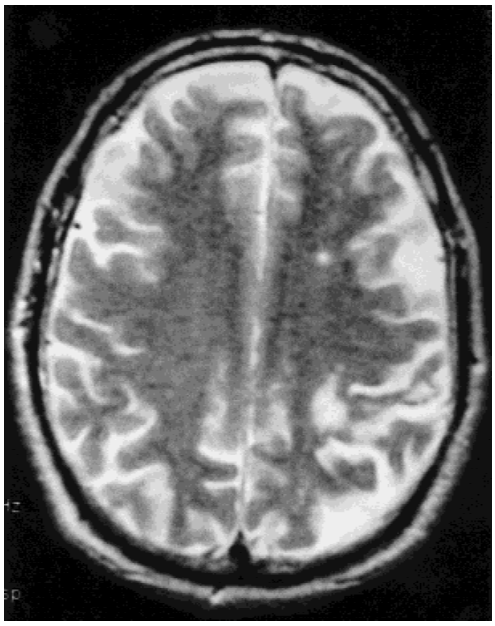

FIG. 1. T_2-weighted MR showing a small cortical infarct affecting mainly the gyrus postcentralis.

tion 3 months later showed normal neuropsychological results. Muscle strength and tendon reflexes were normal. Plantar responses were flexor. There was a loss of position sense, vibration, and two-point discrimination in the right wrist and hand. Light touch and thermal sensation were only slightly impaired. He had a complete astereognosis of the right hand. Muscle tone at rest was normal. Pseudoathetosis was not seen when he was asked to keep his arms and fingers outstretched either with eyes open or closed. The patient was able to open and close his right hand properly. He had a slow and clumsy right finger-tapping rate. This latter manoeuver generated some transient dystonic contraction of forearm muscles. When attempting pincer grip with right index and thumb to pick up an object, a sustained dystonic flexion of right fingers and wrist occurred. The patient was then unable to open his hand voluntarily and the fingers had to be passively extended to reassume a basal condition. There was no improvement after visual hand guidance. We followed up this case carefully for 16 years. Throughout this time the movement abnormality has remained stable and no benefit was observed after drug therapy with anticholinergics, benzodiacepines, baclofen, or carbamazepine. The patient refused botulinum toxin injections. A cerebral MR performed in 1994 showed a chronic small cortical infarct (Fig. 1) affecting the gyrus postcentralis and to a lesser extent the white matter under the sulcus centralis. A SPECT showed hypoperfusion in superior parietal cortex (Fig. 2).

Discussion

Secondary dystonia is known to be produced by lesions in the basal ganglia, affecting mainly the thalamus and striatum.[3] These lesions are thought to cause an abnormal functioning of cortico-striato-pallido-thalamo-cortical loop leading to enhanced excitation of premotor cortical areas.[4] Dystonia arising as a consequence of basal ganglia damage is clinically identical to abnormal movements seen in primary dystonia[3] with the characteristic sustained cocontraction of agonist–antagonists and abnormal spread and involuntary activation of distant muscles.

In Denny-Brown's descriptions,[5] purely cortical lesions are shown to cause abnormal sustained attitudes. Basically, assumed postures are overflexed in frontal injury (grasping reflex) and overextended in parietal lesions (avoiding responses). However, grasping behavior has also been described in association with parietal lesions.[6]

Abnormal postures of the hand are often described in reported series of parietal cortical lesions of vascular origin.[7] In these cases there is an inability to maintain a stable posture of fingers and hand when the patient is asked to keep them outstretched. Fingers then assume dystonic postures and pseudoathetoid wandering. These abnormalities characteristically improve under visual guidance. This postural instability resembles that described after deafferentation and differs from movement disorders arising from lesions in the basal ganglia or primary dystonia. Although our patient harbors a cortical infarct and neuroimaging revealed no basal ganglia lesion, his hand dystonia closely resembles primary action dystonia instead of that

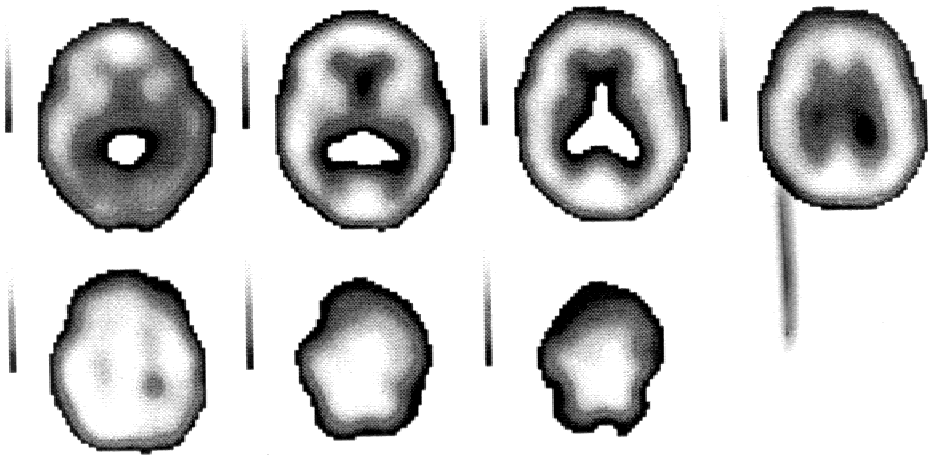

FIG. 2. SPECT image showing decreased tracer uptake in superior parietal cortex.

seen in deafferentation states as would be expected from his profound impairment of sensation in the right hand.

Sensory system disturbances are described in patients with idiopathic dystonia. A recent study shows elemental sensory deficits in graphaesthesia and stereognosis in patients with primary hand dystonia.[8] Other studies have shown increasing evidence of abnormal cortical sensory processing in such patients. Functional imaging of the brain has shown a relative overactivation of prefrontal motor planning areas (where striato-pallido-thalamic projections are received) and underactivation of sensory–motor executive areas during movement in these patients.[9] Interestingly, degraded representation of the hand in somatosensory cortex has been demonstrated in dystonic patients as well as in primate models of dystonia.[10,11] These abnormalities in cortical representation of the hand are thought to play a role in the genesis of dystonia as the parietal cortex is involved in the processing of higher aspects of sensation and motion and is involved in programs for adequate motor behavior.[7]

The parietal lesion of our patient caused abnormalities in cortical sensory processing which were much more severe than those seen in primary dystonia. However, we hypothesize that this incorrect information may have misguided precise functioning of cortical motor programs involved in hand movements, resulting in overlapping activity in agonist–antagonist muscles and an overflow of activity to remote muscle groups.

