Movement Disorders
Vol. 14, No. 6, 1999, pp. 1025–1056

Clinical/Scientific Notes

Striatal D2 Dopamine Receptor Status in Parkinson's Disease: An [^{18}F]Dopa and [^{11}C]Raclopride PET Study

The pathologic hallmark of Parkinson's disease (PD) is the degeneration of the nigrostriatal system with marked dopamine depletion in the striatum.[1] Positron emission tomography (PET) has shown a decrease of [^{18}F]-6-fluoro-L-dopa (F-dopa) uptake in this region, more pronounced in the putamen than in the caudate.[2–4] Striatal D2-dopamine receptor density can be evaluated either postmortem or in vivo using PET and [^{11}C]Raclopride (RACLO) or [^{11}C]N-methylspiperone. Several studies have reported an increased striatal D2 receptor binding in patients with early PD, and unchanged or decreased striatal binding in chronically treated patients.[1,5–12] It was suggested that primary loss of nigrostriatal dopaminergic projections could result in secondary post-synaptic D2-dopamine receptor upregulation, whereas long-term dopaminergic neuronal loss and chronic exposure to L-dopa would be responsible for D2 receptor downregulation. However, such an hypothesis remains controversial. Indeed, normal D2 receptor binding has also been reported in treated and untreated patients with PD postmortem as well as in vivo by PET.[5,7,13–16] Moreover, studies in large groups of patients using single photon emission computed tomography (SPECT) with [^{123}I]Iodobenzamide (IBZM) have shown normal striatal binding in dopa-responsive patients with PD at onset of disease and during follow up, as opposed to reduced binding in other degenerative parkinsonian syndromes with poor or lack of response to levodopa which was also found with PET.[7,17,18] Finally, few PET studies have measured simultaneously both the pre- and post-synaptic aspects of the dopaminergic system in patients with PD.[9,19] Such an approach should, however, provide a more complete and accurate analysis of the functional consequences of the degeneration of the nigrostriatal pathway.

In an attempt to better determine the striatal D2 dopamine receptor status in PD, we performed a PET F-dopa and RACLO study in early drug-naive subjects with further follow up demonstrating levodopa responsiveness, and in patients with long-term dopaminergic therapy and motor fluctuations. We hypothesized that, in contrast to a decreased F-dopa uptake, striatal RACLO binding should be normal in both untreated and treated patients with PD based on the following points. Because one of the important diagnosis criteria for idiopathic PD is the strong and sustained response to levodopa,[20] this suggests normal functioning of striatal D2 receptors at the onset of disease and over time. Experiments in animal models indicate that changes in striatal extracellular dopamine levels and post-synaptic receptor density occur only after an almost complete destruction of the nigrostriatal dopaminergic pathway, which is unlikely to be the case in early or moderate PD.[21–25]

Received November 2, 1998; revision received March 9, 1999. Accepted June 29, 1999.

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Subjects and Methods

Patients with PD and Control Subjects

The present study was performed after approval by the Lyon University Hospitals Ethical Committee, and signed informed consent was obtained according to the declaration of Helsinki.

We investigated 15 right-handed patients (10 men, five women) fulfilling criteria of idiopathic PD[20] and recruited from two departments of neurology (Table 1). This population was classified into two groups. Group 1 ("de novo" patients) included seven drug-naive patients with early PD and Hoehn and Yahr stages 1–2. Subsequently to the PET study, patients were confirmed to be dopa-responsive during 2–3 years of follow up. Group 2 ("treated" patients) consisted of eight long-term treated patients with PD with Hoehn and Yahr stages 2–3. All received levodopa treatment plus a peripheral decarboxylase inhibitor for at least 1 year (mean daily levodopa dosage: 550 mg; range: 250–800 mg), and presented significant motor fluctuations (wearing off) and mild to moderate dyskinesias. Levodopa was the only dopaminergic treatment in one of the eight patients, whereas five cases received bromocriptine, one received piribedil, and two received selegiline.

Disease severity was assessed with the modified version of the Hoehn and Yahr scale and motor performances with the part III (items 18–31) of the Unified Parkinson's Disease Rating Scale (UPDRS).[26] In patients with PD from group 2, on-medication motor score was measured on the day prior to the first PET scan. On each PET day, these patients were in the off-medication state for at least 12 hours. Off-medication motor scores were recorded in all patients just before the first PET scanning.

Patients with PD were compared with nine age-matched, right-handed healthy subjects (four men, five women). Exclusion criteria in control subjects were significant neurologic disease, noticeable medical history or drug treatment, and abnormal finding in the basal ganglia at brain magnetic resonance imaging (MRI).

PET Methods

PET investigation used F-dopa and RACLO, successively, with a 1 day to 2 weeks delay between scans. All drugs were temporarily interrupted as already indicated, and treatment was resumed only after termination of PET scanning. An MRI scan was performed in the morning immediately prior to the first PET scan in all patients and control subjects using a Magnetom 63 SP or a Magnetom Vision 1.5 T magnet (Siemens S. A., Erlangen, Germany), with collection of 3D–T1-weighted 1-mm contiguous sagittal slices.

^{18}F and ^{11}C were produced by a Cypris 325 CGR-Mev Cyclotron (France). Radiosynthesis of F-dopa and RACLO were

TABLE 1. *Demographic and clinical data in patients with Parkinson's disease and control subjects**

	Age† (yrs)	Disease duration (mos)	Hoehn and Yahr stage‡ (0–5)		UPDRS part III motor score‡ (maximum:108)	
			Off	On	Off	On
Control subjects (N = 9)	52.6 ± 9.0 (41–66)	—	—	—	—	—
De novo PD patients (N = 7)	53.1 ± 13.0 (39–69)	16.0 ± 10.6 (5–36)	1.4 ± 0.3 (1–2)	—	12.2 ± 5.6 (4–20)	—
Treated PD patients (N = 8)	59.4 ± 9.5 (40–67)	97.4 ± 18.5 (72–120)	2.3 ± 0.4 (2–3)	1.4 ± 0.9 (0–2)	23.4 ± 8.7 (11–39)	12.0 ± 7.3 (4–26)

UPDRS, Unified Parkinson's Disease Rating Scale.

*Results are expressed as the mean ± standard deviation with range in parentheses.

†No statistically significant difference between the three groups of subjects.

‡Significant difference of the off medication Hoehn and Yahr ($p = 0.002$) and UPDRS motor score ($p = 0.02$) between the two groups of patients with Parkinson's disease (non-parametric Mann-Whitney U-test).

performed as previously described.[27,28] Quality control and radiochemical purity were assessed by HPLC and thin layer chromatography. There was a 92%–96% excess of enantiomeric L form of F-dopa with a radiochemical purity above 98%. One hour before injection of F-dopa, subjects were premedicated with a single oral dose of 50 mg benserazide, a peripheral dopa-decarboxylase inhibitor. The intravenous dose range was 150–260 MBq for F-dopa (specific activity [SA] 111–296 GBq/μmol) and 222–592 MBq for RACLO (SA: 7 ± 0.9 GBq/μmol). The amount of injected cold raclopride was not significantly different between patients with PD and control subjects (*t* test).

PET scanning used a TTV03 LETI positron tomograph which yields seven simultaneous slices (9 mm within and 12 mm between slices) with a resolution in the reconstituted image of 9 mm axial and 7 mm in plane. The subject was positioned in the PET scanner with the head immobilized in a polyurethane mold, which was used for the two PET scans and the MRI. The scanner was aligned parallel to the AC–PC line using a laser beam. The gantry field of view was chosen with the lowest plane at the AC–PC line −24 mm. Continuous PET scanning was started at the time of radioligand injection during 90 minutes for F-dopa and 60 minutes for RACLO. Emission scans were attenuation-corrected with transmission scans collected during exposure to a 68 Ge-68 Ga external rotating source.

PET Data Analysis

Quantification of F-dopa and RACLO was done on SUN Sparc workstations (Sun Microsystems, Silicon Valley, CA, USA). ROIs were composed of circular regions as previously described[3] with a diameter of 8.2 mm placed on the head of the caudate (one in each hemisphere) and on the putamen (three regions lined adjacent to each other along the axis of the putamen for each hemisphere), and a diameter of 32.8 mm placed on the occipital region on the same plane as the striatum. Striatal (putamen, caudate nucleus) and background ROIs (occipital cortex) were co-registered on the MRI and PET images at the same axial level with the help of Surface-Matching software (ANALYZE, Mayo Foundation, Baltimore, MD, USA). In each subject, we retained only the two consecutive PET axial planes showing the highest contrast ratio striatum/background. Following correction for decay, a time activity curve was generated for each ROI.

Specific striatal F-dopa uptake was analyzed using the multiple-time graphic analysis (MTGA) approach with a nonspecific occipital reference tissue input function in preference to plasma. The slopes of such MTGA plots can be regarded as influx constants, Ki (min-1), which reflect specific striatal ^{18}F accumulation.[2,3] Mean right and mean left Ki values for caudate and putamen over the optimal two planes were therefore calculated from the individual hemispheric ROI data. RACLO binding was calculated from the equilibrium striatum/occipital radioactivity ratio using data collected from 25–60 min after tracer injection. This equilibrium can be related to striatal D2 receptor density, because the level of D2 receptor in the occipital cortex is insignificant. The ratio striatal activity–occipital activity/occipital activity (S-O/O) was used as an index of RACLO binding.[7,8] Mean right and mean left caudate and putamen (S-O)/O values over the optimal two planes were therefore calculated from the individual hemispheric ROI data. A mean right and left value of Ki and of (S-O)/O ratio was also derived for each anatomic region.

Statistical Analysis

Statistical analysis used Statview statistical software (Abacus Concepts, Berkeley, CA, USA). Comparison of mean age in control subjects and patients used one-factor analysis of variance (ANOVA). Differences in UPDRS motor scores between the two groups of patients with PD were analyzed by a nonparametric Mann-Whitney U-test. A one-factor ANOVA was applied to study the disparity between control subjects and patients of successively F-dopa Ki and RACLO binding ratio values in caudate or putamenal regions contralateral and ipsilateral, respectively, to the hemibody with the most prominent signs on the UPDRS motor scale. All ANOVA studies were completed by post-hoc analysis using the Fisher *t* test with a significant level at $p < 0.05$. A Spearman rank order correlation analysis with subsequent Bonferroni corrections was then made in patients with PD to study the correlation between mean right and left F-dopa Ki values in the putamen or the caudate, and duration of disease, off-medication Hoehn and Yahr and UPDRS motor scores. A similar analysis was done for RACLO binding ratios. Finally, a correlation analysis in patients with PD between mean right and left F-dopa uptake Ki values and RACLO binding ratios was done for the caudate nucleus and for the putamen. Additional correlation analysis was also made

between F-dopa uptake Ki values and RACLO binding ratios in the more affected putamen, either in the de novo PD patients' group or after combining all patients with PD in one single group.

Results

Demographic and clinical data are presented in Table 1. There was no statistically significant age difference among patients with PD and control subjects, although treated patients were slightly older than de novo cases and normal subjects. The variance of de novo and treated patients with PD UPDRS motor scores in off-medication state was not significantly different (square rank sum test). Mean UPDRS motor performances and mean Hoehn and Yahr scores were significantly higher in de novo than in treated patients with PD ($p = 0.02$ and $p = 0.002$ respectively; non-parametric Mann-Whitney U-test).

The F-dopa influx constant Ki values in putamen and caudate regions of patients with PD and control subjects are shown in Table 2. ANOVA showed a highly statistically significant heterogeneity among groups for caudate and putamen. Post-hoc Fisher test disclosed a meaningful ($p < 0.05$) difference of Ki values between control subjects and each of the patients' groups and between patients with PD from group 1 and group 2 for both more and less affected putamen and for the more affected caudate. In the less affected caudate region, this difference was significant only between control subjects and treated patients. In early PD, a 31.5% and 17.0% decrement of F-dopa uptake was observed for mean right and left putamen and caudate, respectively. In treated patients with more advanced PD, mean right and left Ki values were reduced by 60.4% and 36.6%, respectively, in these brain regions.

The mean RACLO binding ratios in putamen and caudate regions of patients with PD and control subjects are shown in Table 2. Values were similar between the less and the more affected region for both caudate and putamen. No statistically significant differences were found by one-factor ANOVA among groups in the putamen. There was a trend toward a decrement of RACLO binding ratio in the caudate of patients with PD, more in treated than in de novo cases (mean right and left RACLO binding ratio was lowered by 23% and 15%, respectively). This reached statistical significance at ANOVA only in the less affected caudate but not in the more affected caudate with a meaningful decrement of RACLO binding ratio in treated patients with PD on the Fisher test ($p < 0.02$).

A significant inverse correlation was found between mean right and left F-dopa uptake and the duration of disease only for the putamen ($r = -0.75$; $p < 0.01$), but not for the caudate ($r = -0.48$; $p > 0.05$). Again, a significant inverse correlation was noticed between mean right and left F-dopa uptake in the putamen and off-medication Hoehn and Yahr stage ($r = -0.69$; $p = 0.0009$) and UPDRS motor scores ($r = -0.47$; $p = 0.01$). The same analysis for the F-dopa uptake in the caudate revealed significant inverse correlation of this variable only with off-medication Hoehn and Yahr ($r = 0.66$; $p = 0.02$). If Bonferroni correction was applied for these six repeated measures, inverse correlation remained significant ($p < 0.05$) only between putamen F-dopa uptake Ki and duration of illness or Hoehn and Yahr. The same procedure was used with the mean right and left RACLO binding ratio. No significant correlation was found between this variable in the putamen as in the caudate, and any of the three other parameters ($p = 0.16$ and $p = 0.28$, respectively, for the duration of illness; $p = 0.27$ and $p = 0.38$ for the Hoehn and Yahr score; and $p = 0.88$ and $p = 0.79$ for the UPDRS motor score).

Finally, no inverse correlation was found in patients with PD between mean right and left F-dopa uptake Ki and RACLO binding ratio values ($r = 0.032$ for the putamen, and $r = 0.23$ for the caudate; not significant). Because a tendency toward a side-to-side difference in RACLO and F-dopa values was seen on Table 2, we therefore performed an additional correlation analysis in the "more affected" striatal region. Again, no significant inverse correlation was noticed between RACLO and F-dopa values in either putamen or caudate in the de novo patients with PD ($r = 0.001$ and $r = 0.38$, respectively), as well as when combining patients with PD into one group ($r = 0.01$ and $r = 0.17$).

Discussion

The present study shows that in idiopathic PD in which striatal dopaminergic denervation is assessed by PET and F-dopa, D2-dopamine receptor function evaluated by the RACLO binding ratio is normal in untreated de novo patients in both

TABLE 2. *Mean values of F-dopa rate constant Ki and RACLO binding ratio in caudate nucleus and putamen of patients with Parkinson's disease and control subjects**

	Caudate nucleus F-dopa Ki (min-1)		Putamen F-dopa Ki (min-1)		Caudate nucleus RACLO binding (S-O)/O ratio		Putamen RACLO binding (S-O)/O ratio	
	More affected	Less affected	More affected	Less affected	More affected	Less affected	More affected	Less affected
Control subjects	0.0110 ± 0.015	0.0120 ± 0.0019	0.0110 ± 0.0016	0.0110 ± 0.0015	2.02 ± 0.49	1.98 ± 0.46	1.97 ± 0.40	1.98 ± 0.42
De novo PD patients	0.0083 ± 0.0022	0.0100 ± 0.0020	0.0064 ± 0.0026	0.0083 ± 0.0021	1.74 ± 0.35	1.66 ± 0.26	2.00 ± 0.38	1.85 ± 0.36
Treated PD patients	0.0068 ± 0.0012	0.0075 ± 0.0028	0.0039 ± 0.0011	0.0048 ± 0.0015	1.57 ± 0.35	1.46 ± 0.27	1.87 ± 0.30	1.78 ± 0.29
Statistics one-factor ANOVA	$p = 0.0005$	$p = 0.0036$	$p = 0.0005$	$p = 0.0005$	$p = 0.10$ (NS)	$p = 0.02$	$p = 0.79$ (NS)	$p = 0.55$ (NS)
Post-hoc Fisher test	a	b	a	a	—	b	—	—

* Results are expressed as the mean ± standard deviation in the more and in the less affected striatal region (that is, contralateral and ipsilateral, respectively, to the hemibody with the most prominent motor signs at UPDRS). Note for control subjects that the more affected and the less affected region refer arbitrarily to the right and left striatum.

NS, not statistically significant; ANOVA, analysis of variance; UPDRS, Unified Parkinson's Disease Rating Scale.

a: statistically significant at $p < 0.05$ between control subjects and each of the PD group and between the two PD patients groups.

b: statistically significant only between control subjects and patients with Parkinson's disease in group 2.

caudate and putamen, whereas in treated patients, the binding ratio is unchanged in putamen and slightly decreased in caudate.

Only two previous PET investigations have simultaneously determined F-dopa and RACLO uptake in early PD patients. The first study was performed in 10 patients with PD with Hoehn and Yahr stages 1–2, but only three of them were drug-naive.[9] An increased RACLO binding was noted in the putamen but not in caudate. In the second study in eight levodopa-naive patients with PD, the putamen with the lowest F-dopa uptake (contralateral to the clinically more affected side) had the highest RACLO binding ratio and vice versa.[19] The authors suggested that upregulation of the post-synaptic D2 receptors occurred in de novo drug-naive patients with PD. This is, however, not corroborated by our own results in seven early untreated patients with PD. Indeed, we do not disclose any significant changes in RACLO binding in both caudate and putamen and no side-related correlation between RACLO binding and F-dopa uptake.

A number of PET investigations measured D2-dopamine receptor binding in untreated de novo patients with PD. Brooks et al.[7] described a nonsignificant 11% increase of putamen-to-cerebellum RACLO binding ratio in six untreated patients with PD. Other studies performed in drug-naive patients showed significant increases of tracer uptake (generally of 7%–20%), particularly in the striatum contralateral to the more affected side of the body.[6,10–12] In contrast, normal or even decreased striatal D2 receptor binding has been also demonstrated in untreated patients with PD studied with PET and the tracer [^{11}c]-N-methylspiperone[5,14] or SPECT and [^{123}I]-Iodobenzamide. [17]

The apparent discrepancy in early PD between normal putamen RACLO binding, as shown by our study and elevated binding described in some of the above-mentioned reports, do not have a simple explanation. A different selection of radioligands and mostly of patients with PD may be considered. Compared with that of Sawle et al.[19] and Antonini et al.,[9] our early patients with PD had a shorter duration of illness (on average, 16 months compared with 28.5 and 36 months, respectively) and a less pronounced decrement of putamen F-dopa uptake (−31.5% as opposed to −56.9% and −55%, respectively). In contrast, our PET camera and methods were not significantly different. In particular, the resolution of the PET camera and the ROIs were similar to ours.[9,19] In our study, the same methodology was used for both F-dopa and RACLO data analysis, and our F-dopa results are in accordance with those of the literature.

Nevertheless, convergent arguments favor a normal functioning of D2 receptors in early untreated PD. A majority of postmortem studies have shown normal striatal D2 receptor density in drug-naive patients with PD.[13,15,16] Furthermore, animal studies have revealed that rats with unilateral lesion of the substantia nigra presented normal striatal D2 receptor densities and D2 mRNA levels in the striatum ipsilateral to the lesion.[29] In the same rat model, striatal tissue dopamine concentrations are proportional to lesion severity, and supersensitivity of D2 receptors as judged by induction of rotational behavior after apomorphine or L-dopa administration occurs only when 90% or more of the nigrostriatal neurones are destroyed.[21] Accordingly, studies with intracerebral microdialysis demonstrate that extracellular dopamine concentration in the lesioned striatum remains unchanged in rats with 60%–90% striatal tissue dopamine depletion.[22] More extensive lesions (96%–99% tissue dopamine depletion) are needed to produce a fall in extracellular dopamine.[22,23] Besides these pre-synaptic compensatory mechanisms, increase in post-synaptic dopamine receptors (that is, receptor supersensitivity) takes place only if depletion of striatal dopamine exceeds 80%–90%.[24] Similarly, in monkeys with MPTP-induced lesion of the substantia nigra, increased density of D2 receptors in the striatum occurs, but again, this is secondary to massive drop (90% or more) of striatal dopamine.[25] The clinical model of PD differs from the experimental ones by the fact that the degeneration of the nigrostriatal dopaminergic pathway is progressive. Putamen tissue dopamine loss is approximately 70%–80% of normal levels in patients with PD studied postmortem,[1] but may reach more than 95% in some subregions of the putamen in advanced disease.[30] However, it is unlikely that tissue dopamine loss is as severe in early PD. Accordingly, the decrement of PET F-dopa uptake in such patients is approximately one third in the present work as in other reports.[3] This argues against the hypothesis of an upregulation of putamen D2 receptors in de novo PD. Taken together, these data are consistent with our finding of normal D2 receptor function in drug-naive patients with PD.

Our group of eight treated patients with PD with longer-standing disease showed a moderate but significant decline of RACLO binding ratio in caudate, whereas normal values were observed in putamen. This finding has not been constantly found by others, either in the caudate, or in both caudate and putamen.[1,5–12] Only one study simultaneously determined PET F-dopa and RACLO uptake in treated patients with PD who had advanced illness.[9] In patients with PD with Hoehn and Yahr stages 3–4, RACLO binding was normal in putamen and diminished in caudate, similar to our own findings. Because dopaminergic treatment may reduce binding of D2 receptor ligands,[8,31] the question arises as to whether the medication of the treated patients with PD interfered with their striatal tracer binding. However, the plasma and cerebrospinal fluid half life of levodopa is approximately 1–2 hours, and only acute levodopa infusion appears to displace RACLO binding,[31] whereas our treated patients were off levodopa for 12 hours before PET. Besides, the influence of dopaminergic agonists on D2 receptor binding must be minimal, because in that case RACLO binding ratio should decrease not only in caudate, but also in putamen. Alternatively, reduction in caudate RACLO binding could be the result of reduced dopamine D2 receptor density subsequently to changes in post-synaptic nondopaminergic striatal neurons. This definitely occurs in other degenerative parkinsonian syndromes as multiple system atrophy.[18] It remains unclear, however, why in such an instance reduction of RACLO binding is found in caudate but not in putamen of chronically treated patients with PD.

In conclusion, the present study does not elicit upregulation of D2 receptors in untreated de novo patients with PD despite significant striatal dopaminergic denervation. In treated patients with PD with sustained response to levodopa, D2 receptor binding status remains stable at least in the putamen. These findings are consistent with preserved extracellular dopamine levels in patients with PD denervated striatum at onset of disease and even with longer disease duration.

Acknowledgments: This work was supported by a grant from Région Rhône-Alpes 1994–1997 Neuroscience Program.

The authors thank Dr. V. Leviel and Dr. N. Ginovart for their comments on the manuscript.

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Primary Writing Tremor Treated by Chronic Thalamic Stimulation

Primary writing tremor (PWT) is considered to be a type of focal tremor of the upper limb that predominantly occurs during, and interferes with, writing. The term was first introduced by Rothwell et al.[1] and has since been used in several publications,[2–10] but its precise clinical definition and nosology are controversial. This type of occupational tremor can cause considerable social and employment disabilities in certain patients,[1,3,10] and standard medical treatments sometimes offer no satisfactory long-term solution.[3] In this context, functional neurosurgical treatment may be considered an alternative for selected patients.

In 1982, Ohye et al. reported complete relief of PWT in three patients after stereotactic thalamotomy.[3] Deep brain stimulation (DBS) of the ventral intermediate (Vim) thalamic nucleus is currently considered an effective procedure for the control of upper limb tremor secondary to various diseases. Unlike thalamotomy, this technique is reversible, adaptable to the clinical situation, and is likely associated with a lower morbidity.[11]

We present a patient with PWT at 1-year follow up who was satisfactorily treated by thalamic stimulation. To our knowledge, this is the first description of a patient with an occupational kinetic tremor in whom this procedure yields a significant benefit.

Case Report

A 40-year-old man was referred to our unit in 1996 with a tremor in the right hand that predominantly appeared during handwriting, which it hampered. His father had a similar tremor. The remaining medical history was of no interest. When he was 16 years old he noticed a tremor in the right hand when writing, initially in stressful situations, and which worsened gradually over the years. Sometime later he occasionally felt a mild tremor if the arm was in particular postures and when performing skilled manual tasks, but it was always less severe than during writing. At the age of 26 he sought medical care because the writing tremor was affecting his work. Brain computed tomography scan, thyroid hormone, and copper metabolism results were all normal. The patient reported that alcohol intake improved the tremor. Treatment with up to 160 mg propranolol per day provided some benefit but was not well tolerated and its efficacy reduced with time. Primidone was not tolerated. Intermittent courses of benzodiazepine treatment brought some relief. He tried unsuccessfully to learn to write with his left hand during this period. Since the age of 30 the features and intensity of the tremor have remained unchanged. Subjectively, a greater effort has been required to achieve acceptable handwriting at the expense of gripping the pen tightly. Because handwriting is often required in his occupation as a clerical worker, he tried to change his employment without success. Because the patient was disabled and had found no satisfactory relief, he was referred to our center for a possible surgical approach.

The neurologic examination showed a mild postural and kinetic tremor in the right arm that was greatly exacerbated during handwriting. The tremor was present on adoption of the writing posture and increased in amplitude when he put pen to paper and during writing. The frequency of the tremor was approximately 5 Hz and the maximum amplitude was 2 cm. On a Clinical Tremor Rating Scale,[12] the total score was 27 points (17.3% of the maximum score). The writing was distorted when done with his arm unsupported (Fig. 1A). Many legible words were written when he rested his arm on the table (Fig. 1B), but slowly and with considerable forearm muscular effort. Drawing of a spiral was also problematic (Fig. 1C). Other manual activities, such as using a spoon or drinking from a full glass, were also affected by the tremor but less severely and without causing a serious disability.

Surgical Procedure

In March 1997, a quadripolar electrode for DBS (model 3387 Medtronic, Minneapolis, MN, USA) was implanted into the left thalamus under local anesthesia. The Cosman-Roberts-Wells (CRW) stereotactic system was used and the coordinates for the anterior commissure, the posterior commissure, and the anatomic midline were determined from computed tomography images. Vim thalamic nucleus coordinates were defined from data of the Schaltenbrand and Wharen atlas[13] with the support of a software package described elsewhere.[14] This anatomic target was localized 5 mm behind the midpoint of the intercommissural line, 1 mm above that line, and 14 mm distant from the midline of the brain. The tetrapolar electrode was implanted so that its distal contact coincided with this theoret-

A videotape accompanies this article.

Received October 19, 1998; revision received March 9, 1999. Accepted July 14, 1999.

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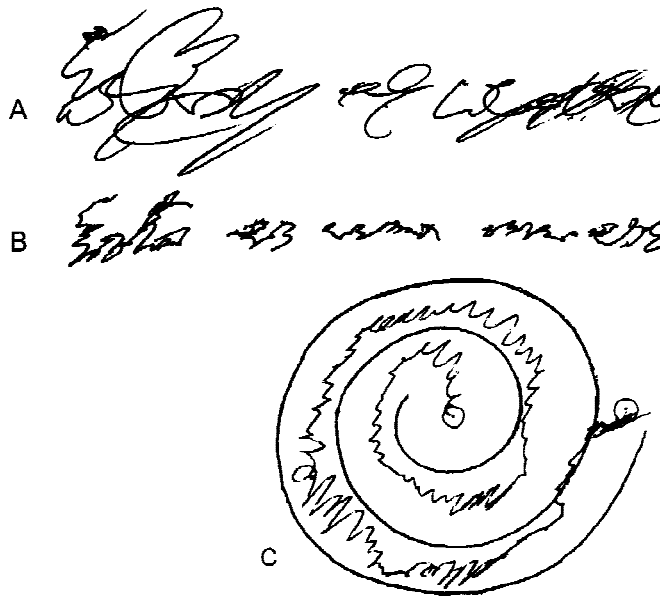

FIG. 1. Presurgical: (**A**) writing with the arm unsupported; (**B**) writing with the arm supported; (**C**) drawing of spiral with the arm unsupported.

ical target. For the intraoperative neurophysiological evaluation, we used high-frequency electrical stimulation tests at the different electrode contacts while the patient was writing and drawing spirals with the right arm elevated. Stimulation of the distal contact completely abolished the tremor at low amplitudes (approximately 1 V) and there were no side effects, thus the position of this contact was identified as the final target. The electrode was attached to the skull and connected to a provisional external lead. Over the next few days, various stimulation tests were done to confirm clinical effects using this connecting lead. A postoperative computed tomography scan showed the tip of the electrode in the left ventrolateral thalamus and no other intracranial lesions. Four days after the first intervention, a pulse generator (Itrel II model, Medtronic, Minneapolis, MN, USA) was implanted into the homolateral subclavicular region under general anesthesia. After determination of the optimum combination of parameters, the generator was programmed to deliver monopolar stimulation at the distal contact (negative) at a frequency of 130 Hz with pulses of 60 μs width and 1.5 V amplitude. The patient was instructed in turning the stimulation on and off with a control magnet.

Clinical Outcome

The patient has had no complications related to the surgery or stimulation. Within a few seconds of connecting the generator, there is almost complete control of the right arm tremor in all positions and activities, including writing and drawing with the hand elevated (Fig. 2). Over the first 3 months the stimulation amplitude had to be raised to 2.2 V to achieve the same clinical effect, from which time the parameters were unchanged. The video recording shows this clinical effect 1 year

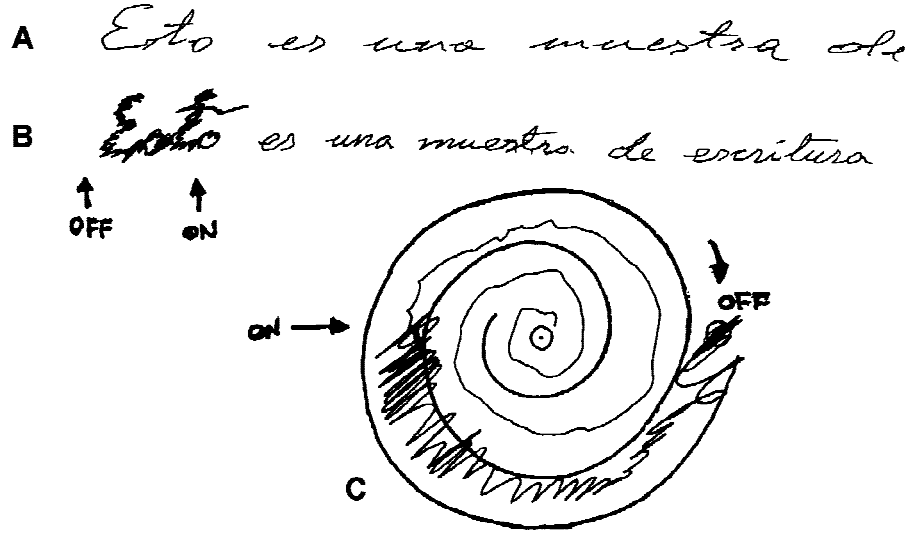

FIG. 2. Postsurgical: (**A**) writing with the arm unsupported and stimulation on; (**B**) writing with the arm supported, indicating the moment when stimulation was connected; (**C**) drawing of spiral, indicating the moment when stimulation was connected.

after the surgery and it continues to date. With the stimulation on, the total score on the Clinical Tremor Rating Scale[12] was only 4 points (2.56% of the maximum score) with no functional disability scored. Following our instructions, the patient disconnects the stimulation at night and whenever he does not have to write, like on days off from his job. At work, the stimulator allows him to write continuously without effort. He has not returned to any drug treatment. After 1 year the patient's overall evaluation of the treatment continues to be positive, and its social and employment benefits have been considerable.