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Hand Orthosis as a Writing Aid in Writer's Cramp

Nihal Taş, MD,* Gülçin Kaymak Karataş, MD, and Vesile Sepici, MD

Department of Physical Medicine and Rehabilitation, Gazi University Faculty of Medicine, Ankara, Turkey

Abstract: Writer's cramp is a focal, task-specific dystonia of the hand and wrist. It primarily affects people who do a significant amount of writing, and causes difficulties in writing. We present five cases with writer's cramp who showed improvement in their writing ability with an applied hand orthosis.

Writer's cramp is a focal, task-specific dystonia involving the dominant hand and wrist.[1–3] It is characterized by the dystonic contraction of all the muscles of the thumb and fingers on attempting to write. Writer's cramp is usually restricted to writing; other coordinated movements of the hand remain normal. In some patients it may involve other manual tasks and is called "dystonic writer's cramp". This occupational dystonia of the hand causes difficulties in writing by excessive and uncontrollable grip of the pen, flexion, occasional ulnar deviation at the wrist, and marked pressure against the paper. Dystonic posturing of the hand and attempts to correct the abnormal posturing, hesitations, or arrests cause slowing of writing and often the script is difficult to read. As writer's cramp primarily affects people who do a significant amount of writing, it causes a significant functional loss in their daily life. Most of the patients perform compensatory manoeuvres to overcome this dystonia that interferes with their occupation, and some writing devices have been used in the management of the disability.[4,5]

We report on five patients clinically diagnosed as having writer's cramp who had improvement in their writing ability with an applied hand orthosis.

Patients and Methods

Case 1

A 38-year-old right-handed woman had a 6-year history of weakness and progressive clumsiness during writing. She also complained of pain, discomfort, and tension. She was a high school teacher and noticed that she could write on the blackboard without difficulty but had difficulty in writing on a table.

Case 2

A 49-year-old woman experienced weakness, cramp, and difficulty during writing with her right hand beginning 2 years prior to study. She was a medical doctor on a faculty of medicine. She had to prepare lectures and papers, but was not able

*Correspondence to: Dr. Nihal Taş, 60. sokak No: 9/8, Emek 06500, Ankara-Turkey.

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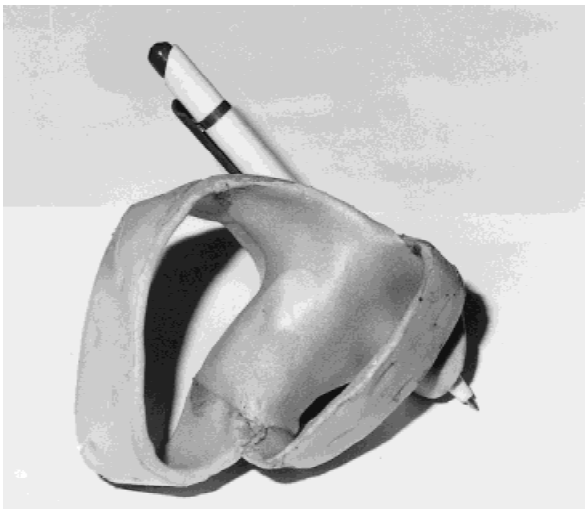


FIG. 1. The appearance of the hand orthosis.

FIG. 2. Picture of a patient using the hand orthosis.