Discussion

Our patient consulted for a tremor of the upper right extremity that predominantly occurred and interfered with handwriting; we therefore diagnosed PWT, using the generic term as commonly used. However, this concept has been used to describe patients with different clinical features and lacks a widely accepted definition. The nosology of PWT is also controversial: various studies have stressed its possible relationship to essential tremor,[3,4,6] to writer's cramp,[5,9,15–17] and to both processes.[7,8,18] However, clinical and physiological differences between PWT and both conditions may signal PWT as a distinct nosologic entity.[10] Patients with PWT can be classified as having either task-induced tremor (type A: tremor appears during writing) or positionally sensitive tremor (type B: appears also when adopting the hand position normally used for writing).[10] According to the above classification, our patient has type B PWT. The family history, associated postural tremor, and response to alcohol and propranolol might suggest a variant of essential tremor, but his tremor clearly differs from essential tremor because it is unilateral, tends to remain focal, and is induced rather than suppressed during skilled manual tasks (that is, it has a negative coefficient of suppression).[10]

PWT can cause a marked functional disability in some patients, occasionally with employment consequences.[1,10] Initial measures, such as learning to write with the other hand or finding an alternative to handwriting, are often unsatisfactory. Different drug treatments can be of value: some patients improve to an extent with administration of propranolol,[4,10] primidone,[6,10] or anticholinergics[2,5]; however, the clinical response is often partial and side effects can limit their use. Periodic injections of botulinum toxin may be an alternative[10] but its long-term benefit is yet to be demonstrated. In this context, functional neurosurgical treatment may be considered an option for selected patients.

Stereotactic Vim thalamotomy has been widely used as symptomatic treatment of tremor secondary to different diseases. In 1982, Ohye et al. reported the satisfactory treatment of three patients with PWT using this procedure.[3] Chronic thalamic stimulation is currently considered an effective alternative to thalamotomy, offering advantages of reversibility, adaptability to changing clinical situations, and being likely associated with a lower incidence of postsurgical neurologic deficits.[11]

Our patient with type B PWT achieved an excellent outcome with complete control of the tremor after over 1 year of follow up and no complications related to surgery or stimulation. This result suggests that thalamic stimulation should be considered for selected patients with PWT who have major social or employment disabilities when non-surgical approaches fail.

Nevertheless, the major concern in selecting the surgical approach is that an otherwise normally functioning person must be willing to accept the risks and drawbacks related to the procedure. In the Grenoble series,[11] thalamic DBS was responsible for intracranial bleeding in six of 117 patients (5.1%) and skin problems (scalp infections or granuloma) in five patients (4.2%). Thirty-seven patients (31.6%) experienced minor side effects related to stimulation (mainly dysarthria, paresthesias, limb dystonia, or disequilibrium), which were well tolerated and reversible by reducing the voltage. Furthermore, the patient must be willing to be dependent on an implanted device, to take the appropriate precautions, and to visit a referral center for regular check-ups.

Therefore, the surgical decision for a patient with disabling PWT depends on balancing the expected benefits that controlling the tremor would have on a particular individual's life against the risks and drawbacks of the procedure. At any rate, greater clinical experience and longer follow up is necessary to precisely define the role of thalamic stimulation in the symptomatic treatment of this peculiar condition.

Legends to the Videotape

The video recording shows the patient 1 year after the surgery.

Segment 1: With the stimulation off, the patient is shown adopting a posture with his arms, writing with his arm unsupported, writing with his arm supported, and drawing a spiral.

Segment 2: The stimulation is connected while the patient is writing (first sequence) and drawing a spiral (second sequence). The immediate effect on the performance of these tasks is evident.

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A Case of Myoclonic Cortical Tremor After Extirpation of a Parietal Meningioma

Cortical myoclonus is often seen in generalized neurologic conditions such as progressive myoclonic epilepsies or after hypoxic brain damage,[1] but only rarely occurs with focal brain lesions. [2] Because cortical reflex myoclonus can be indicated by an irregular tremor, it was subsequently called cortical tremor.[3] This syndrome has been described previously only in patients with generalized brain disease.[4] We report a patient with cortical myoclonus who presented with a tremor caused by a focal brain lesion, that is, after removal of a large meningioma impinging on the sensorimotor cortex.

Case Report

A 61-year-old woman experienced clumsiness of her right hand and occasional headache for 7 months prior to the diagnosis of a large left-parietal meningioma. The meningioma had a diameter of 4.5 cm and impinged on the pre- and postcentral as well as adjacent parietal gyri. The lateral ventricle was displaced ventrally by 7 mm. Preoperatively, a slight paresis of the finger flexors and extensors of the right hand but no sensory deficits were seen. The meningioma was removed neurosurgically. A postoperative computed tomography scan showed normal cortical gyri and sulci; there was no evidence of edema or hemorrhage. After the operation, a slightly irregular tremor of the right hand was observed at rest with a frequency of 12–14 Hz and an amplitude of 1–2 cm (Fig. 1). It was enhanced on action, that is, during volitional movements or posturing of the arm, and subsided during sleep. Because of the tremor, handwriting was severely impaired. No irregular movements were seen in the face, in the left hand, or the feet. On the third day after the operation the patient experienced two focal epileptic seizures causing tonic contractions of the right arm. The routine electroencephalogram (EEG) showed a focal slowing over the left central region but no spikes. Therapy with 300 mg phenytoin per day was begun but it had no influence on the tremor. The neurologic examination on the seventh postoperative day revealed a normal mental status and normal cranial nerves. Muscle strength was slightly reduced in the right arm and hand. The deep tendon reflexes were brisker in the right arm; Babinski's sign could not be elicited. The somatosensory functions were intact. Phenytoin was discontinued and valproic acid was given on the 15th postoperative day. The jerks completely ceased when a daily dose of 1200 mg was reached (1 week after the start of therapy). Valproic acid was slowly withdrawn from the fourth to the seventh postoperative month. When last seen 11 months after the operation, the patient had a normal neurologic examination and no problems with the functioning of her right hand.

Recording of the muscle twitches underlying the tremor revealed an irregular pattern with short bursts at irregular intervals ranging from 20–100 ms (Fig. 1). The bursts varied in duration from 10–30 ms, frequently occurring synchronously in agonistic and antagonistic muscles on the right. No muscular twitches were seen in the recordings of the left abductor digiti minimi (muscle) and orbicularis oris on the right. The frequency of the muscular twitches increased when the patient lifted both hands compared with when at rest.

To investigate the cortical events associated with the muscle jerks, the EEG was recorded from 21 Ag/AgCl electrodes fixed to the scalp according to the International 10/20 system. Then, the EEG was averaged time-locked to the jerks in the right ADM at rest. This revealed a positive–negative–positive (latencies: −40, −10, +25 ms) EEG component at parietal electrodes (Fig. 2). The scalp distribution of the spike 10 ms before the electromyographic (EMG) onset was dipolar with a left parietal (negative) trough and a frontal peak (positivity). With these data, a dipole analysis was computed (BESA program, Neuroscan Inc, Herndon, VA, USA). The analysis of the parietal negative component peaking 10 ms before the EMG onset resulted in a dipole in the left central region near the central sulcus at a depth of 20 mm below the scalp. The orientation of the positive end was anterior–ventral.

Somatosensory evoked potentials (SSEPs) were obtained following electrical stimulation of the median nerve at the wrist. The cortical channel consisted of a bipolar recording between a point 2 cm behind C3 or C4 and Fz as reference electrode. Filters were then set from 0.3 s to 1000 Hz. The amplitude of the SSEP peaks was measured against a prestimulus baseline. The SSEPs after right median nerve stimulation showed a N20 peak at 19.9 ms with an amplitude of 3 μV

Received May 22, 1998; revisions received January 11 and March 1, 1999. Accepted July 23, 1999.

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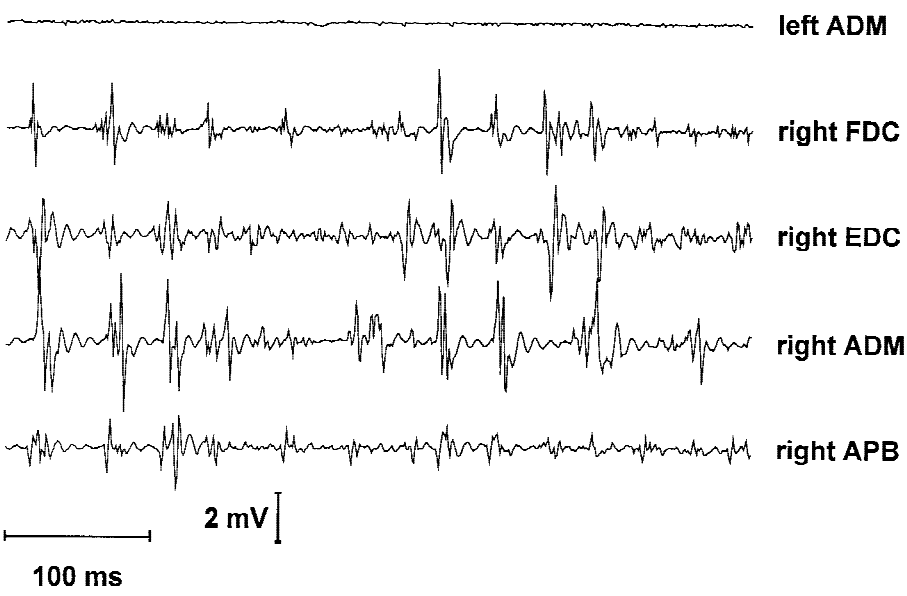

FIG. 1. Electromyogram of left abductor digiti minimi (ADM), right flexor digitorum communis (FDC), right extensor digitorum communis (EDC), right abductor digiti minimi, and right abductor pollicis brevis (APB) (arms elevated).

and a similar peak at 19.3 ms with an amplitude of 3.0 μV following left median nerve stimulation. Only stimulation on the right evoked a positive peak at 23 ms (P23) with an amplitude of 5 μV, which was followed by a negativity reaching the pre-stimulus baseline. Stimulation on both sides showed a late positive peak (stimulus right: 7.0 μV, 32 ms; left: 6.8 μV, 35 ms). In another SSEP recording 11 months after the operation, again, only stimulation of the right side evoked a P23 component now measuring 3.7 μV.

Discussion

Our patient developed an irregular tremor of the right hand after the surgical removal of a large meningioma overlying the left central and parietal cortex. Despite massive compression of the cortex and white matter by the tumor, subjective disorders and clinical signs prior to the operation were relatively few, probably as a result of compensatory mechanisms made possible by the slow development of the lesion. The neurophysi-

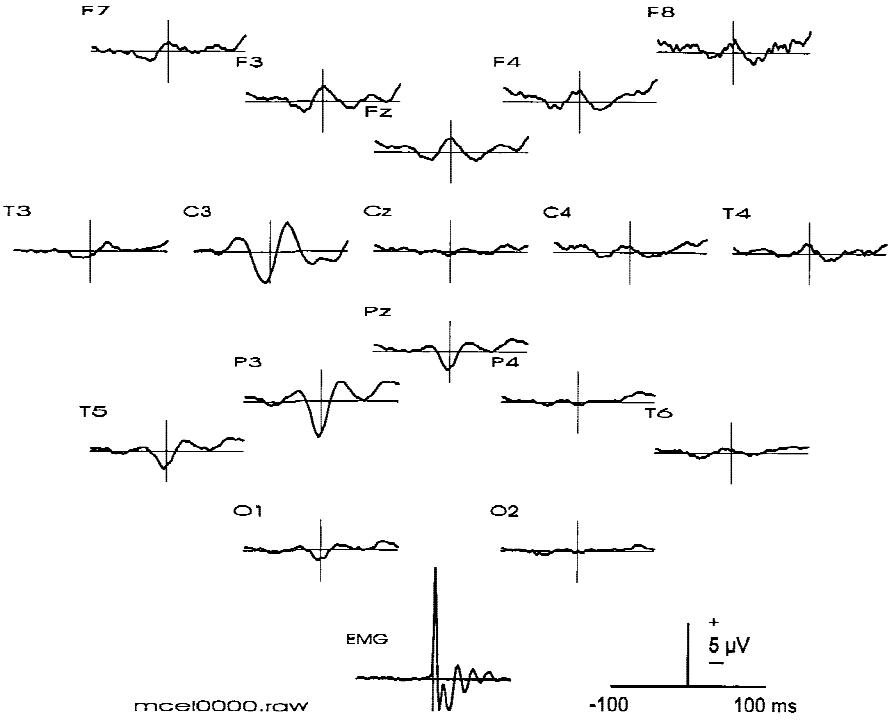

FIG. 2. Cortical event preceding electromyographic burst in the right abductor pollicis brevis muscle. Three hundred averaged sweeps, linked ear lobe reference. Averaged EMG signal of the right ADM (trigger).

ological evaluation showed that this "tremor" consisted of myoclonic jerks. The occurrence of this cortical myoclonus after an operative decompression of the sensorimotor cortex and its disappearance after several months make this case unique. In view of the short duration of the muscle twitches and the cortical spike preceding them, these jerks must be classified as cortical myoclonus.[5] The spike could be mapped on a tangential dipole with a position compatible with a location in one bank of the central sulcus. Similar dipoles were found preceding volitional hand movements[6] and when the N30 component of the median nerve SEP[7] was analyzed. The SSEP studies showed the presence of a P23 component only over the operated hemisphere. Because all other SEP components were of similar amplitudes on both hemispheres, an effect of the craniotomy is unlikely. An enhanced P25 has been described in cortical myoclonus.[8] However, because the different shapes of the SSEP persisted even after the myoclonus had subsided, a persistent enhanced cortical excitability is probably not indicated by the SSEP findings.

In our case, the syndrome is akin to epilepsia partialis continua (EPC) because myoclonic jerks can also occur at rest in EPC, may be enhanced by action, and can be of relatively high frequency.[9] The enhanced cortical excitability of the patient presented here seems to be a transient effect of the decompression of the cortex and the underlying white matter. One possible explanation may be that thalamocortical fibers may be stretched while the cortex is moving back into its usual position and thus be damaged, becoming vulnerable to depolarizations. Thalmocortical afferents establish synaptic contacts with smooth stellate cells of layer IV known to have an inhibitory effect on pyramidal cells.[10] Damage to these connections may decrease the surrounding intracortical inhibition of the pyramidal cells, thus leading to increased excitation and myoclonus. Alternatively, a relative cortical ischemia resulting from distended cortical vessels or disturbed postoperative venous drainage may have led to increased cortical excitability. This could explain why the neurologic deficits in the patient were transient. Generalized brain ischemia is known to cause post-hypoxic myoclonus,[11] which can be transient[12,13] as in our case. Transient ischemia may have been sufficient to cause damage only to GABAergic inhibitory interneurons in layer IV of the cortex. In animal models, similar cells are known to be selectively vulnerable to hypoxia,[14] and their damage may lead to increased excitation.[15,16] Another possibility is a disturbed connection with parietal areas. This explanation is supported by a case of a parieto-occipital infarction causing a continuous jerking of the contralateral arm[9] (case 10).

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Arm Elevation in Huntington's Disease: Dystonia or Levitation?

We present several patients with Huntington's disease (HD) who developed an unusual movement disorder characterized by involuntary arm elevation. To our knowledge, this type of posture has not been previously described in HD. It is not certain whether the posture represented dystonia or a problem with arm positioning in space, that is, arm levitation. The phenomenology could have multiple etiologies.

A videotape accompanies this article.

Received March 26, 1999; revisions received June 4 and July 14, 1999. Accepted July 26, 1999.

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Case Reports

Patient No. 1

A 57-year-old man initially developed chorea at the age of 43 years. The patient's father had been hospitalized for psychiatric problems and involuntary movements. When initially evaluated by us at age 50 at the New York State Psychiatric Institute Huntington's Disease Center, the patient scored a 39 out of 57 on a modified Mini-Mental Status Examination[1] with deficits in registration (digit span), calculation (adding change), recall, and naming. His ocular smooth pursuits were jerky, saccades were slow, and chorea was present in all limbs. There was motor impersistence and mild retrocollis but no other dystonia. He was taking no medications, and there was no history of previous exposure to neuroleptic medications. A head computed tomography (CT) scan revealed decreased size of both caudate heads suggestive of HD. The diagnosis of HD was made on the basis of clinical signs (chorea, dystonia, eye motion abnormalities, motor impersistence, and cognitive decline) and family history of a similar disorder characterized by psychiatric changes and chorea. CAG repeat length analysis was not performed. A videotape performed at age 52 revealed new spontaneous, intermittent elevation of his left arm. This elevation occurred eight times during an 11-minute videotape, and the arm remained elevated for periods of 2–80 seconds. His left arm would elevate to assume an outstretched position in front of him. In this position, the arm was straight, the elbow fully extended, and the hand sometimes open and at other times closed. He was able to move the arm out of this position and relax it easily when asked to do so without needing to use a sensory trick. At that time, his neurologic examination was notable for incomplete ocular smooth pursuits, moderately slow saccades with inability to suppress head movements during these saccades, inability to fully protrude his tongue, moderately impaired rapid alternating movements, mild to moderate arm rigidity, and chorea of moderate severity in his face, trunk, and limbs. The examination was otherwise unchanged. The only medication was 5 mg buspirone per day for anxiety. Because it was not bothersome, he was not prescribed any medication to treat the arm elevation.

Patient No. 2

A 38-year-old woman first developed chorea at the age of 29 years. The patient's father and paternal grandfather had been diagnosed clinically as having HD. When initially evaluated at age 33, the patient scored 48 out of 57 on a modified Mini-Mental Status Examination[1] with deficits in registration (digit span), attention and calculation (performing serial sevens, spelling "world" backwards, adding change), recall, and naming. Her eye movement examination was notable for ocular smooth pursuits which were mildly jerky, saccades which were slow, and inability to suppress blinking during saccades. There was frequent chorea of moderate severity in her face, trunk, and limbs, mild slowing of rapid alternating movements in her left arm, and motor impersistence (difficulty maintaining a protruded tongue). There was no dystonia and limb tone was normal. She was taking no medications, and there was no history of previous exposure to neuroleptic medications. A head CT scan revealed marked dilatation of the lateral ventricles and atrophy of the caudate heads suggestive of HD. Thyroid function tests and sedimentation rate were normal. The diagnosis of HD was made on the basis of clinical signs (chorea, eye motion abnormalities, motor impersistence, and cognitive decline), a family history of HD, and CAG repeat length analysis which revealed an abnormal repeat length which was within the HD range. A videotape performed when she was 34 years of age revealed the presence of intermittent right arm elevation which occurred twice during a 1.5-minute videotape segment. Her neurologic examination was otherwise unchanged, and her only medication was 100 mg amantadine twice a day, which was prescribed by an outside doctor to give her "more energy." Because the arm elevation was not bothersome to this patient, she was not prescribed any medication for it.

Patient No. 3

A 55-year-old woman had a history of depression from the age of 14 years. At age 43, her family noted choreiform movements. Her mother had had similar choreiform movements, and her son, who had severe depression, had had 40 CAG repeats within the region of the HD gene on chromosome 4. At age 50, she was initially evaluated and the examination was notable for a score of 48 out of 57 on a modified Mini-Mental Status Examination[1] with deficits in digit span, attention, calculation, and general knowledge. Her ocular smooth pursuits were jerky. Saccades were slow and she was unable to suppress head movements during these saccades. Signs of motor impersistence included milkmaid grips and difficulty maintaining tongue protrusion. She had chorea of moderate severity in her limbs, trunk, and oral region. There was mild foot inversion dystonia on the right. The diagnosis of HD was made on the basis of clinical signs (chorea, eye motion abnormalities, motor impersistence, psychiatric signs, and cognitive decline) and a family history of HD confirmed by CAG repeat length analysis. CAG repeat length analysis was not performed on our patient. She was evaluated again at age 52 when she developed bothersome chorea and falls. The examination was unchanged with the exception of an increase in the severity of her chorea. She had been taking 50 mg sertraline per day for depression and 0.5 mg clonazepam per day for anxiety. Haloperidol at a dosage of 1 mg twice a day was started. Her examination had not changed 1 month later, and haloperidol was increased to 1 mg three times a day. When examined 3 months later, she reported that "my [left] arm goes up." When seated or standing, her left arm spontaneously elevated to assume an outstretched position in front of her. At times, the elevation was rapid (1 second) whereas at other times it was more gradual (4–6 seconds). In the elevated position, the arm was straight, the elbow fully extended, and the wrist and fingers hyperextended. She was fully aware of the posture, but stated that she did not know how to suppress it on her own so that the posture was often present and bothersome. Initially, the examiner suggested that she place her left hand in her pocket or touch her waist, and she was able to suppress the posture for periods of time ranging from 5 seconds to 3 minutes until she became distracted. Later, she was able to suppress the posture on command without having to touch her waist, but again, when distracted, the arm would spontaneously rise up. There was no rest tremor, rigidity, or bradykinesia. The haloperidol was discontinued. The arm elevation improved but did not entirely resolve over the next 6 months. On subsequent follow-up visits (ages 53–55 years), she continues to exhibit infrequent left arm elevation, but because it is not bothersome to her, no other medication has been instituted.

Discussion

We report three patients with HD and an unusual arm posture which has not been reported in the HD literature and which may even have heterogeneous origins. It is not certain whether the posture represented dystonia or a problem with arm positioning in space, that is, arm levitation. In favor of dystonia is the observation that one of the three patients (patient no. 3) exhibited dystonic extension of the fingers and wrist in the same arm, and this patient often, but not always, used a sensory trick to lower her arm. However, another patient (patient no. 1) did not require sensory tricks. In all three patients, the arm elevated rapidly, a feature inconsistent with arm levitation,[2] although a slow, gradual elevation was observed occasionally in patient no. 3. In patient no. 3, the affected limb would rise again when her attention was diverted elsewhere, a feature consistent with either dystonia or arm levitation.[2] Chorea is one of the hallmark features of HD, and each of the patients had limb chorea which contributed to the observed movements; however, the prolonged posturing observed in these patients (greater than 1 minute in patients no. 1 and no. 3) would not be typical of chorea, which has been described in the literature as brief, jerky movements that move quickly from one part of the body to another.[3,4]

Dystonia is highly prevalent among patients with HD,[5] and while some of the more typical forms of dystonia may be observed in HD (for example, blepharospasm, torticollis), other unusual forms of dystonia, including sustained fist clenching, excessive knee flexion during ambulation, and handbagging (a sustained posture that results in internal rotation of the shoulder[s] and flexion of one or both elbows and wrists as if the patient were holding a handbag), are commonly observed as well.[5] The mechanism of this dystonia in HD is presumably the result of involvement of the basal ganglia.

Arm levitation, during which the limb rises spontaneously to maintain a fixed elevated posture, has been distinguished from the alien limb syndrome which frequently also involves the presence of complex semi-purposeful involuntary movements and a subjective feeling that the limb feels foreign.[6,7] It is not clear whether isolated arm levitation, in the absence of complex involuntary movements or the subjective feeling that the limb feels foreign, represents a forme fruste of the alien limb syndrome or a distinct clinical–pathologic entity. Arm levitation may be a feature of cortical–basal ganglionic degeneration (CBGD),[7,8] progressive supranuclear palsy (PSP),[6] and hemiparkinsonism–hemiatrophy.[9] The etiology of the alien limb syndrome is thought to involve frontal or callosal lesions,[7,10] although many of these patients also exhibit parietal lobe pathology.[6,7] The etiology of arm levitation is less certain, but it is possible that it involves parietal lobe pathology.[2,8] Denny-Brown[2] described a patient with a presumed parietal lobe lesion (left-sided neglect, left attention hemianopia, extinction on the left to double simultaneous stimulation) who exhibited isolated levitation of the left arm, with the outstretched arm assuming a posture that was similar to that seen in our patients (see Figure 2B of Denny-Brown). Other reported cases of arm levitation have exhibited pathology in the parietal cortex as well as other cortical areas.[6] The parietal cortex is involved with modulation of the body's spatial mapping system with regard to right versus left, up versus down, and near versus far.[11] Cortical sensory testing was not routinely performed in our HD cases, and none had PET, SPECT, or neuropathologic studies; therefore, we do not know whether there was parietal lobe dysfunction or pathology. However, there are several lines of evidence that the pathology in HD may extend to the parietal lobe. First, recent primate studies have demonstrated connections between the parietal lobe and the caudate nucleus.[12] Second, while there is generalized brain atrophy in the later stages of HD with losses of total brain weight between 300 and 500 g, the frontal and parietal lobes are usually preferentially affected.[13–16] Recently, MacDonald et al.[17] quantified the extent of neuronal loss, demonstrating a profound loss of pyramidal neurons in the angular gyrus (inferior parietal lobule) of patients with HD compared with control subjects (mean reduction = 55%). Third, several studies[18,19] have demonstrated a prolongation of the N20 component of the somatosensory evoked in patients with HD compared with control subjects. This has been interpreted by some as physiological evidence of suprathalamic, that is, parietal lobe, pathology.[18,19] Finally, neuropsychological testing in patients with HD using a parietal lobe battery (including figure drawing, stick construction task, and block construction) revealed that the majority of patients had abnormalities that were suggestive of parietal lobe involvement.[20]

One of the patients initially developed this posture in the setting of neuroleptic medications; therefore, there is the possibility that the posture represented a form of tardive dystonia. While we cannot exclude this possibility, as noted above, the posture in this patient resembled that seen in the other two cases, and it did not resemble the postures typically described in patients with tardive dystonia.[21,22]

In summary, arm elevation may be a clinical sign observed in patients with HD. Whether this represents a form of dystonia or arm levitation is not clear. Further study of the prevalence and underlying etiology of arm elevation in HD would be important.

Legends to the Videotape

Segment 1: Patient no. 1. When the videotape begins, both of the patient's hands are on the table. His left arm elevates while he intermittently swats flies, touches his hair, and wipes his nose with his right hand. The swatting movements are purposeful because the patient comments on multiple occasions that this is what he is doing. With left arm elevation, there is some superimposed chorea. There may also be some elevation of the right arm. He then rests both arms on the table. He gesticulates with the right arm and then elevates the left arm. He is asked to put his hand down and puts both hands on the table. His left arm then elevates while he swats flies at the back of his head with the same hand. He uses his right arm to point at the table and to swat flies. Meanwhile, his left arm remains elevated for some time. Near the end, he puts both arms down and grabs the arms of the chair. At the end, his left arm elevates.

Segment 2: Patient no. 2. She hits the ball and then runs. While running, her right arm elevates. There is also some wrist flexion and it is not clear whether she is also trying to adjust her cap. When she reaches the base and stops running, she adjusts the back of her cap with her left hand while her right arm elevates over her head. This entire segment is repeated one more time. The terminal portion of the videotape is also repeated several times.

Segment 3: Patient no. 3. Her left arm is elevated. At one point, she puts it down at her side and then pulls her right shirt

sleeve up using her left hand. Her left arm then elevates again. She is asked to hold onto her shirt using her left hand. She is then asked to let go and her left arm immediately elevates. She is again asked to hold her shirt using her left hand and does so. She is walking and her left arm is elevated. She is asked to put her left arm down at her side. She grabs onto her shirt using the arm, like the examiner had instructed her to do many times. The examiner then asks her to keep her arm down without holding onto her shirt. She is able to do this, but still exhibits some dystonic hyperextension of her fingers on the left. She is still walking and suppressing the elevation, but when distracted, the left arm elevates slowly over several seconds. She is asked to hold both arms extended in front of her. Her left arm slowly elevates.

Acknowledgments: This work was supported by Federal Grant NIH NS01863 and the Paul Beeson Physician Faculty Scholars in Aging Research Award. The authors thank the Huntington's Disease Society of America Summer Camp Program.

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Nabilone Increases Choreatic Movements in Huntington's Disease

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder characterized by behavioral changes, impaired cognition, and movement alterations. Although the HD gene and its protein product called huntingtin has been identified, it is unknown how the mutant protein causes preferential neurodegeneration in the striatum and cortex. Until now, symptomatic treatment is unsatisfactory.[1]

Cannabis sativa and its ingredients have been suggested to be effective in the therapy of movement disorders like tremor,[2–4] dystonia,[5–7] L-dopa-induced dyskinesia in Parkinson's disease (PD),[8] and Gilles de la Tourette syndrome (TS).[9,10] In HD, however, a controlled trial investigating the effect of cannabidiol (CBD), a major nonpsychoactive constituent of cannabis sativa, in 15 neuroleptic-free patients failed to demonstrate any symptomatic effect on chorea.[11] It is known that CBD has a low affinity for the cannabinoid receptor compared with other cannabinoids.[12] In addition, CBD was found to behave as an antagonist acting in the micromolar range.[13] It has been suggested that clinical trials using agonists with higher affinity for the cannabinoid receptor might be more efficacious.[14]

Therefore, in an uncontrolled open clinical trial we investigated whether nabilone, a classic synthetic cannabinoid ago-

Received February 3, 1999; revisions received March 31 and April 30, 1999. Accepted July 14, 1999.

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nist, would be effective in the therapy of HD. Here we report a single-dose treatment with nabilone in one patient with HD which resulted in a marked increase in choreatic movements.

Case Report

A 58-year-old man noticed brief, irregular movements of his legs at age 52. Since then, movements increased and spread to other parts of the body like his face and arms. In addition, he noticed a deterioration in his short-term memory.

The diagnosis of HD was made at age 58 at our clinic. Neurologic examination revealed mild choreatic movements at rest. During voluntary movements, stress, and conversation, movements increased. Speech was slow and mildly dysarthric. Repeated movements were bradydyskinetic. Gait was wide-based and the play of finger and arm movements increased during walking. Apart from these findings, the neurologic and medical examination was normal. Psychiatric examination demonstrated impairment in visual memory function (Benton test), information processing/attention (visual searching task, reaction time measurement), and intelligence (Standard Progressive Matrices Test). Short-term verbal memory functions measured by the German version of the California Verbal Learning Test and the Digital Span Test of the HAWIE were normal.

Direct DNA analysis yielded 42 (CAG)n repeats confirming the diagnosis of HD. However, the family history of HD was unremarkable. So far the patient had had no symptomatic treatment for HD and was drug-free at the time of investigation.

In an uncontrolled open clinical therapeutic trial, we investigated whether nabilone is effective in the therapy of choreatic movements as well as cognitive impairment in HD. Written informed consent was obtained from the patient after a complete description of the study. The patient was treated once with 1.5 mg nabilone. Using the chorea and the motor impairment scale by Folstein et al.,[15] the chorea score was 10 and the movement impairment score 6 before treatment. Three hours after treatment the chorea score was increased to 17 and movement impairment scale to 13. On neurologic examination, there was a marked deterioration of choreatic movements at rest and during movement. Gait was reeling and almost impossible without assistance. This deterioration lasted for more than 1 day (after 24 hours chorea score was reduced to 12 and motor impairment score to 7) and completely disappeared within 2 days.

All neuropsychological tests mentioned were performed again 2 hours after treatment with nabilone but there were no differences compared with cognitive functions measured before treatment.