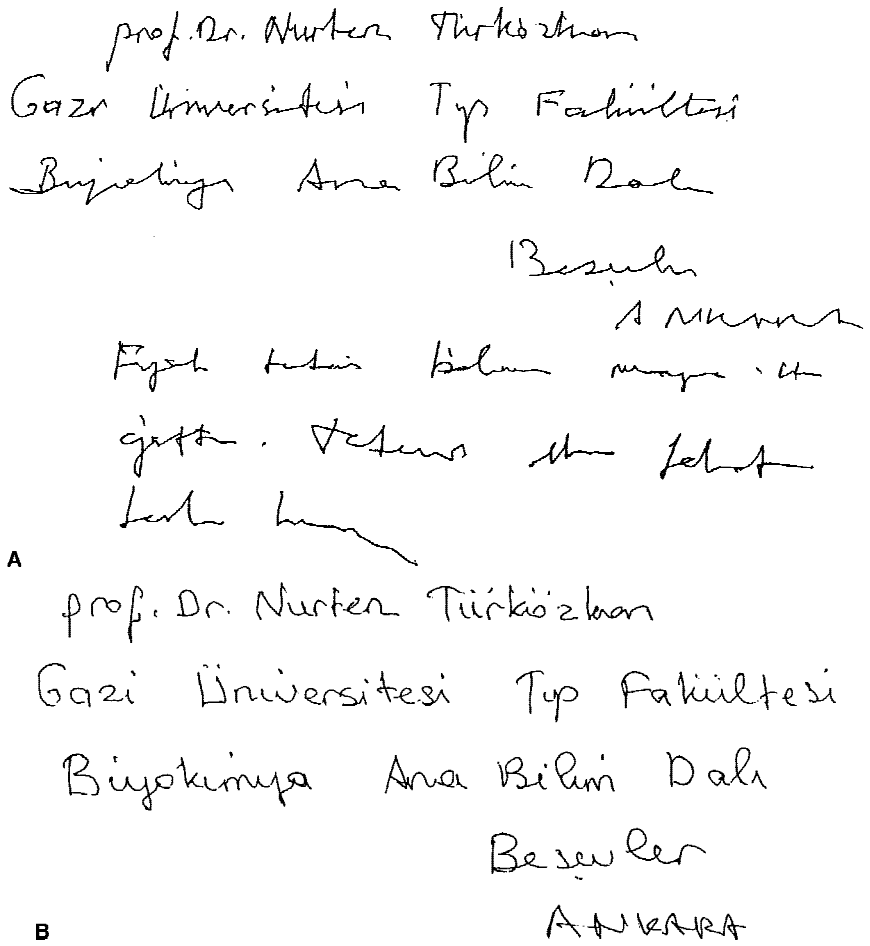
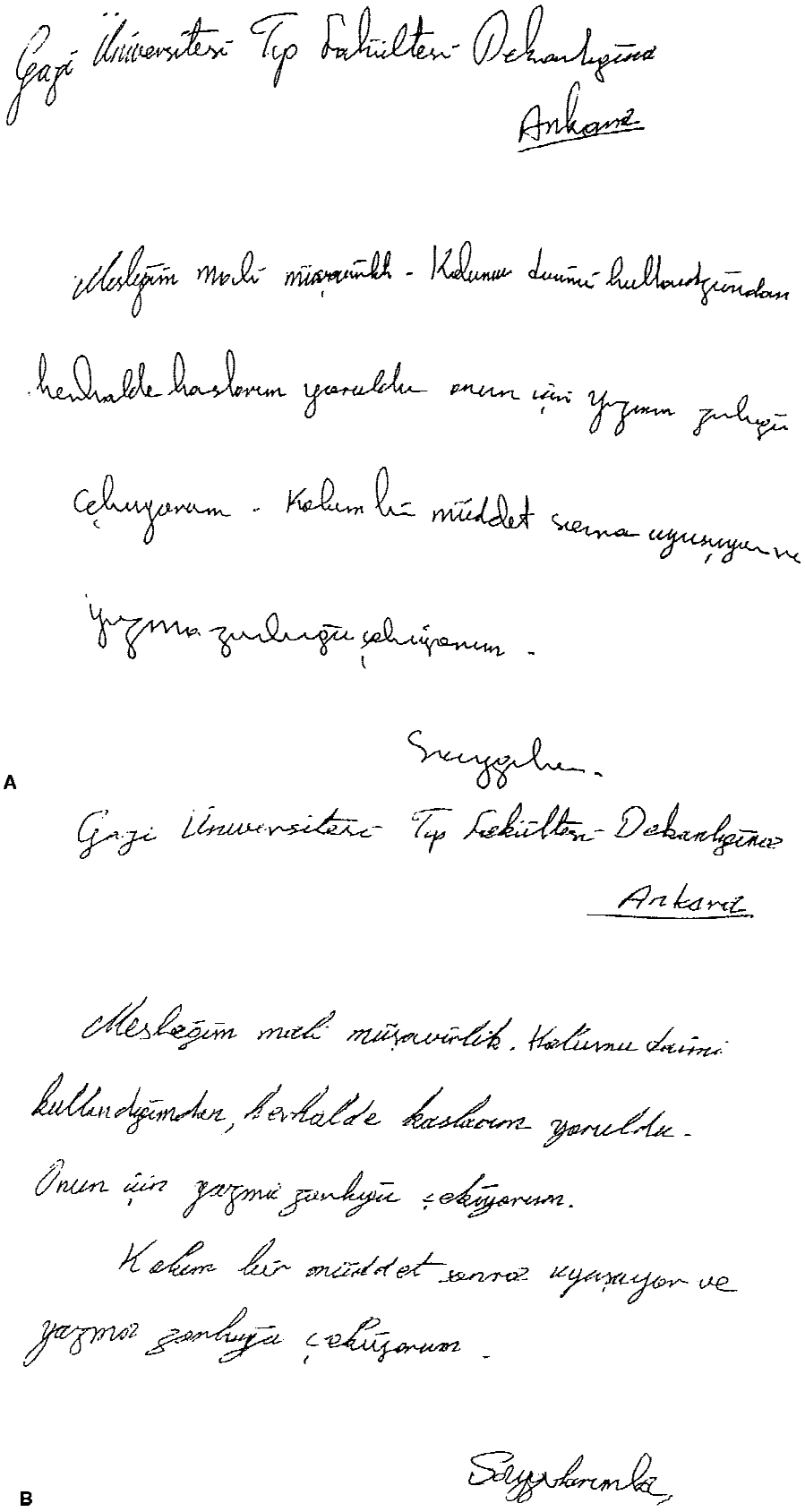


FIG. 3. a: Handwriting of a patient (case 2) without hand orthosis, and (**b**) with hand orthosis. (Reduced 23%).



A

B

FIG. 4. Handwriting of a patient (Case 3) without hand orthosis **(A)**, and with hand orthosis **(B)**. (Reduced by 23%).

to do so as well or as quickly as she wanted to because of the progressive course of her complaints.

Case 3

A 59-year-old, right-handed man experienced pain, cramp, weakness, and clumsiness in his dominant hand during writing beginning 10 years previously. Before his complaints had started, he was proud of his beautiful script. When his script was no longer legible, his students had difficulty reading his notes.

Case 4

A 35-year-old, right-handed man, a teaching assistant, described spasm and feeling of stiffness while writing, which had started 2 years prior to study. He had to stop after writing a few words. Because of these hesitations, it took him a long time to complete his work.

Case 5

A 47-year-old, right-handed woman, a primary school teacher, had difficulty in writing, and discomfort in her fingers and wrist for two years prior to study. It was not only difficult to hold the pen in the proper position but sometimes the paper was torn because of the excessive pressure.

Patients' clinical, musculoskeletal, and neurological examinations were normal. Laboratory and radiographic investigations were within normal limits, except for Case 4, who had minimal bulging at C4–5 level in cervical magnetic resonance imaging (MRI). On examination, all patients had the typical hand posture and writing. All were using compensatory manoeuvres in their own way. No other disease that may have caused the same clinical problem and weakness of the hand was identified, and the diagnosis of writer's cramp was made. Pharmaceutical therapy such as anticholinergics and carbamasepin was prescribed and physical therapy was started. As all of the patients are teachers, they must write as part of their vocation. To adapt their disability to their occupation, a thermoplastic hand orthosis was applied, substituting the action of distal muscles with the unaffected more proximal ones. The static orthosis was designed specifically for each patient according to his or her writing characteristics. The writing device supported and immobilized the segments of the hand (thumb, fingers or wrist) that interfere with writing and allow the proximal large muscles to control the coordination of movement for writing. Because of the difficulty in holding the pen, a place for grasping was also made (Figs. 1 and 2). All patients became used to this orthosis in a very short time. They could write without discomfort and their script was legible while the orthosis was worn (Figs. 3 and 4). They were able to write uninterrupted for at least an hour after becoming familiar with the device, whereas they had to stop after writing a few words without the orthosis. When the device was removed, they could not write because of spasms and feeling of stiffness.

Discussion

Some pharmacological agents have been reported to have some effect in treatment of focal dystonias.[3,6,7] Writer's cramp is generally resistant to these agents, although anticholinergics, dopaminergics, benzodiazepines, baclofen, and carbamasepin may help some patients.[8] The benefit of pharmaceutical therapy is quite variable and some medications have only minimal reduction of dystonia. Adverse reactions are common and many cannot tolerate these drugs. Local anaesthetics such as lidocaine and injection of botulinum toxin A are the most recent forms of therapy.[2,3,9–12] While results of botulinum toxin A injection appear promising, side effects such as excessive weakness or antibody production may occur. Spread of toxin to adjacent unaffected muscles causes excessive weakness, which was a major factor contributing to suboptimal outcome in some patients.[10] Physical therapy modalities such as relaxation techniques, strengthening and conditioning exercises, and biofeedback can be planned in conjunction with medical therapy[1,2,13]; however, their effectiveness is limited and short-lasting.

In view of the fact that the clinical problem is a task-specific dystonia, various writing devices have been reported to be used. Ranawaya and Lang[5] evaluated the writing abilities of 20 patients treated with a device called the Blackburn writing system. This device had a tripod design; two legs were mounted on ball bearings, and the pen was the third leg when inserted into the holder. Patients put their palm on the device and glided it over the paper using only the proximal muscles. After 4 weeks of trial period, 15 patients showed improvement in their writing ability. Although the results seemed promising, the authors reported that only 30% had obtained useful benefit in practical terms. Because some felt that the device was awkward and embarrassing to use, they preferred to use an alternate method. Koller and Vetere-Overfield[4] reported a different type of device in a single case: a writing block to be used by patients with arthritis. A pen was inserted through a small cubic block, making grasping easier. They reported that similar devices might be useful and should be tried for writer's cramp.

Because of limited effectiveness of pharmacotherapy, physical therapy was also initially considered for our patients. In spite of pharmacotherapy and additional physical therapy, no improvement in writing ability was achieved. Disability caused by the functional loss in writing was the primary complaint to overcome. After informing the patients about the alternative of a writing device, an individually designed hand orthosis was applied to each patient. They became used to this orthosis in a very short time and could write without discomfort with the hand orthosis. In writer's cramp, the excessive cocontraction of agonist and antagonist muscles is the main mechanical problem that causes difficulty during writing. Because some patients may be able to write on a blackboard by using their proximal muscle groups, we believe that the applied hand orthosis prevents development of the cramp by substitution of the action of distal muscles that show cocontraction with unaffected more proximal muscles.

Our findings demonstrated an improvement in writing ability of patients while using the hand orthosis. Considering the adverse effects of pharmacotherapy and poor response in physical therapy, we recommend the application of this hand orthosis in conjunction with other therapies to overcome a disability that handicaps the patient's daily life and vocation.

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Stiff Leg Syndrome: Case Report

Mahmut Edip Gürol, MD,* Mustafa Ertas, MD, Hasmet Ayhan Hanagasi, MD, Hüseyin Alparslan Sahin, MD, Gençay Gürsoy, MD, and Murat Emre, MD

Department of Neurology, Istanbul School of Medicine, University of Istanbul, Istanbul, Turkey

Abstract: We report on a 28-year-old woman with insulin-resistant diabetes mellitus with a 5-year history of progressive stiffness and painful spasms of the right leg, exaggerated by sudden auditory and tactile stimuli or by emotional stress. There were no signs of truncal rigidity or exaggerated lumbar lordosis. Anti-glutamic acid decarboxylase antibodies were positive in her serum. She improved substantially with clonazepam 4 mg/day. She presented with electrophysiological findings not previously reported in stiff leg syndrome, which may suggest increased inhibition in the uninvolved upper extremities. © 2001 Movement Disorder Society.

Stiff person syndrome (SPS) is characterized by axial rigidity, progressive stiffness, and spontaneous, reflex- or action-induced painful spasms of the paraspinal, abdominal, and occasionally proximal leg muscles associated with a lumbar hyperlordosis.[1–7] Electrophysiological findings are typically continous motor unit activity with abnormal exteroceptive reflexes but a normal interference pattern during spasms.[8,9] Most patients have antiglutamic acid decarbolxylase (GAD) antibodies in both serum and cerebral spinal fluid (CSF) with additional evidence of autoimmune disease. During the last 2 years, several cases with SPS were reported whose symptoms were confined to one lower limb.[1,10,11] The condition was named as the "stiff leg" or "stiff limb" syndrome (SLS) and the necessity of revising the diagnostic criteria for SPS was emphasized.

We describe a patient with signs and symptoms closely resembling those seen in cases of SLS, with some electrophysiological findings not previously reported.

Case Report

A 28-year-old woman presented with a 5-year history of progressive stiffness and painful spasms of her right leg, considerable difficulty in walking, and unprovoked falls. She was able to perform all daily activities including walking and running until 5 years prior to study, when she first noticed a dull pain in her right leg. She was admitted to another hospital where the diagnosis of type I diabetes was made. Three years before, she felt stiffening of her right leg worsening over several months, accompanied by intense pain, followed by spasms characterized by dorsiflexion of her right foot with extension of the leg. The leg stiffness progressively worsened and the frequency and duration of the spasms increased, resulting in unprovoked falls. The spasms were elicited by leg movements and emotional, auditory, or tactile stimuli. A lesser degree of stiffness was noted in her left leg 1 year before, and she was having difficulty walking without assistance. Levodopa (L-dopa) was administered without improvement.

On admission, there was abnormal posturing of the right leg with extension of the hip and knee and dorsiflexion of the foot. The leg was rigid, movements were severely limited and painful. Sudden auditory and tactile stimuli caused spasms and involuntary jerky movements of the right leg. Motor examination was normal on the rest of the body but the right leg could not be evaluated because of rigidity and spasms. Sensory examination was normal except for reduced vibration sense with a marked deficit distally in both lower extremities. Deep tendon reflexes were normal in upper limbs; patellar jerk was hyperactive and the Achilles jerk could not be elicited. Standing up from bed was very difficult and could only be achieved with assistance. She could walk very slowly with a severely stiff right leg and maintaining the abnormal posture described above.

Her past medical history was remarkable for a diagnosis of hyperthyroidism in 1992. She used propylthiouracil for 1 year and remained euthyroid afterwards. She also had type I diabetes and very poor control of blood glucose level despite regular use of insulin.

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values and blood chemistry were normal except for the elevated glucose, fructosamine, and glycosylated hemoglobin levels. The electrocardiography (ECG), chest X-ray, serum copper level, ceruloplasmin, vitamin B12 level, thyroid hormones, antinuclear antibody (ANA), RF, anti-ds DNA, extractable nuclear antigen (ENA) screening were all within normal limits. Direct X-rays of lumbar spine did not reveal an exaggerated lordosis. Magnetic resonance imaging of the whole neuraxis and EEG were also normal. Antibodies against GAD (anti-GAD) were found in a high titer in the serum (7,120 mGAD/ml; n < 1,500). Cerebrospinal fluid examination was

*Correspondence to: M. Edip Gürol, MD, Atakoy 4. kisim O-169, D:20, 34750, Bakirkoy-Istanbul, Turkey. E-mail: egurol@yahoo.com

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unremarkable except for a high protein content (174 mg/dl); there were no atypical cells found on cytopathological analysis; oligoclonal bands and anti-GAD antibodies were negative. Immunological studies for evidence of herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV), and Brucella infection were negative for both CSF and serum. The ophtalmologic consultation showed no other abnormality than a moderate myopia. Neuropsychological testing showed findings associated with a low I.Q. and a mild to moderate attention deficit.