Discussion

HD is neuroanatomically characterized by a degeneration of "medium size spiny neurons" in the striatum. In the early course of the disease, there is an involvement of striatal gamma-aminobutyric acid (GABA)/enkephaline neurons projecting to the lateral globus pallidus (GPl). Later in the course there is also a degeneration of the GABA-substance P-containing striatal neurons projecting to the medial globus pallidus (GPm).[1]

Cannabinoid receptors have been found to be located in the basal ganglia with high concentrations on the axon terminals of striatal efferent neurons projecting to the globus pallidus and substantia nigra pars reticulata (SNr)[12,16] suggesting that cannabinoids regulate neurotransmission in the basal ganglia. Cannabinoid receptors are co-localized both with dopamine D1 receptors on striatonigral dynorphin/substance P containing neurons and with dopamine D2 receptors on striatopallidal enkephalinergic neurons.[17] In the globus pallidus, cannabinoid receptors are localized presynaptically on terminals of GABAergic inputs from the striatum.[18] Activation of cannabinoid receptors reduces GABA reuptake in the GPl.[19] In addition, cannabinoids regulate the activity of SNr neurons by presynaptic inhibition of GABA inputs[20,21] and inhibit the release of glutamate from the subthalamic terminals in the SNr.[22,23]

In people beneficial effects of cannabinoids have been reported in tremor,[2–4] dystonia,[5–7] and TS.[9,10] In PD, it has been demonstrated that nabilone reduces L-dopa-induced dyskinesias without aggravating parkinsonism.[8] A controlled trial investigating the effect of CBD in HD failed to demonstrate any symptomatic effect on chorea.[11] It could be speculated that CBD was ineffective either as a result of the extremely low affinity of CBD for the cannabinoid receptor,[12] as a result of a massive loss of cannabinoid receptor binding which has been found in the GPl[14] and the SNr[24] in HD, or as a result of methodologic problems such as small sample size or the dose of CBD.[14]

In HD it is thought that degeneration of striatal neurons projecting to the GPl results in increased activity of inhibitory GPl neurons which causes increased inhibition of the subthalamic nucleus (STN). The resultant decrease in STN output reduces the firing rates of the SNr and GPm. In turn, the ventrolateral thalamus (VL) is disinhibited. The excessive activity of glutamatergic thalamocortical projections is thought to underlie the pathophysiology of chorea in HD.[25]

In PD it has been suggested that nabilone may reduce L-dopa-induced dyskinesia as a result of enhancement of GABA transmission in the GPl.[8] In the patient presented here it can be speculated that an activation of cannabinoid receptors did not enhance GABAergic transmission in the GPl and, therefore, did not reduce choreatic movements because in HD, striatal neurons projecting to the GPl already degenerate in the early course of the disease. It can be hypothesized that treatment with nabilone resulted in a marked increase of chorea as a result of a modulation of the direct pathway resulting in an enhanced GABA transmission in the GPm, an activation of cannabinoid receptors located on striatonigral GABAergic neurons, a decreased release of glutamate from the subthalamic terminals in the SNr, or an interaction with the dopaminergic system.

Therefore, it can be speculated that cannabinoid receptor antagonists might be useful in symptomatic therapy of chorea in HD. Further examination should be done to investigate the role of the cannabinoid system in HD because there is evidence that cannabinoid receptors are involved in the control of motor function.

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Concordant Late Onset of Craniocervical Dystonia in a Pair of Monozygotic Twins

Clinicogenetic investigations of patients with primary generalized and focal dystonia suggest autosomal-dominant inheritance as the likely mode of transmission in affected families.[1,2] The recent identification of the DYT1 dystonia gene[3] and two gene loci[4,5] in families with autosomal-dominant primary torsion dystonia (PTD) has substantiated genetic factors in the etiology of generalized,[3] a "mixed" type,[4] and one form of focal dystonia.[5] While a 3-bp (GAG) deletion in the DYT1 appears to be responsible for the majority of cases with early-onset, generalized PTD, there is evidence for genetic heterogeneity, because linkage to the above-mentioned loci was not found in various other families with different forms of PTD.[6–8] Furthermore, a reported linkage disequilibrium between several chromosome 18p markers and focal dystonia in sporadic patients from Northern Germany[9] was not confirmed in another large cohort of Northern German patients with focal dystonia and ethnically matched control subjects. This indicates that focal dystonia in patients from this area is unlikely to be the result of the same founder mutation.[10] With the exception of single case reports,[11,12] there is no systematic twin study in index patients with primary dystonia. We report a pair of monozygotic twins with concordant expression of cervical dystonia and blepharospasm with a similar age of onset in late adulthood.

Case Report

The identical twin sisters, aged 74 years, were first seen by the authors in early 1998. The index patient (twin A) first noticed involuntary "eyelid spasms" at age 65 followed by intermittent, involuntary painless head turning to the left at age 66. Her medical history revealed breast cancer in 1971 without metastatic invasion which was successfully operated and did not relapse. The patient had no history of infectious diseases, head or neck trauma, or neuroleptic drug intake prior to onset of dystonia. On examination, there was mild tonic antecollis, right-sided laterocollis (10°–20°), and tonic left torticollis (20°). On voluntary turning of the head to the right, coinnervation of the right sternocleidomastoid was seen. The geste antagoniste was positive. In addition to occasional contractions visible in both orbicularis oculi muscles, the patient showed bilateral ptosis. This was a side effect resulting from periorbital

A videotape accompanies this article.

Received July 24, 1998; revision received February 5, 1999. Accepted June 2, 1999.

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botulinum toxin A injections which had been applied at another center 8 days prior to our examination. The remainder of twin A's neurologic examination was normal, and she had no intellectual impairment.

Twin sister B reported onset of blepharospasm and involuntary head twisting to the left which had started at age 67. She did not have neck pain or a history of head or neck injury, infectious disease, or neuroleptic drug intake. Medical history was unremarkable. On examination, she showed blepharospasm severe enough to interfere with everyday activities, tonic rotational torticollis (30°) to the left with slight dystonic tremor, and antecollis (50°). The geste antagoniste was positive. Otherwise, the neurologic examination was unremarkable. There was no intellectual impairment. Magnetic resonance imaging scan of her head showed some small bilateral white matter changes frontoparietally and temporo-occipitally, most likely resulting from mild microangiopathy.

The families of the nonconsanguineous parents were of Northern German ancestry. Both twins independently reported that their mother had developed mild "head shaking" and blepharospasm at approximately 55 years of age. Their mother had died from a stroke at age 70. Inspection of family photographs taken some years before death showed marked periorbital wrinkling but no torticollis. The mother had one sister who was reported to be unaffected by any neurologic condition. The twins were born after an uneventful pregnancy and delivery (twin A was born 15 minutes prior to twin B). Early childhood development, motor milestones, and school education were normal in both twins. They were raised together in a Northern German village and had no other siblings. Twin A did not have children; she worked on her own farm and in a bakery until retirement. Twin B worked in her own bakery throughout her adult life and had three living daughters (45, 43, and 41 years), all of them being free from any neurologic disorder by history. A detailed history taken from other family members did not disclose any neurologic condition.

Zygosity testing was done by the following serologic and DNA-based investigations: blood group typing, five different serotypes, three erythrocytic enzyme types, 10 different S-T-R-based systems, and 6 DNA-single-locus polymorphisms. The results were identical in both patients, and, therefore, indicated that the twins are monozygotic with a probability of greater than 99%. Serum analyses of copper, ceruloplasmin, thyroxine, and lactate levels were unremarkable in both twins, as were the results of blood counts and smears. Search for the GAG deletion in the DYT1 gene on chromosome 9q34[8] was negative in both twins. Genotyping was performed under standard conditions using polymorphic DNA markers D18S1105—3.2 cM—D18S1098—1.2 cM—D18S481—1.5 cM—D18S54 covering approximately 6 cM on chromosome 18p (genetic distances in the region containing DYT7 according to reference 9). To ensure comparison of identical alleles, a control DNA sample (CEPH 1331-02) was run for each marker, and alleles were designated as specified by the same authors.[9] Genotyping revealed the twins to potentially share an allele (unfortunately, the chromosomal phase is unavailable) with affected members of family K[9] at the markers D18S1098 and D18S481, but not at the flanking markers D18S1105 and D18S54 (Table 1).

TABLE 1. *Results of genotyping of twins A and B and of CEPH control individual 1331-02 and comparison to "Family K dystonia haplotype" (alleles assigned according to table 1 in ref. 9)*

DNA marker	Twins A/B*	CEPH 1331-02*	Family K dystonia haplotype
D18S1105	7,7	7,7	2
D18S1098	1,6	1,6	1
D18S481	5,7	7,7	7
D18S54	3,4	6,6	2

* Chromosomal phase unknown.

Discussion

To our knowledge, this is the second report of a monozygotic twin pair concordant for primary focal or segmental dystonia, and it seems to be the first report of a concordant monozygotic *female* twin pair with this form of dystonia. Like a previously reported concordant twin pair with focal dystonia,[11] our patients are of German extraction and have a positive family history of focal dystonia. In some family members of the twin pair described by Uitti et al.,[11] cervical dystonia, head tremor, and postural hand tremor were noted to a variable degree. In contrast, our twins first presented with blepharospasm rather than tremor, leading to a diagnosis of craniocervical dystonia.[13] Concurrent blepharospasm occurs in 10% of patients with cervical dystonia.[14] Patients with sporadic cervical dystonia have an onset age beyond 60 years in approximately 8%[14] to 16%[15] of all cases, whereas the onset age of blepharospasm is known to extend more readily to higher age groups.[16] In view of these data, we consider the late age of onset in our twins not to be unusual per se; it is, however, remarkable that they both developed dystonia within such a narrow interval of only 2 years. Thus, concordance in our pair does not only cover the diagnostic classification, but extends to a similar age of onset, clinical features, and disease course, suggesting common genetic or environmental mechanisms leading to dystonia in both twins.

In accordance with results from the literature, showing that the GAG deletion in the DYT1 gene is a rare cause of adult-onset focal dystonia,[8,10] this mutation was not found in our twin pair. The results of the genotyping with markers on chromosome 18p have to be interpreted with care, because the chromosomal phase could not be set. Assuming that the "1" allele at the marker D18S1098 and the "7" allele at the marker D18S481 were located on the same chromosome, the twins would share alleles with affected members of family K[9] at the two middle markers of the "family K dystonia haplotype" (that is, 2—1—7—2), but not at the two flanking markers (D18S1105 and D18S54). However, the genotypes "1X" at D18S1098 and "7X" at D18S481 are frequent in both the CEPH and the local population. In a previous study, they were found in 48% (D18S1098) and 44% (D18S481) of focal dystonia patients from Northern Germany and in 52% (D18S1098) and 51% (D18S481) of control subjects from the same geographic region.[10] Furthermore, Leube and Auburger[17] recently failed to confirm the initial allelic association in their sporadic patients using a new highly polymorphic microsatellite located at a physical distance of only 50–100 kb from D18S1098. In fact, no evidence exists for the involvement of the DYT7 locus in dystonia families[18] or sporadic dystonia cases[10,17] other than the original family K.[4] Therefore, it is highly unlikely that our twins carry the same mutation in DYT7 as affected members of family K.

Despite recent evidence that genetics have an important role in the etiology of some forms of PTD, there are surprisingly

TABLE 2. *Summary of reported twin pairs with the index twin showing primary generalized or focal dystonia**

First author, year	No. in pedigree	Ancestry	Other dystonia in family	Index twin, age of onset, sex	Clinical feature	Cotwin, age of onset, sex	Clinical feature	Zygosity
Generalized dystonia								
Winkler 1943[21]	NA	German	−	8, M	TD	12, M	TD	MZ*
Eldridge 1970[19]	Category IVA Pedigree 20 Pa.	English	−	14, F	TD	15, F	TD	MZ*
Elridge 1984[20]	NS	Jewish	+	16, F	TD	23, F	TD	MZ
Focal dystonia								
Zeman 1960[27]	IV/20+21	English	+	15, M	Dysarthria +MR ("forme fruste")	15, M	Dysarthria +MR ("forme fruste")	MZ
Ludolph 1992[28]	NS	German	+	NS, M	WC	NS, M	WC	DZ
Uitti 1993[11]	III/2+3	German	+	49, M	ST	41, M	ST	MZ
Chan 1997[12]	NA	NS	−	44, M	ST	51, M	None	MZ
Present case 1999	NA	German	+	65, F	CCD	67, F	CCD	MZ

NS, not stated; NA, not applicable; TD, generalized torsion dystonia; MZ, monozygotic; DZ, dizygotic; MR, mental retardation; WC, writer's cramp; ST, spasmodic torticollis; CCD, craniocervical dystonia.

*Pairs with unknown zygosity or clinical features incompatible with a primary etiology of dystonia are not included.

few reports of twin pairs with this condition (Table 2). In generalized torsion dystonia, two concordant monozygotic female twin pairs, one of non-Jewish ancestry[19] and one of Jewish ancestry,[20] have been reported. In the first twin pair,[19] age of onset differed by 1 year, similar areas of the body were involved, and the second-born (having "complications" at birth) was slightly more affected. In the second pair, age of onset was different by 7 years and dystonia was mild and confined to the lower limbs in both twins, with the second-born intermittently being more severely affected.[20] Only one report describes an identical non-Jewish male twin pair without a family history of dystonia, in which both twins developed mild generalized dystonia with onset in childhood within an interval of 4 years.[21] In single instances, the twins have other relatives with dystonia.[22,23] Sometimes zygosity remained unidentified,[22,24–26] or there were associated features incompatible with primary torsion dystonia.[22,23] Other twins died before the typical age of onset; thus, clinical concordance cannot be assessed in such pairs.[24,25] In contrast to generalized PTD, the role of genetic factors in the etiology of the focal dystonias still remains elusive. Systematic twin studies may help to identify etiologically relevant genetic and/or environmental factors in focal dystonia.

Legend to the Videotape

The videotape shows twins A (left) and B (right) while being examined in twin B's home. Twin B (first examined) has mild blepharospasm, tonic rotational torticollis (30°) to the left with slight dystonic tremor and antecollis (50°). Twin A has mild tonic antecollis, right-sided laterocollis (10–20°), and tonic left torticollis (20°). She also has severe visual impairment from bilateral ptosis as a side effect of recent periorbital botulinum toxin A injections. Insufficient attempts of fixation despite this ptosis give the inadequate impression of retrocollis. In both twins, successive maneuvers on command are seen, such as head turning to both sides, arm posture, diadochokinesis, and, finally, a test of speech.

Acknowledgments: The authors thank P. Hinse, MD, for referral of the index case and Professor X.O. Breakefield, PhD, for generous use of equipment. LJO was supported by the NINDS (NS38142-01); CK was supported by the Deutsche Forschungsgenmeinschaft (DFG).

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Painful Cervical Dystonia: Clinical Features and Response to Treatment With Botulinum Toxin

Pain is a unique feature of cervical dystonia (CD) which distinguishes it from other focal dystonias, occurs in two thirds of patients with CD,[1,2] and is a major contributor to disability.[2] In published reports, 76%–93% of patients experienced reduced pain following treatment with botulinum toxin (BTX).[3–9] In some studies, subjective pain relief is frequently more impressive than objective improvement in head posture.[4,10] We found that in 24% of patients with CD, BTX produced pain relief without accompanying improvement in head posture.[11] The pathophysiological basis of pain associated with CD is unknown, and the magnitude and duration of its response to treatment with BTX has not been studied in detail. This retrospective study was carried out to gather more data concerning the character and distribution of pain associated with CD and the magnitude and duration of its response to BTX treatment.

Received April 1, 1999; revision received June 17, 1999. Accepted July 20, 1999.

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Methods

A pain questionnaire was designed for retrospective assessment of pain and its response to BTX treatment in a group of patients with primary CD. The questionnaire was mailed to 72 patients randomly selected from our BTX clinic population all of whom had been treated with BTX by the same injector (DT) on a regular basis for several years. Patients with tardive or posttraumatic CD were excluded. Questions were questioned about the following features of pain: *pain location;* patients were asked to indicate presence or absence of pain in the neck, shoulder, arm, upper back, and lower back. More than one choice was allowed. Patients were also asked to mark the site of maximal neck and shoulder pain on a lateral and posterior drawing of the head and neck. *Pain quality;* patients were asked to indicate which one of the following choices best described their pain: aching, pulling, burning, tightness, or other. *Sensory tricks;* patients were asked whether they had a sensory trick that relieved either their abnormal head posture or pain and to describe the sensory trick. *Pain severity;* this was assessed using a modified Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) for pain[12] to estimate worst, best, and usual level of pain before initial BTX treatment, during the first month after injections, and at the time of follow-up treatments. *Pain duration*; this was assessed using the TWSTRS pain scale to estimate percentage of time each day spent in pain before initial BTX treatment, during the first month after injections, and at the time of follow-up treatments. Patients were asked whether their greatest relief following BTX had been reduced pain, reduced torticollis, or equal improvement in pain and torticollis. They were also asked whether their pain had ever returned to pretreatment levels since initiation of BTX treatment.

Patient charts were reviewed only after receipt of the completed questionnaires to obtain data not elicited in the questionnaire such as type of CD, direction of head deviation, age of onset, duration of CD before treatment, and presence or absence of pain in patients who failed to respond or fully complete the questionnaire.

Results

Of 72 questionnaires that were mailed, 48 were returned. No attempt was made to repeat mailings or to telephone nonresponders. Thirteen questionnaires were returned incomplete, leaving 35 suitable for analysis. Mean age of onset of CD was 41.4 years (standard deviation [SD] 13.9 yrs), mean duration of CD was 13.7 years (SD 10.4 yrs), and mean duration of CD before beginning BTX treatment was 9.9 years (SD 1.7 yrs). Twenty-five patients were women and 10 were men. Eight had

pure rotational torticollis, eight had pure laterocollis, three had pure retrocollis, and 16 had mixed patterns of CD. Mean number of BTX treatments was 10.0 (SD 5.8); mean BTX dose per treatment was 200.8 units (SD 67.2).

Fifty-four of the original 72 patients (75%) who were mailed a questionnaire had painful CD. Of the 35 patient questionnaires suitable for analysis, 32 (91%) had painful CD. Only 22 of the 37 patients (59%) who either failed to return or fully complete the questionnaire had painful CD. Two of the three patients without pain had pure retrocollis whereas pure retrocollis was absent in the 32 patients with pain.

All 32 patients who experienced pain prior to BTX treatment reported relief of pain following treatment. Location of pain was most frequent in the neck (100%) followed by the shoulder (73.5%), lower back (29.4%), upper back (17.6%), and arm (14.7%). Neck pain was further localized as follows: right posterior 56.3%; left posterior 34.5%; bilateral posterior 6.2%; right anterior 3.1%; and left anterior 0.0%. Maximal neck pain was significantly more frequent ipsilateral (71.8%) than contralateral (28.2%) to the side of head deviation (tilt, turn, or both; $p < 0.05$, chi square). The most common quality of pain was "aching" (43.8%) followed by "pulling" (34.3%), "burning" and "tightness" (9.4% each), and "other" (3.1%). A sensory trick improved torticollis in 59.4% of patients but reduced pain in only 26.6% of patients. Common sensory tricks that reduced torticollis included touching the face or chin with the fingers or repositioning the neck. By contrast, sensory tricks or maneuvers that reduced pain consisted of physically supporting the neck or lying down.

Mean pain severity was significantly less during the month following BTX treatments than prior to initial treatment and did not return to baseline at the time of follow-up treatments ($p < 0.001$, repeated measures of analysis of variance and post hoc analysis; (Fig. 1). Pain never returned to pretreatment levels in 59.4% of patients. With respect to duration of pain, the majority of patients had pain more than 75% of the time before initial treatment, less than 50% of the time during the 1 month following treatment, and 50%–75% of the time at the time of follow-up treatments. Pain and torticollis were equally relieved in 58.8% of patients, pain was more satisfactorily relieved than torticollis in 23.5% of patients, and torticollis was more satisfactorily relieved than pain in 11.8% of patients.

There was no statistically significant correlation between type of CD and severity or location of pain, between pain location and pain severity, or between pain severity and quality of pain.

Discussion

Pain is prominent in two thirds of patients with CD and is often the most disabling manifestation of the disorder.[1,2] In this retrospective study, 91% of patients who responded to the questionnaire had painful CD. Because the questionnaire primarily concerned pain, it is not surprising that by contrast only 59% of the patients who failed to respond or fully complete the questionnaire had painful CD. The overall frequency of pain in the original group of patients who were sent a questionnaire was 75% which is in general agreement with prevalence figures for painful CD in previous studies.[1,2] Future studies of pain incidence should include a more comprehensive review of patient records.

The cause of pain in CD is unknown but suggested causes include continuous muscle contraction, cervical radiculopathy, cervical spondylosis, and mechanical traction on musculoskeletal structures.[1,2,13] Jankovic et al.[1] found that 31.5% of patients with CD experienced radicular pain whereas 68.5% experienced local pain. In this study the incidence of arm pain was only 14.7% indicating that radiculopathy was a less frequent cause of pain in our patients. By contrast, the neck (100%) and shoulder (73.5%) were the most frequently involved areas suggesting the greater importance of local musculoskeletal causes. In most patients with CD, the sternomastoid muscle strongly contributes to abnormal head deviation and becomes hypertrophied secondary to excessive contraction.

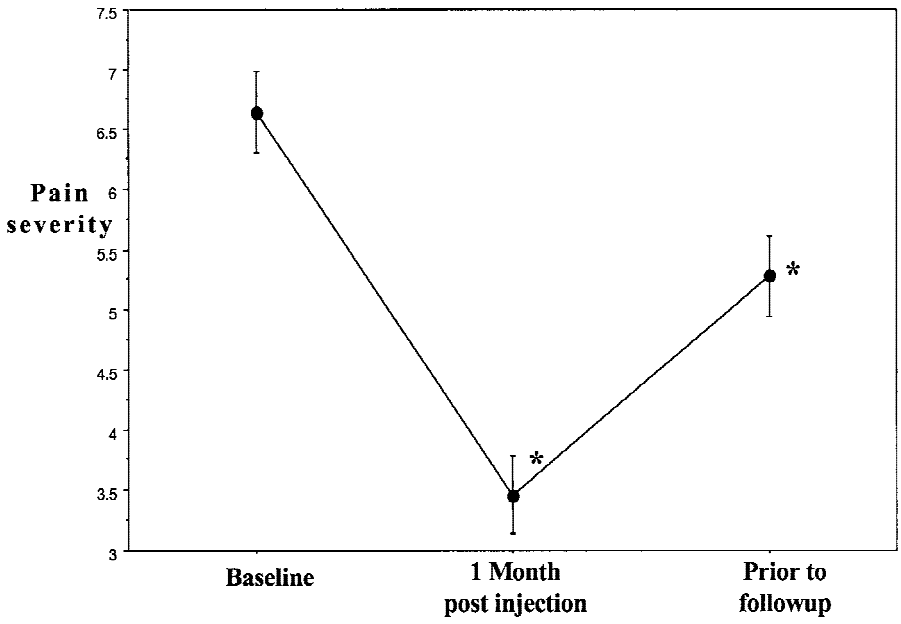

FIG. 1. Representation of pain severity at three times in the course of BTX treatment. A modified TWSTRS pain scale was used to estimate pain before BTX (baseline), 1 month after BTX, and at the time of follow-up BTX treatment. *Significantly less than baseline ($p < 0.001$).

The sternomastoid is involved contralaterally in all cases of rotational torticollis and ipsilaterally in most cases of laterocollis.[6] If pain is primarily muscular in origin, the anteriorly located sternomastoid region would have been expected to be a frequent location of pain. However, only 3.1% of our patients reported anterior cervical pain compared with 96.9% who reported posterior cervical pain. Further indication that the sternomastoid was not a significant source of pain is that, in the majority of patients, maximal neck pain was located ipsilateral to the side of head deviation. The location of pain posteriorly and ipsilateral to the side of head deviation reported by most patients indicates that pain probably originates from posterior cervical muscles or their skeletal attachments while sternomastoid contraction is not painful.

Kutvomen et al.[14] also found that neck pain in patients with CD was asymmetric involving primarily the splenius capitis and trapezius muscles with relatively little cervical radicular pain. Whether posterior cervical pain originates from muscle, tendon, or periosteal attachments remains unknown and is not clarified by this or previous studies.[14] The qualities of "aching" and "pulling" pain most frequently selected by our patients also does not clarify the issue. Chan et al.[2] raised the possibility that a higher density of deep pain receptors in neck muscles may account for the unique association of pain with CD. Although this is not an established fact, the high frequency with which chronic neck pain occurs as a complication of head and neck trauma may be a relevant observation.

All patients who completed the questionnaire experienced pain relief following BTX treatment. However, this is not a valid indicator of BTX response because this group of patients had been returning for regular treatment and had also been motivated to participate in the study. The finding that in 23.5% of our patients pain was more satisfactorily relieved than torticollis is consistent with previous observations that pain is frequently more BTX-responsive than abnormal head posture.[4,10,11] Pain severity and pain duration decreased significantly following BTX injections and slowly returned toward pretreatment levels by the time of the next injections which are usually given at 3-month intervals in our clinic population. The finding that pain severity did not return to baseline at the time of follow-up treatment (Fig. 1) likely reflects the fact that it is customary practice in our clinic to re-treat patients before they return to their baseline level of pain.

In summary, we conclude that in this group of patients, pain associated with CD was responsive to BTX, did not return to baseline levels prior to follow-up treatment, did not originate from sternomastoid muscle, and probably originated from posterior cervical muscles or their skeletal attachments.

Acknowledgments: Supported in part by the Shirley and Edgar Grossman Movement Disorders Fund. The authors thank Dawn Mechanic, Deborah Maher, Patricia Ryan, and Loren Morse for providing technical and clinical assistance.

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Blepharospasm Induced by an LED Flashlight

Blepharospasm is a focal dystonia characterized by excessive contractions of the orbicularis oculi muscles. Most of the cases are primary or the causes are unknown, although there have been a few reports of secondary cases.[1,2] Abnormal blink reflex recovery functions were documented in this condition, and the motor control of blinking appears to be involved.[3] Focal dystonias such as occupational cramps often follow repetitious use of the affected body part.[4] They are also characterized by a peculiar phenomenon of symptomatic relief after the patient assumes a specific posture or touches a specific

Received February 18, 1999; revision received July 16, 1999. Accepted July 30, 1999.

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FIG. 1. A part of the devise (goggle) for LED stimulation. Four separate LEDs are placed in front of each eye. Colored glasses provide a dark background.

body part (sensory trick).[5] A recent experimental study successfully induced a dystonia-like state in a monkey which, after a repetitious task of precision grip, showed disorganization of the primary somatosensory cortex.[6] In fact, the clinical benefit from performing a sensory trick in these patients suggests a disturbed sensorimotor integration or an abnormal motor subroutine.[7]

Patients with blepharospasm frequently experience excessive brightness at the early clinical stage, and they try to reduce the brightness by wearing sunglasses.[3,4] This indicates a mismatch between the input, or the light, and the output, or the contraction of the orbicularis oculi muscles that control blinking. Like in the experimental study for hand dystonia, blepharospasm might be induced by repetitive exposure to bright light.

We report here a patient who developed blepharospasm after the use of a device generating highly repetitive bright LED (light-emitting diode) flashlight.

Case Report

A previously healthy 25-year-old man began using a "brain synchronizer" (Fig. 1), or a device generating high-frequency (120 or 240 Hz) red LED flashlight and pulse sound, for the purpose of relaxation and meditation in April 1994. After wearing it approximately 1 hour a day for 3 months, he noticed daytime excessive brightness with a newly formed wrinkle on his forehead. Despite discontinuing the use of this, he developed frequent blinking and then severe eye-closing spasms, which made him unable to read books or walk outside in the daytime of midsummer (end of July 1994). He had a clinical benefit from wearing dark sunglasses during the day, but he could not walk without pulling up his upper eyelids with the fingers. There was no past history of antipsychotic medication or drug abuse and he has no family history of movement disorders.

He was referred to our clinic in September 1994. On examination, severe muscle spasms were found in the orbicularis oculi, and there was a mild but synchronous spasm of orbicularis oris muscle as well. They were aggravated by talking with friends, reading, or watching television, but improved when talking to an unfamiliar person or lying down on a bed. No abnormal contractions were seen in the other oromandibular muscles and the tongue. He could normally chew, swallow, and speak without difficulty. The exposure to the bright LEDs of the "brain synchronizer" markedly deteriorated his symptoms, but applying its pulse sound did not. The neurologic examination revealed no other abnormal findings. Magnetic resonance imaging of the brain, blood screening for infection, and immunologic tests were normal.

Trihexyphenidyl at a dosage of 6 mg per day was effective for reducing the spasm, but clonazepam or baclofen was not. He was injected with a total of 40 units of botulinum toxin (BOTOX, Allergan K. K., Tokyo) on November 17, 1994, which significantly improved his symptoms within a few days; he could read and walk without difficulties despite the persistence of frequent blinking. He followed our advice of not using the device again. In April 1995, he was seen at our clinic for a regular follow up and was entirely free from symptoms. His blinking rate was normal. The symptoms never relapsed in the following 4 years of observation without botulinum treatment or medication.

Discussion

Presenting with typical clinical symptoms and responses to the therapy, this patient was diagnosed to have blepharospasm. There was no previously recognized conditions that would induce blepharospasm. His symptoms were markedly aggravated by the flashlight but not by the pulse sound. He never developed symptoms after discontinuing the use of the device. All these points indicate that the bright flashlight of the device induced the spasm.

In a previous report,[3] we demonstrated that blink reflex recovery function was more abnormal for the light than for the electric stimulation in patients with blepharospasm. Indeed, blepharospasm may be regarded as a disorder of controlling blinking in response to light.[8] The normal input–output relationship between the light and the muscle contraction of blinking seems disturbed by the repetitious presentation of excessive input in this case. Wearing dark sunglasses may be a maneuver that alleviates the mismatch by diminishing the input.

This case may be regarded as a natural experiment for inducing blepharospasm, and there may be similar cases of "occupational" blepharospasm, especially among workers exposed to repetitiously presented brightness.

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Localized Neuromyotonia of Neck Muscles After Radiotherapy for Nasopharyngeal Carcinoma

Neuromyotonia is a clinical syndrome manifested by continuous and spontaneous muscle fiber contractions resulting from hyperexcitability of motor nerves. The diagnosis is largely based on a combination of clinical and electromyographic (EMG) findings. The clinical presentation is heterogeneous not only in terms of features and severity, but also in its association with a variety of other disorders. We describe an unusual case of a patient with isolated neuromyotonia in right neck muscles 3 years after radiotherapy to the neck for treatment of nasopharyngeal carcinoma (NPC). Electrophysiological studies showed evidence of neuromyotonia and myokymia.

Case Report

The patient is a 40-year-old man who was diagnosed with stage I NPC in early 1995. He was treated with radiotherapy (60 Gy in 15 fractions) to the right upper cervical region. The NPC has been in remission since then. Three years later, he gradually developed visible spasms of his right neck muscles. The twitches occurred throughout the day and when he was asleep. Occasionally, it caused a mild lateral rotation of his head to the left, especially when he was tired. There was no problem with his speech, swallowing, or vision. It caused only minimal disturbance to his activities of daily living.

Three months after the onset of his symptoms, physical examination revealed continuous, irregular, and fluctuating spasms of the right trapezius (Segment 1), sternocleidomastoid (Segment 2), and scalene muscles. The neck muscles on the opposite side were not involved (Segment 3). There was no muscle wasting. Power was fully preserved. Examination of the cranial nerves and extraocular movements was normal. The rest of the examination was normal.

Needle EMG of the right sternocleidomastoid and trapezius muscles at rest showed continuous firing of motor unit potentials at slow and variable rates (Segment 4). Some myokymic discharges were also recorded. Typical neuromyotonic discharges were present, with sudden bursts of high-frequency (50–60 Hz) motor unit potentials, which progressively decreased in number (Fig. 1). The right scalene muscles demonstrated similar neuromyotonic discharges but with less magnitude. EMG sampling of other neck muscles was normal. No abnormalities were found in the nerve conduction studies of upper limbs. Serum electrolytes including calcium, creatine kinase, and full blood count were normal. Cerebrospinal fluid examination did not show any oligoclonal bands. Electroencephalograph, somatosensory evoked potentials, and magnetic resonance imaging of the brain stem and upper cervical cord were unremarkable. Malignancy screen including tumor markers (that is, α fetoprotein [AFP], carcinoembryonic antigen [CEA], prostate-specific antigen [PSA], and CA19-9) were normal. Computed tomography of his thorax and abdomen were normal. He was given 400 mg carbamazepine twice daily which partially decreased his spasms but he declined botulinum toxin A therapy.