Thyroid scan demostrated a hypertrophic multinodular gland, the dominant nodule being hypoactive. Needle aspiration biopsy from the hypoactive nodule revealed cytological findings compatible with a partially hyperplasic micromacrofollicular colloidal nodule.

Clonazepam 4 mg/day in divided doses was introduced, providing significant improvement of the symptoms. Stimulus-induced myocloni disappeared totally, with marked reduction of the rigidity of the leg. She could walk unaided in a nearly normal manner.

Electromyographic examination performed before the symptomatic treatment revealed axonal motor–sensory polyneuropathy (low sensory action potential [SNAP] amplitudes with normal conduction velocities [CV] in upper and lower limbs, and low compound muscle action potential [CMAP] amplitudes with modestly low CVs in lower limbs) and spontaneously discharging motor unit action potentials in right tibialis anterior (TA) muscle at rest. Repetitive myogenic bursts and exaggerated late (exteroceptive) reflex responses spreading to ipsi- and contralateral TA muscles were evoked bilaterally by electrical stimulation (40 V square pulse of 0.5-msec duration) of either fibular nerve (Fig. 1). No cutaneous silent period (CSP) was observed in either TA muscle following noxious electrical stimulation (100 V square pulse in up to 1-msec duration) of either big toe (Fig. 2). Local anesthetic blockage of fibular nerve with lidocaine at right capitulum fibula resulted in termination of spontaneous motor unit activity in right TA muscle. In right arm, CSP was recorded from the first dorsal interosseous muscle (FDI) following noxious electrical stimulation of the right index finger with a stimulus intensity twice above the sensory threshold (Fig. 3A). In the repeated electromyographic examination under treatment with clonazepam, neither spontaneous muscle activity nor repetitive myogenic bursts induced by electrical stimulation were observed in the right TA muscle. In addition, the threshold for eliciting CSP from right FDI muscle was nine times higher than the sensory threshold (Fig. 3B). No CSP was observed in either TA muscle with the stimulation of big toe.

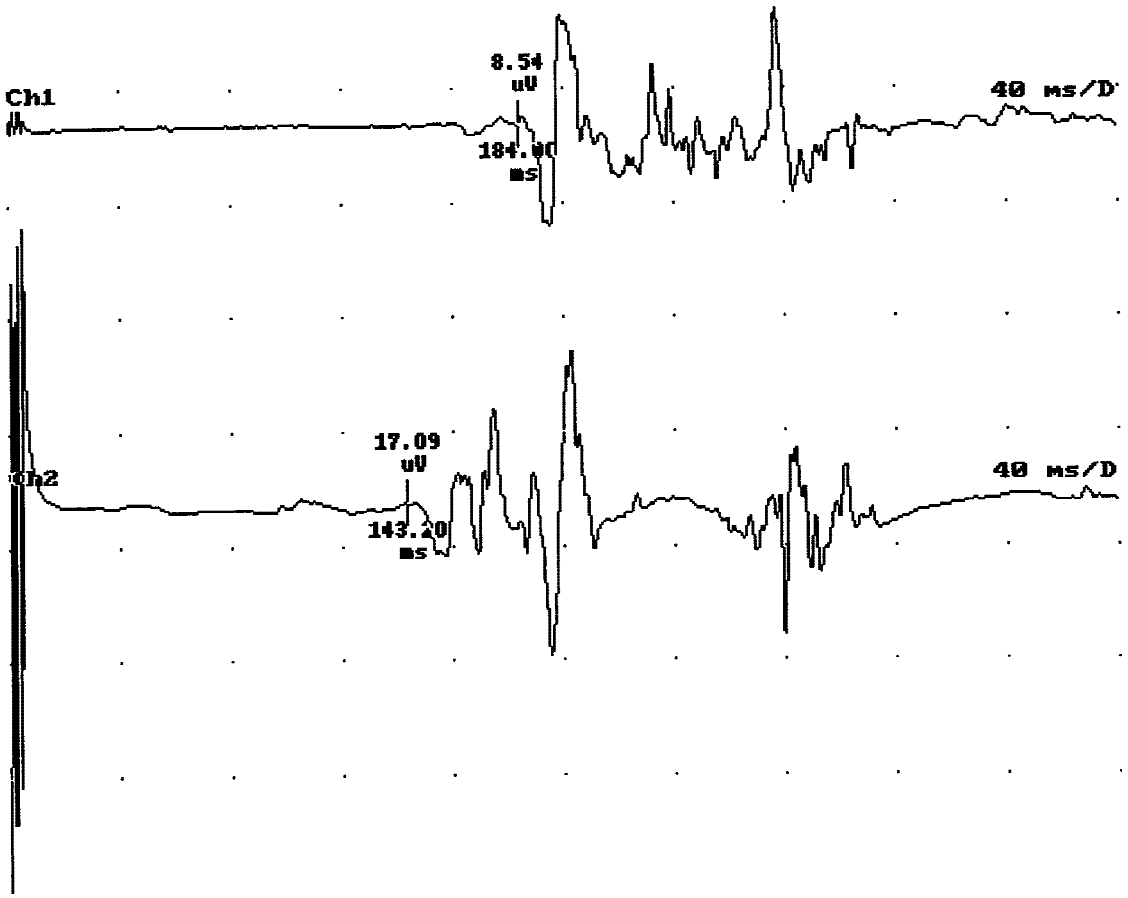

FIG. 1. Late reflex responses in both tibialis anterior (TA) muscles evoked by electrical stimulation (40 V in 0.5-ms duration) of right fibular nerve. Upper trace is from left TA muscle; lower trace is from right TA muscle (0.5 mV/division and 40 ms/division).