Discussion

To our knowledge, our patient is the first case of focal neuromyotonia involving the upper cervical region. It occurred 3 years after irradiation of nasopharyngeal carcinoma and without evidence of tumor recurrence. Neuromyotonia was first described as a "syndrome of continuous muscle fiber activity" which typically presents with transient, involuntary, discrete muscle contractions, stiffness, and delayed muscle relaxation. The characteristic EMG findings in neuromyotonia consist of spontaneous activity with repetitive discharges with duplets, triplets, and multiplets. These neuromyotonic discharges have a high (40–300 Hz) intraburst frequency at irregular intervals of 1–30 seconds. They are distinct from dystonia in that the neuromyotonic contractions are persistent during sleep and have characteristic EMG discharges. Whereas myotonia is defined as a delayed muscular relaxation following normal contraction, neuromyotonia is characterized by delayed relaxation after impulse-induced repetitive discharges in peripheral nerves.[1] In his original paper, Isaacs pointed out that the generation of ectopic impulses were in the peripheral nerves, based on the response to general anesthesia and proximal nerve blockade.[2] EMG findings support this postulation.[3–5] In contrast, the generation of ectopic impulses in myotonia arise from the muscle fibers. Myokymia is most often recognized clinically as continuous, involuntary, rippling, or undulating movement of muscle. It characteristically continues during sleep and under general anesthesia. Myokymic discharges consist of bursts of rhythmic, grouped, repetitive discharges of single motor potentials firing spontaneously, with a frequency of 5–60 Hz, and each burst lasting up to 2 seconds. Our patient had both neuromyotonic and myokymic discharges on the EMG. The neuromyotonic discharges are more irregular and longer in duration than the myokymic component.

Neuromyotonia may be idiopathic (Isaacs' syndrome) or secondary to other disorders. In idiopathic neuromyotonia, auto-

A videotape accompanies this article.
Received January 19, 1999; revisions received March 19 and March 26, 1999. Accepted June 29, 1999.
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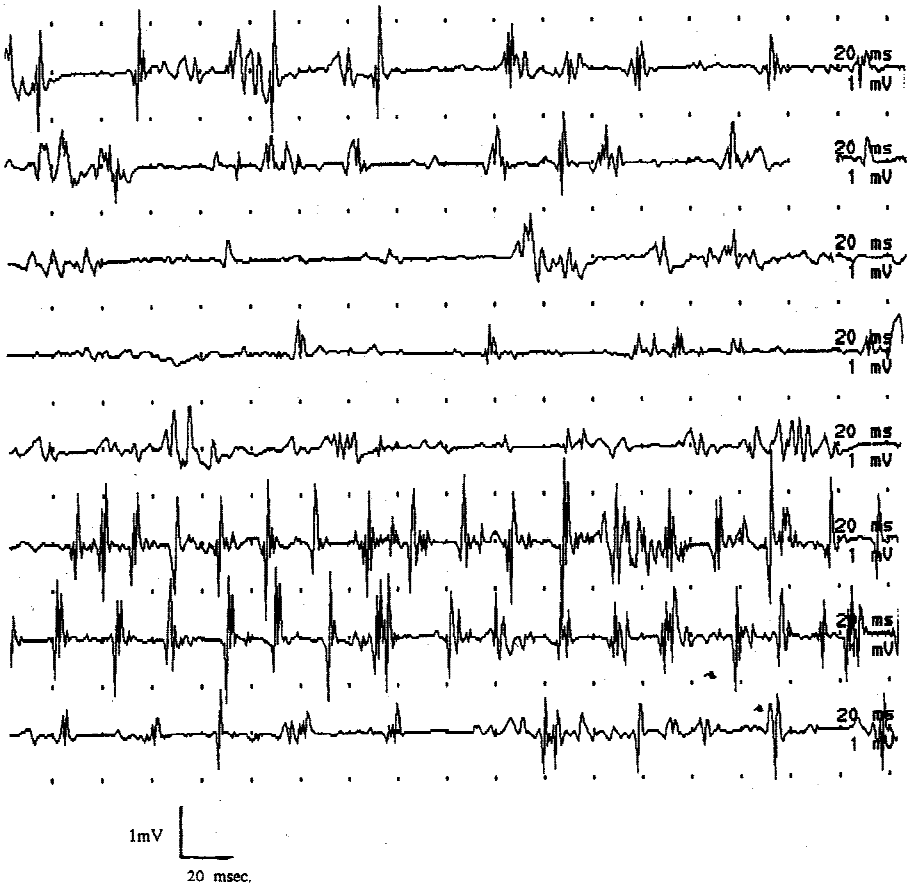

FIG. 1. EMG of the right sternocleidomastoid muscle showing neuromyotonic discharges with bursts of high frequency (50–60 Hz) motor unit potentials.

antibodies were found to be directed against voltage-gated potassium channels (VGPCs) on peripheral nerves.[6,7] This may prolong the action potential resulting in increased quantal acetylcholine release and repetitive discharges. Secondary generalized forms of neuromyotonia are associated with polyneuropathy, hereditary neuropathies, toxic exposures, and malignancy, notably, immune cell neoplasms (for example, thymoma, plasmacytoma, lymphoma) and bronchial carcinoma.[8] The abundance of VGPCs in proliferating lymphoid cells implies that in patients with neuromyotonia and immune cell tumors, antibodies directed against VGPCs in the tumor cross-react with similar channels in peripheral nerves producing spontaneous neuromyotonia.[9] We did not test for autoantibodies for VGPCs in our case because this test was not available to us.

The neuromyotonia in our case is probably related to the delayed effects of the irradiation on the spinal accessory nerve and the anterior rami of the cervical nerves on his right side 3 years after receiving his radiotherapy at that site. Both the sternocleidomastoid and trapezius muscles receive their innervation from the spinal root of the accessory nerve. The scalene muscles, which were also involved in our patient, are innervated by the ventral rami of the third to eighth cervical spinal nerves and branches from the brachial plexus. It suggests that the lesion was located at the nerves of the cervical region rather than the brain stem. The magnetic resonance image scans of his upper cervical cord and brain stem were normal. Delayed radiation-induced damage may be the result of direct nerve injury or damage to the vascular endothelium which results in nerve ischemia and connective tissue fibrosis. Both myokymia and neuromyotonia are thought to originate along segments of the motor axon, and the mechanism is thought to involve segmental demyelination, axonal degeneration, and axon sprouting and remyelination.[10,11] Reports of neuromyotonia related to radiation-induced damage exist. Ocular neuromyotonia (ONM) is manifested by transient ocular misalignment with diplopia develop spontaneously after sustained eccentric gaze.[12] An important feature of ONM was that most patients had radiotherapy to the parasellar and sellar regions.[13] The latency to onset of ONM ranged from months to 17 years. Other cases of neuromyotonia have involved a man with radiation-induced bulbar palsy 14 years after the radiotherapy for NPC,[14] two women with neuromyotonia at the floor of the mouth (involving the mylohyoid and anterior belly of digastric) 2 and 14 months, respectively, after radiotherapy to the base of the skull,[15] and a man with neuromyotonia of the lower facial muscles and masseter muscles bilaterally 14 months following radiotherapy for a right tonsillar tumor.[16] Two women were reported to have developed isolated neuromyotonia in their latissimus dorsi mammoplasty flaps 7 and 10 years, respectively, after postoperative radiotherapy for breast carcinoma.[17,18] Both these women did not have any evidence of tumor recurrence. Their neuromyotonia was thought to be related to either stretching or surgical trauma of the thoracodorsal nerve when the latissimus dorsi muscle was brought anteriorly.

The symptoms of neuromyotonia can be improved using carbamazepine and phenytoin. Their mechanism of action is thought to be related to a reduction in maximal sodium conductance in axonal membranes.[9] Plasma exchange may be considered in a minority of patients with idiopathic neuromyotonia who failed to respond to drugs.[7] Neuromyotonia has also responded well to botulinum toxin A injections to the affected muscles, noticed within days of the treatment, and a response which persisted following repeat injections at regular intervals.[17,18]

Legend to the Videotape

Segments 1–3: Continuous, spontaneous, and irregular spasms were seen in the right trapezius muscle (Segment 1) and right sternocleidomastoid muscle (Segment 2), both innervated by the right spinal accessory nerve. Apart from the scalene muscles, other neck muscles were not involved (Segment 3).

Segment 4: EMG of the right trapezius muscle showed spontaneous motor unit potentials at slow and variable rates, with the highest frequency at approximately 60 Hz.

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Slow Rhythmic Dyskinesia of the Shoulder: One Idiopathic and Two Symptomatic Cases

Caviness et al.[1] reported six patients who had slow, sinuous, semirhythmic dyskinesia of the shoulder. Surface polymyographic study showed a mixture of intermittent rhythmic and prolonged bursts of muscle activities, suggestive of a dystonic nature of the dyskinesia. Brain imaging studies performed on three of the six patients were normal.

Herz[2] introduced the term "myorhythmia" to describe somewhat rhythmic dyskinesia associated with dystonia. Later, the spectrum of myorhythmia was expanded to include rhythmic dyskinesia following a lesion in the dentato-rubro-olivary circuit.[3] Myorhythmia can be characterized by intermittent or continuous coarse, alternating dyskinesia at rest with a frequency of 50–240 oscillations per minute. It may affect the proximal or distal part of the limbs.[2,3]

We describe three patients with slow, rhythmic dyskinesia confined to the shoulder. One patient showed no lesion on brain magnetic resonance imaging (MRI), but one had a posterolateral thalamic infarction and the remaining one had lesions in the bilateral lenticular nuclei. Polymyographic study showed a mixture of 1–4 Hz rhythmic and prolonged bursts of muscle activities lasting up to 2 seconds. We suspect that the dyskinesia seen in these patients is an unusual manifestation of dystonia.

Case Reports

Case 1

A 12-year-old, otherwise healthy girl developed rhythmic, jerky movements of the right shoulder while she was raising her right arm. The dyskinesia lasted approximately 1 month and

Received November 16, 1998; revision received March 19, 1999. Accepted June 28, 1999.

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disappeared spontaneously. One year later, she developed mild pain and rhythmic dyskinesia with a more or less phasic nature in the right shoulder. It was present at rest but was suppressed while moving and maintaining posture. She could not suppress the dyskinesia voluntarily, but it disappeared completely when sleeping. On neurologic examination, there were no cranial nerve deficits. There was no motor weakness. She showed stereotypical sinuous, repetitive abduction and adduction movements of the right shoulder. One-way mirror observation, intramuscular injection of placebo, and distraction of mental concentration showed no alterations in amplitude and frequency of the dyskinesia. She had no dystonia in the hands. There were no sensory deficits. Cerebellar function tests were normal. Deep tendon reflexes were normoactive. Plantar responses were flexor bilaterally. Liver and thyroid function tests were normal. Serum ceruloplasmin and copper levels were normal. Surface polymyographic electromyographic (EMG) recording showed 1 Hz rhythmic bursts with intermittent prolonged bursts of muscle activities lasting 600–2000 msec in the right trapezius muscle. Electroencephalography study was normal. Brain MRI study was normal. Routine cerebrospinal fluid analysis was normal. Treatment with 0.5 mg clonazepam three times a day for 1 month was not helpful. The dyskinesia disappeared spontaneously over a period of 5 months.

Case 2

A 67-year-old man suddenly developed unsteady gait and electric sense in the left middle and ring fingers. Three months later, he developed spontaneous pain and painful dysesthesia in the left forearm. Around that time, he developed dyskinesia of the left shoulder. The dyskinesia had progressed to become continuous over a period of 2 years. The dyskinesia was attenuated markedly while maintaining posture and moving. The dyskinesia disappeared when sleeping. On neurologic examination, he had no cranial nerve deficits. There was no motor weakness. He had no sensory deficits. He showed rotation of his left shoulder and elbow. The dyskinesia was rhythmic, slow, and sinuous with a tonic component. There was no dystonia when he stretched out both hands in front of him. There was occasional terminal tremor on finger-to-nose tests, but other cerebellar function tests were normal. On finger dexterity tests, minimal clumsiness was observed in the left hand. Finger tappings and foot tappings were normal. Deep tendon reflexes were hypoactive but symmetric. Routine laboratory tests were all normal. T2-weighted brain MRI scan showed high signal-intensity lesions confined to the right posterolateral thalamus (Fig. 1). Surface polymyographic EMG recording showed a mixture of 1–2 Hz rhythmic bursts and prolonged bursts of muscle activities lasting 600–1200 msec in the left trapezius muscle. The dyskinesia continued for 7 years but it did not disturb his daily activities. No medical treatment was given.

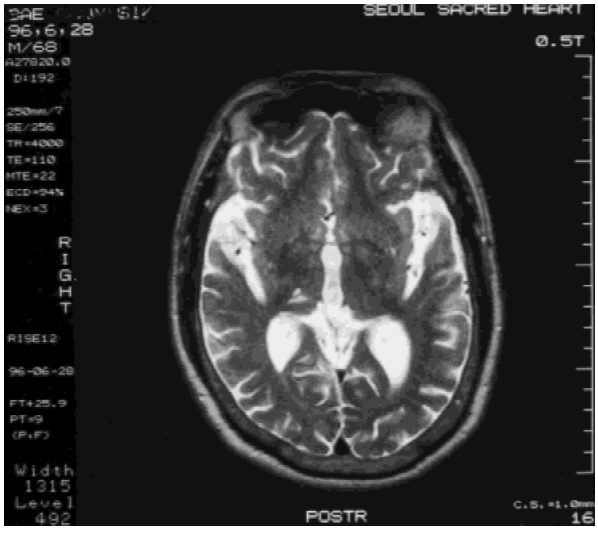

FIG. 1. Axial T2-weighted brain MRI scan of case 2 shows high signal-intensity lesions confined to the right posterolateral thalamus.

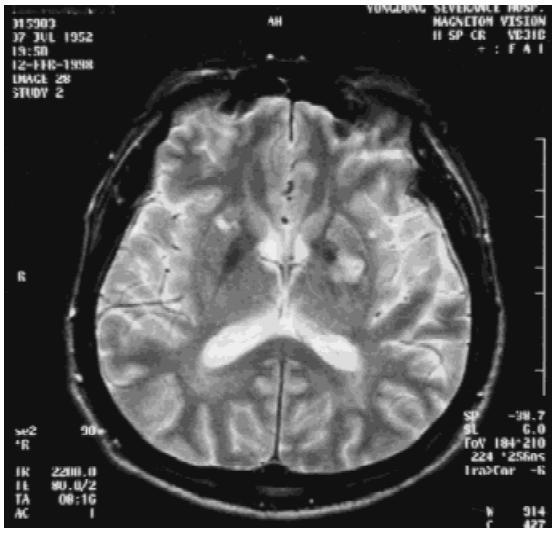

FIG. 2. Axial T2-weighted brain MRI scan of case 3 shows high signal-intensity lesions involving the anterior part of the right putamen and the posterior part of the left lenticular nucleus.

Case 3

A 46-year-old man developed dyskinesia involving his right shoulder. The dyskinesia was suppressed while maintaining posture and moving. On neurologic examination, there were no cranial nerve deficits. There was no motor weakness, but he showed minimal clumsiness on the right finger dexterity tests. There was no dystonia in either hand. He showed intermittent rhythmic elevation and subsequent brief posturing of the right shoulder. Surface polymyographic EMG recording showed a mixture of prolonged bursts lasting 450–1500 msec and 4 Hz rhythmic bursts of muscle activities in the right trapezius, pectoralis major, supraspinatus, and latissimus dorsi muscles. T1-weighted brain MRI showed a hyperintensity lesion involving the left lenticular nucleus. T2-weighted brain MRI showed hyperintensity lesions involving the bilateral lenticular nuclei (Fig. 2). Duodenal biopsy study with periodic acid-Schiff staining was negative. Over a period of 1 year, the dyskinesia disappeared completely.