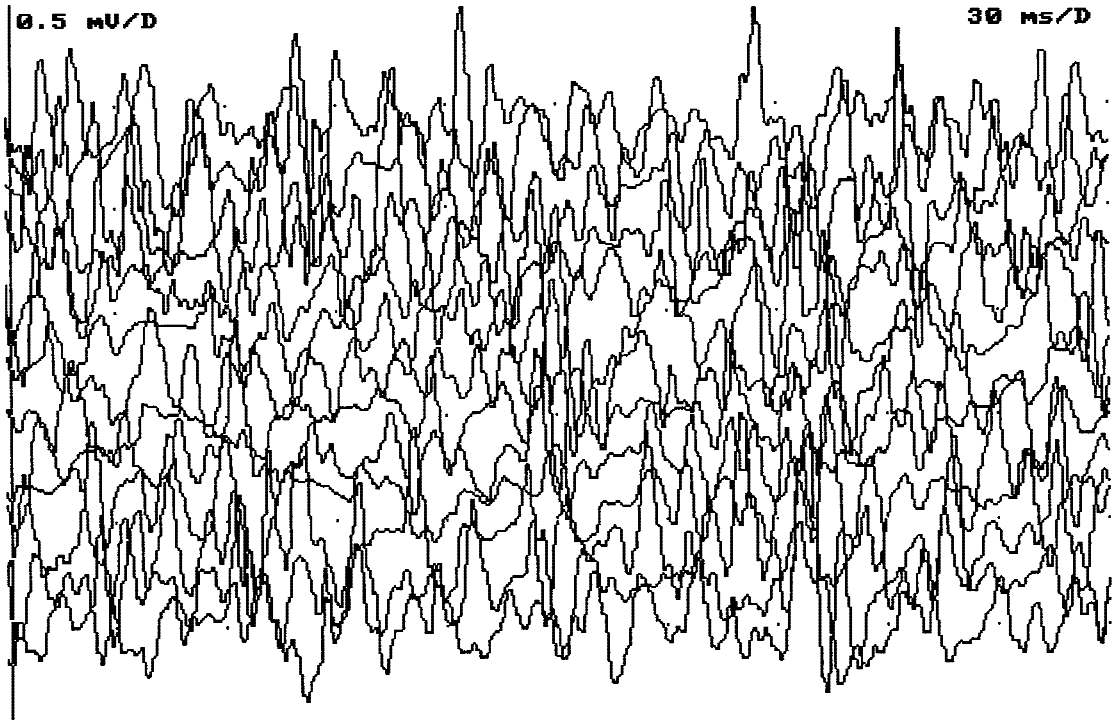

FIG. 2. No cutaneous silent period following noxious electrical stimulation of right big toe by recording from right TA muscle. Upper first trace was recorded with electrical stimulation in sensory threshold. From up to down, in each trace, stimulating electrical current is twice higher than the previous one.

Discussion

This patient's symptoms had an insidious onset and chronic progressive course. The stiffness and painful spasms were confined to one lower limb, the axial muscles being spared. Spasms induced by movement or auditory/tactile stimuli were an important cause of disability. Brainstem and pyramidal signs were absent and muscle strength seemed to be normal except when interrupted by spasms or hampered by severe rigidity. Extensive diagnostic work-up including imaging of the whole neuraxis and search for evidence of an infectious, malignant, or inflammatory cause did not reveal another cause. Other potential causes of similar symptoms such as radiculopathy or neuromyotonia were also ruled out by neuroimaging and electrophysiological studies. She had type I diabetes mellitus highly resistant to insulin therapy, a history of hyperthyroidism, and anti-GAD antibodies were found in a high titer in the serum. With these features, she was considered to have a stiff leg syndrome.

SLS is a newly emerging entity considered as a focal form of SPS in which the symptoms are confined to a distal limb (usually the leg). In this group of patients, abnormally segmented electromyographic (EMG) activity is recorded during spasms in addition to the electrophysiological findings of SPS; anti-GAD antibodies and autoimmune diseases are less common.[1,2,10,11] A significant overlap exists between SPS and SLS, but recognition of SLS as a subtype may have important therapeutic and prognostic significance. To date, histological characteristics have been reported in only one patient with a clinical history consistent with SLS.[12] The clinical and electrophysiological findings of our patient were similar to previous reports of SLS.[10,11] The findings in lower limbs such as muscle cramps and spontaneous EMG activity, indicating increased excitability, disappeared to a large extent following clonazepam therapy. Interestingly, the threshold for eliciting silent period in upper limbs became higher than the initial threshold following the treatment. CSP precedes the onset of voluntary muscle relaxation and is generally accepted to be an inhibitory spinal reflex.[13] CSP can be used to assess the afferent sensory impulses and the integrity of the intraspinal pathways that mediate this inhibitory response. Conditions that interrupt this pathway may be associated with absence or delay of CSP. The increase in threshold for eliciting silent period in upper limb after clonazepam therapy may be due to the direct effect of medication, normal variation in the threshold of CSP, or alternatively to the resetting of the inhibitory and excitatory circuits in spinal cord after cessation of hyperexcitability in lower limbs as a result of treatment. If confirmed in other cases, this observation may imply an increased spinal inhibition as an attempt to compensate for segmental hyperexcitability.

This case lends further support to the view that SPS is a heterogenous disease and may involve just one part of the body. Accumulation of data from cases with axial as well as distal limb involvement may help to refine the diagnostic criteria and improve our knowledge of the pathophysiology and treatment of these rare clinical entities.

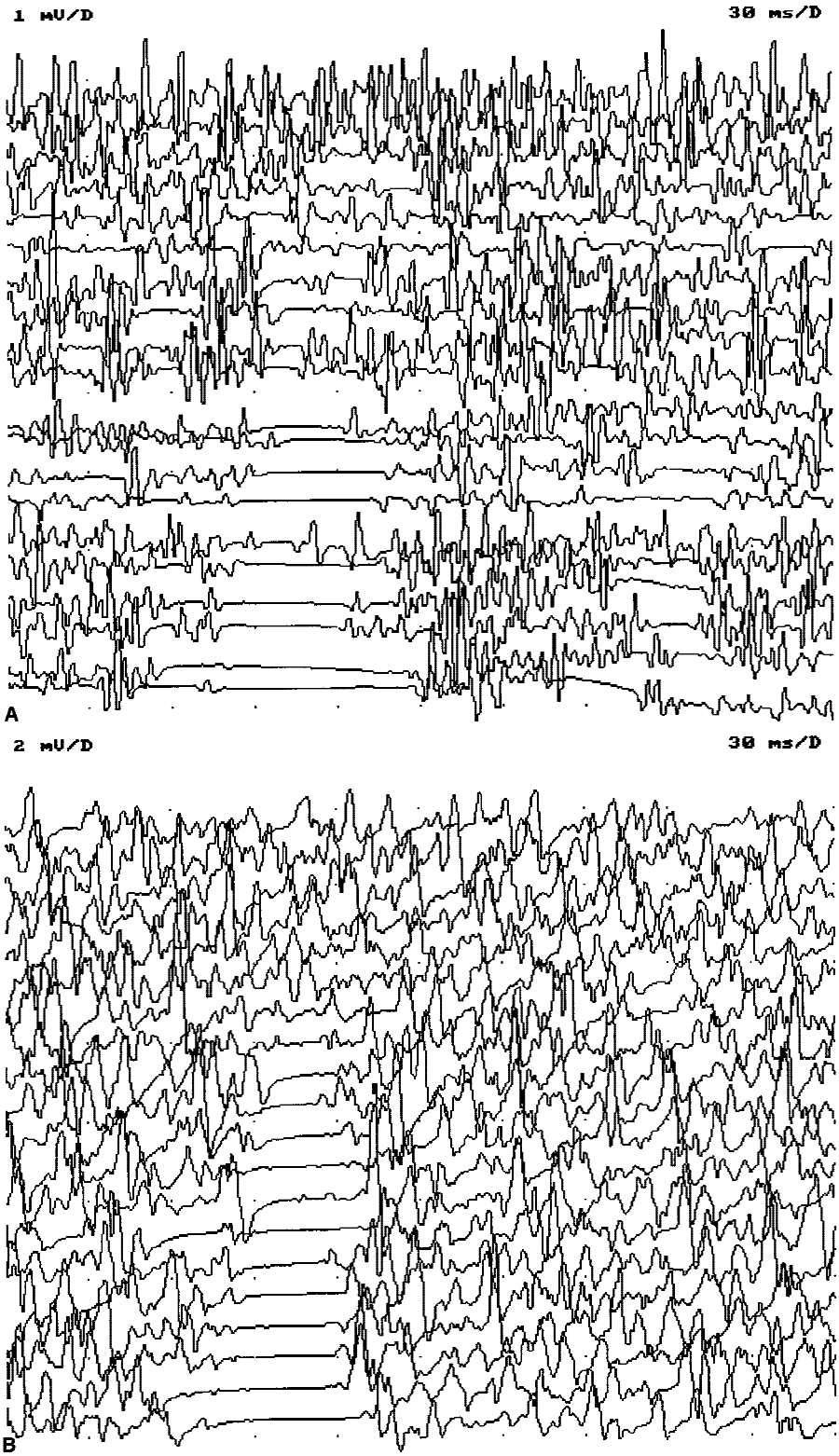

FIG. 3. Cutaneous silent period (CSP) following noxious electrical stimulation of right index finger by recording from right first dorsal interosseous (FDI) muscle. Upper first traces in both figures were recorded with electrical stimulation in sensory threshold. **A:** From up to down, in each trace, stimulating electrical current is 1.5 times higher than the previous one. CSP appeared with a stimulus intensity twice higher than the sensory threshold. **B:** From up to down, in each trace, stimulating electrical current is two times higher than the previous one. CSP appeared with a stimulus intensity nine times higher than the sensory threshold.

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Voluntary Palatal Tremor Is Associated with Hyperactivation of the Inferior Olive: A Functional Magnetic Resonance Imaging Study

Matthias F. Nitschke, MD,[1]* Gunnar Krüger, PhD,[2] Harald Bruhn, PhD,[2] Christine Klein, MD,[1] Eckart Gehrking, MD,[3] Karl Wessel, MD,[4] Jens Frahm, PhD,[2] and Peter Vieregge, MD[1]

[1]*Department of Neurology, Medical University of Lübeck, Lübeck, Germany*
[2]*Biomedizinische NMR Forschungs (GmbH), Max Planck-Institute for Biophysical Chemistry, Göttingen, Germany*
[3]*Department of Otolaryngorhinology; Medical University of Lübeck, Lübeck, Germany*
[4]*Department of Neurology, Clinic of Braunschweig, Braunschweig, Germany*

Abstract: Voluntary palatal tremor in a patient with essential palatal tremor induced activation predominantly within regions corresponding to the inferior olive, adjacent brainstem, and dentate nuclei. Finger movements elicited only ipsilateral lobular cerebellar activation, suggesting a dysfunctional nuclear activation by palatal tremor. © 2001 Movement Disorder Society.

Palatal tremor (PT) is a rare hyperkinetic movement disorder with involuntary rhythmic jerks of the soft palate, sometimes associated with synchronous movements of adjacent structures including pharynx, larynx, face, and diaphragm. A lesion affecting the pathway from the dentate nucleus to the red nucleus and the inferior olive is thought to be involved in the generation of PT that can be either essential (EPT) or symptomatic (SPT). EPT is clinically characterized by the occurrence of ear clicks with no signs of anatomical abnormalities and normal cerebellar function.[1]

Here we report on a functional magnetic resonance imaging (fMRI) study of the brother of a sib pair with EPT according to the above definition, i.e., who had accompanying ear clicks. Both sibs are peculiar in their ability to voluntarily elicit, modulate, and stop both movements and sounds by what they call an active thinking process. We investigated PT-induced brain activations and compared the results with activation maps obtained for a voluntary finger opposition task.

Methods

Case Report

A 21-year-old university student had a 1-year history of clicking sounds predominantly in the left ear. He could voluntarily "switch" the sounds on or off by just thinking about them. On examination, the patient showed a rhythmic tremor on both sides of the soft palate, but predominantly on the left. For the PT and ear clicks to occur, the patient had to provoke them voluntarily by "concentrating on the sounds." He could both start and stop them without any visible latency and maintain PT and clicks for several minutes. In a two-channel electromyograph (EMG) with clamp electrodes, rhythmic contractions of the muscles of the soft palate could be recorded only when the patient voluntarily elicited the PT. The remainder of the otolaryngeal, neurological, general, and psychiatric examination was normal. MRI scans of the skull, brain, and brainstem showed no abnormalities. Clinical details of the sibpair have been published elsewhere.[2]

Functional Magnetic Resonance Imaging

The study was performed at 2.0-T (standard headcoil; Siemens Magnetom Vision, Erlangen, Germany). A total of 12 coronal and transverse sections were selected from three-dimensional T1-weighted MRI (repetition time [TR]/echo time [TE]/flip angle = 15 msec/6 msec/20 degree, 4-mm slice thickness) to cover the brainstem, the inferior olive, and the cerebellar nuclei. The macrovasculature was further delineated by flow-sensitized images (TR/TE/flip angle = 70.313 msec/7.15 msec/60 degree, 4-mm slice thickness). Functional brain mapping was based on dynamic acquisitions of blood oxygenation

*Correspondence to: Dr. M.F. Nitschke, Department of Neurology, Medical University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany. E-mail: nitschke_m@neuro.mu-luebeck.de

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level dependent (BOLD) signal changes in these sections (TR/TE/flip angle = 62.5 msec/30 msec/10 degree, in plane resolution 0.78 × 1.56 mm^2, slice thickness 4 mm, measuring time 6 seconds). Each dynamic series comprised six cycles of 18 seconds of palatal tremor or finger opposition movements versus 36 seconds of rest, triggered by a soft touch of the patient's leg. The PT frequency was self-paced at the maximum possible rate (about 1–2 Hz). The finger task consisted of sequential self-paced oppositions of the thumb to all remaining fingers at a frequency of about 2 Hz. The subject wore ear plugs and his head was immobilized in a vacuum cap. Informed written consent was obtained before examination. Activated areas were determined by a pixelwise correlation of signal intensity time courses with an external reference representing the stimulation protocol. The MRI data were subject to a temporal low-pass filter (1–2–1-weighted). Maps of correlation coefficients were thresholded in accordance with the individual noise distribution. Only pixels with an error probability set at a 99.93 percentile rank were included in the final activation map.

Results

Voluntary triggered performance of PT was associated with significant activation within regions corresponding to the inferior olive, a brainstem region, and the cerebellar dentate nuclei. In the transverse sections shown in Figure 1, activation of the inferior olive was located on the left side. Finger opposition movements of the right hand elicited predominantly ipsilateral activation within the Larsell lobules HIV–V, the dentate nuclei, and no activation within the inferior olives. We also investigated the activation pattern resulting from a simultaneous performance of PT and finger opposition movements. Although the results were impaired by motion artifacts, we found activation within both the inferior olive and the dentate nuclei (not shown).

Discussion

Our study demonstrates activation within regions corresponding to the inferior olive, a brainstem region, and the dentate nuclei during execution of PT. The activation of the inferior olive and of the dentate nuclei could reflect the activity of a putative generator within the dentato–rubro–olivary pathway.[1] This was also hypothesized by other neuroimaging studies. A positron emission tomography (PET) study demonstrated PT-induced increased glucose metabolism in the medulla, but due to limited resolution could not identify a distinct anatomical structure.[3] Another fMRI study demonstrated activation of the inferior olive and of the cerebellar dentate nuclei in a patient with unclear classification but suspected EPT because of ear clicks and the absence of structural changes.[4] The results by the finger opposition task also support a possible dysfunctional hyperactivation within these structures. Previous imaging studies of finger or tongue movements revealed activation within the anterior cerebellum but did not demonstrate involvement of the inferior olive.[5,6] Finger movements in our patient resulted in a similar activation pattern. A possible dysfunctional hyperactivation of the inferior olive by finger movements that provide prominent relevant sensory feedback through the olivary nuclei could not be detected. With respect to the physiology of EPT, the data for a combined performance of PT and finger opposition movements suggest activation of both the inferior olive and the Larsell lobules IV–V without a substantial change compared with the individual activation maps. This observation corresponds to electrophysiological data where EPT, in contrast to SPT, did not exert any remote effects on the activity of the upper extremities.[1] Although it cannot be excluded that our finding of predominant left-sided activation of the inferior olive emerges from a technical condition such as section orientation positioning the optimal sample volume only on the left side, it is possible that a left-sided predominance for the control of PT prevails regardless of the clinical presentation. This latter explanation also corresponds to other reports of unilateral changes in some patients with PT.[1]

The detected brainstem activation could reflect the control of the palatal musculature especially the tensor veli palatini muscle innervated by the fifth cranial nerve that mediates the symptoms in EPT.[1,7] It is also possible that the brainstem activation represents an anatomically distinct generator that could be located within the formatio reticularis, the cranial nerve nuclei, the nucleus ambiguous, or other oscillatory brainstem nuclei.[8,9] However, one has to keep in mind that even a high

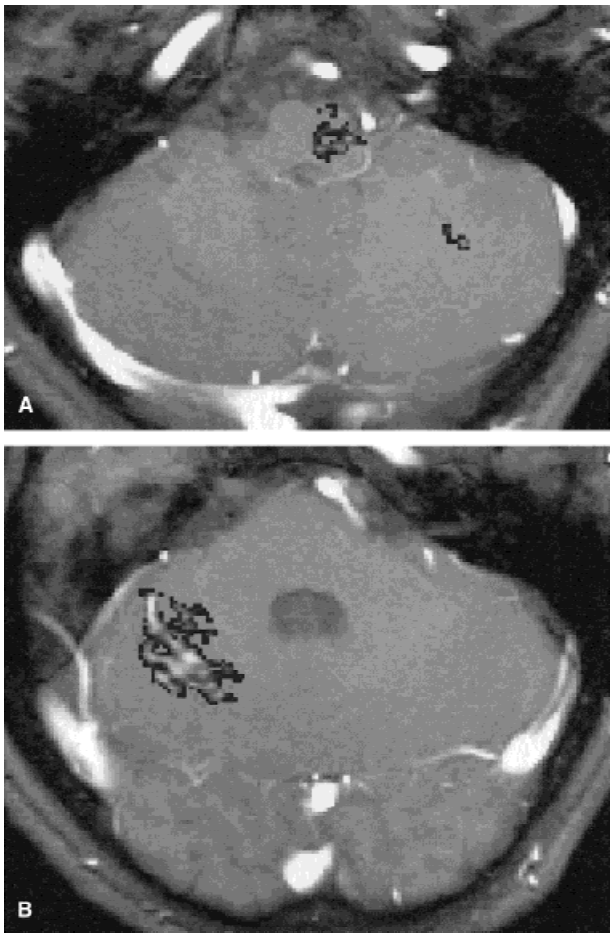

FIG. 1. A: Significant activation predominantly within the inferior olive on the left side, an adjacent brainstem region, and within the cerebellar dentate nucleus elicited by voluntary controlled palatal tremor. **B:** Significant activation within the ipsilateral Larsell lobules H IV–V is elicited by finger opposition movements of the right hand. The hand motor task does not lead to activation of the inferior olives.

spatial resolution of the activation maps as chosen here may not be sufficient to distinguish activation foci with certainty.

Despite some of these caveats, our data support the contention that EPT is associated with dysfunctional activation predominantly within the dentato–rubro–olivary pathway. Our study therefore demonstrates the ability of functional MRI to detect subtle changes associated with pathological dysactivation even within brainstem structures.

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