Discussion

According to the Consensus Statement of the Movement Disorder Society on Tremor, dyskinesia seen in our patients can

most likely be classified as Holmes' tremor. It encompasses previous terms of myorhythmia, rubral tremor, midbrain tremor, and thalamic tremor. It has a frequency less than 4.5 Hz and occurs frequently as a consequence of a lesion in the brain stem, the cerebellum, the thalamus, or the cerebral cortex.[4]

Not only does tic disorder manifest as rapid jerks, but it can also manifest as slow, rhythmic dyskinesia. However, our case 1 did not have the urge to move and could not voluntarily suppress the dyskinesia. Our trials failed to prove that she had psychogenic tremor.[5]

A posterolateral thalamic lesion can cause a 3–4 Hz rest tremor, usually affecting distal parts of the contralateral upper limb. Such tremor is frequently enhanced while maintaining posture and moving.[6,7] However, our case 2 showed different dyskinesia from thalamic tremor in frequency, distribution, and effect of maintaining posture and movement.

Rarely patients have been reported who developed myorhythmia in association with paramedian thalamic infarctions. However, they had additional lesions in the subthalamic region and the brain stem. Therefore, the role of thalamic damage in the development of the myorhythmia was uncertain.[6,8,9] However, our case 2 showed that a lesion confined to the posterolateral thalamus could cause 1 Hz slow, rhythmic dyskinesia.

Our case 3 had multiple lesions involving the bilateral lenticular nuclei. In a study including 240 reported patients who developed dyskinesia following basal ganglia lesions, only three with tremor were identified. However, none had low-frequency rhythmic dyskinesia confined to the shoulder.[10]

In approximately half of the patients with central nervous system Whipple's disease, brain imaging studies show focal lesions without mass effect. They characteristically present with oculo-masticatory myorhythmia.[11] At least one patient with limb myorhythmia and supranuclear gaze palsy was reported.[12] In our case 3, there were no neurologic deficits except myorhythmia of the shoulder, and duodenal biopsy was negative.

We suspect that functional alterations or structural damage to the parts of basal ganglia-thalamo-cortical circuits critical for the suppression of unwanted movements cause rhythmic synchronization of the thalamo-cortical neurons and subsequent myorhythmia seen in our patients. However, in this study, polymyographic analysis of the dyskinesia showed a mixture of prolonged and rhythmic bursts of muscle activities. These findings suggest that myorhythmia can be an unusual manifestation of dystonia.[1]

Acknowledgment: The authors thank Dr. H. Y. Oh for helping in the preparation of the manuscript.

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Shoulder Girdle Dyskinesia Following Local Surgery

Shoulder girdle dyskinesia is an unusual focal dyskinesia. Caviness et al.[1] have described five idiopathic cases. Recently Wali[2] reported the first symptomatic case of this disorder in which it was associated with a contralateral thalamic infarct.

This report describes another case of symptomatic shoulder girdle dyskinesia following surgery in that region. This case fulfills the criteria for peripherally induced movement disorders as suggested by Jankovic.[3]

Case Report

This 58-year-old man presented for evaluation of involuntary movements involving his right shoulder for the last 18 months following surgery for squamous cell carcinoma of the lower third of the esophagus. The surgery was performed through an extensive curvilinear incision starting from the medial end of the acromion, sweeping the medial margin and inferior angle of the scapula, and extending up to the anterior axillary line at the level of the fifth rib. The surgery involved resection of the fifth

A videotape accompanies this article.
Received September 29, 1998; revision received February 25, 1999. Accepted July 12, 1999.
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rib. The scar healed well in approximately 2 weeks and he made a good recovery.

Six weeks later he started experiencing dull pain over the right scapular and periscapular region. A month later he noticed sinuous involuntary movements of the scapula which progressed in severity over the next month and remained the same thereafter. By this time the pain had spontaneously regressed. The involuntary movements remained localized even after a lapse of 18 months.

He was a known diabetic for nearly 10 years and was well controlled with antidiabetic medication. He was treated for pulmonary tuberculosis 3 years ago. There was no history of vaccination or consumption of neuroleptic drugs. He gave no history of head trauma at any time. There was no family history of movement disorders.

He was 162 cm tall and weighed 56 kg. General examination was remarkable for the scar described above. He had no cervical or axillary lymphadenopathy which could involve the brachial plexus.

Neurologic examination was unremarkable except for the focal dyskinesia. This was limited to the right shoulder girdle. It was characterized by the sinuous rhythmic/semirhythmic rotatory movements of the right scapula leading to repeated upward and anterior thrusting of the right shoulder. Overcontraction of the trapezius, rhomboids, and latissimus dorsi could be easily appreciated (see the videotape). The dyskinesia was not influenced by movements of the right upper extremity or any other part of the body either active or passive. There was no stimulus-sensitive behavior either to touch, pain, or vibration. It was not provoked by hyperventilation. There was no pain or tenderness associated with the involuntary movements. It disappeared during sleep.

Electromyographic (EMG) studies, using surface electrodes placed on the overcontracting muscles, demonstrated rhythmic/semirhythmic repetitive bursts of prolonged EMG activity lasting 700–1300 msec separated by periods of relative silence lasting 300–400 msec. Spontaneous crowding of such bursts was seen at times. Needle EMG of the periscapular muscles did not reveal evidence of local denervation. Electroencephalogram was normal.

Magnetic resonance imaging scan of the brain and cervical cord was normal. X-rays of the chest and spinal column revealed no evidence of secondary deposits.

Attempts to treat the dyskinesia with up to 606 mg clonazepam per day and up to 600 mg carbamazepine per day tried separately over a minimum period of 8 weeks was not successful.

Discussion

This patient developed right shoulder girdle dyskinesia within 3 months of undergoing surgery in that region. The dyskinesia remained focal even after a lapse of 18 months. The nature of the involuntary movement and associated EMG findings permit it to be classified as a focal rhythmic mobile dystonia. Obviously this case is an example of peripherally induced movement disorder because the criteria suggested by Jankovic[3] are fulfilled.

Shoulder girdle dyskinesia is an uncommon focal dyskinesia. Caviness et al.[1] have reported on five cases of shoulder girdle dyskinesia. The involvement was bilateral in three of the cases and unilateral in the remaining two cases. Neuroimaging of the brain and spinal cord did not reveal any lesion. Although two of the cases had a history of trauma, they do not fulfill the criteria suggested by Jankovic.[3] Thus, their cases can be classified as idiopathic.

Recently Wali[2] reported the first case of symptomatic unilateral shoulder girdle dyskinesia. It appeared following sensory stroke resulting from infarction of the right posterior thalamus. The present case of peripheral origin is the second symptomatic case of this focal dyskinesia.

The presence of pain, dysesthesia, or both in the affected region preceding the focal dyskinesia appears to be an important factor associated with peripherally induced dyskinesia. Such an observation also has been made in reference to focal dyskinesia involving other sites.[3–10] The prominent feature of pain in trauma-induced dystonia calls attention to the sensory system as a potential pathophysiological key.[11] Schott[6] has suggested that peripheral nerve lesion could alter sensory inputs and induce central reorganization generating the movement disorder.

The presence of a preceding focal deficit involving the affected region, paroxysmal behavior of the focal dyskinesia, its provocation by factors like action, sensory stimulus, and hyperventilation favors a central origin. Similarly, a positive response to clonazepam therapy favors a central origin. The critically placed lateral thalamic lesion in the central type of shoulder girdle dyskinesia may be responsible for these findings. Similar observations have been noted in the cases reported by Sunohara et al.[12] and Nijssen and Tijssen.[13]

This report draws attention to the fact that focal dyskinesias which are induced by peripheral injury differ in some clinical characteristics from those with a demonstrable central focal lesion.

Legend to the Videotape

This video segment demonstrates the rhythmic or semirhythmic rotatory movements of the right scapula leading to elevation and protrusion of the right shoulder tip. The extensive curvilinear healed surgical scar is also seen.

Acknowledgment: The author thanks Mr. Anand I. Gundapi and Mr. Guggari for technical assistance.

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Painful Legs and Moving Toes Associated With Neuropathy in HIV-Infected Patients

The syndrome of painful legs and moving toes (PLMT) was first described by Spillane et al.[1] in 1971. It consists of pain in distal lower limbs, varying from a "constant discomfort to an intractable torment," and involuntary movements of the toes. The pain is usually constant with a burning, crushing, or throbbing character. Toe movements are spontaneous and purposeless, with flexion, extension, adduction, and abduction combined and leading to circular and fanning movements. The symptoms may be unilateral or bilateral. Pain usually precedes the abnormal movements from days to years.[1,2] In rare instances, abnormal movements are not accompanied by pain.[2,3]

PLMT may be idiopathic[1–3] but has been related to traumatic lesions of foot soft tissue and bone,[2,4,5] peripheral neuropathies,[2,6,7] *cauda eqüina*,[2,4] and root lesions. These may be the result of compression[1,2,4,8] or *Herpes zoster* infection.[2,4] Rarely, the syndrome occurs in the upper limbs rather than the lower limbs. In these specific cases, suggested causal factors are soft and bony tissue trauma following amputation (movements in the remaining fingers and the stumps of the amputated ones)[9] and radiotherapy-related lesion of the brachial plexus.[10] The electromyography may relate the toe movements to long-duration (500 msec–2 sec) bursts of activity from normal motor units with normal recruitment patterns.[2]

In this article, we report two patients with PLMT and HIV-related neuropathy. To our knowledge, this is the first description of the association.

Case Reports

Patient 1

A 38-year-old man had AIDS diagnosed on March 1991 following chronic diarrhea related to *Cryptosporidium sp.* infection. From that time to April 1993, he had *Candida sp.* esophagitis, recurrent lung and sinus infections, cytomegalovirus (CMV) esophagitis, pulmonary tuberculosis, and thoracic Herpes zoster. He has been taking zidovudine, didanosine, rifampin, isoniazide, pyrazinamide, ganciclovir, and cotrimoxazole. In June 1993 he noticed a progressive, ascending burning pain in both legs. Amitriptyline at a dosage of 75 mg per day and pyridoxine were introduced with no benefit. Bilateral involuntary toe movements appeared 3 months later, whereas pain subsided shortly thereafter. The movements consisted of complex sequences of flexion and extension movements occurring in the first and second toes of both feet, predominantly the right one. These slow movements were exaggerated in the lying position. They could be inhibited voluntarily but only for short periods. The neurologic examination revealed absent ankle reflexes and symmetric lower limb superficial hypoesthesia up to the knees. A cerebrospinal fluid examination was normal.

On October 2, 1993 the patient was admitted to this hospital with headache, confusion, depressed consciousness, and partial seizures of the right face. A computed tomography scan disclosed cortical atrophy and a non-enhancing hypodensity in the left posterior caudate nucleus and thalamus. Sulfadiazine and pyrimethamine were started for presumed cerebral toxoplasmosis but the patient developed bacterial sepsis shortly after and died on November 1. Moving toes were present continually while in the hospital. Electromyography could not be performed.

Patient 2

A 51-year-old man had AIDS diagnosed in 1992 at the age of 46, following *Pneumocystis carinii* pneumonia. Since then, he has been taking zidovudine; indinavir and lamivudine were added in May 1997. Despite the introduction of multiple antiretroviral drugs, his CD4 cell counts remained around 75/mm^3 with high viral loads (>100,000 particles/mm^3), and the patient was switched in February 1998 to a new treatment regimen including nevirapine, stavudine, and didanosine. In 1995, the patient noticed slowly ascending paresthesias, initially restricted to the lower limbs but also affecting the fingertips on both sides 1 year later. In May 1997, he also noticed bilateral involuntary, uncomfortable, and sometimes painful movements of the toes, which were more prominent in the supine position. From that time, multiple drugs were prescribed to control painful symptoms (for example, up to 100 mg amitriptyline per day, up to 60 mg baclofen per day, up to 600 mg mexiletine per day, up to 800 mg carbamazepine per day, up to 2.100 mg gabapentin per day) without any consistent benefit. The sequential neurologic examination (June and October 1997, February and August 1998) disclosed absent ankle reflexes and mild nonprogressive hypoesthesia affecting both feet and legs. Abnormal slow and asymmetric toe movements (more coarse on the right side) were seen. They were more prominent while lying but still evident in the sitting position with legs hanging, and consisted of flexion–extension and adduction–abduction movements in all toes. Pain accompanied the abnormal movements.

Electroneuromyography in February 1997 revealed absent sensory sural nerve potentials and relatively spared sensory and motor conduction velocities. Cerebrospinal fluid disclosed increases in mononuclear cell counts (14/mm^3) and total protein (79 mg/dL). Polymerase chain reaction for CMV was negative (two samples). A sural nerve biopsy was performed and disclosed a slight to moderate decrease in large myelinated fiber

A videotape accompanies this article.

Received September 11, 1998; revision received March 19, 1999. Accepted June 29, 1999.

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density with axonal degeneration of some fibers. There was a slight increase in endoneural connective tissue with no amyloid deposit or inflammatory cell infiltration. These findings were considered consistent with a diagnosis of HIV-related axonal neuropathy.

Discussion

PLMT has been previously associated with peripheral neuropathy (especially of the axonal type) from many etiologies.[2,6,7] To our knowledge, this is the first report of PLMT associated with HIV-related axonal polyneuropathy.

Although this could not be substantiated by electroneuromyography in one case, our patients are thought to have developed PLMT in relation to axonal HIV neuropathy. However, the possible role of drugs, especially didanosine and isoniazide, in the genesis of neuropathy in the first patient cannot be confidently ruled out.

The second patient was better documented and there is little doubt about the HIV etiology. In this patient, typical features of axonal polyneuropathy were present in both the electromyographic and biopsy study without any evidence for associated vasculitis.

The pathophysiology of PLMT is not well known. Nathan[4] suggests that the posterior nerve root or dorsal root ganglion could be implicated in the generation of frequent and spontaneous impulses. These inputs from posterior root fibers would then excite local spinal interneurones and lead to the abnormal movements and pain. Afferent stimulation would trigger this phenomenon in lesions of the peripheral nerves, root nerve fibers, or even limb soft tissue and bone. Other authors[2,5,7,10] implicate additional suprasegmental involvement of structures above the spinal segmental level in the genesis of PLMT. The complex nature of the toe movements (independent contractions of agonist and antagonist muscles of each toe or finger) cannot be adequately explained by a spinal cord mechanism and suggests some participation of cerebral neurons in its genesis.[2,10] This model suggests that the abnormal sensory inputs from the periphery to the spinal cord could lead to a reorganization of subsequent cerebral processing and generate pain and involuntary movements.

The pathogenesis of HIV-related predominantly sensory polyneuropathy is also unresolved. HIV is only rarely detected in macrophage infiltrates of neural tissue.[11] Painful neuropathies also occur with varying frequencies in patients with the use of certain antiretrovirals (for example, zalcitabine, stavudine, and didanosine) or drugs needed for the prevention and treatment of HIV-associated conditions.

As shown by the two cases reported here, the treatment of PLMT is difficult. Drugs such as carbamazepine,[2,5] tricyclic antidepressants,[2,5,8] diazepam,[2,5,9] baclofen,[2,5,9] beta-blockers,[9] corticosteroids,[5] and analgesics[5] have been tried in different combinations. Lumbar sympathetic blockade with aqueous phenol or guanethidine causes only transient remission of the symptoms.[1,2,4,5] Even sympathectomy may only lead to transient remission.[1,2] Both our patients experienced poor response to the given drugs, but the first patient had spontaneous pain relief after some months. A marked and desired reduction of the viral load has not been attained in our second patient (no viral load tests in patient 1), and therefore we can only speculate about the effects of adequate control of the systemic infection on symptoms. Antiretroviral therapy is usually unable to control pain in HIV-related sensory neuropathy.[12]

In conclusion, this report suggests that HIV-related neuropathy should now be seen as a possible etiology for PLMT. The role of antiretroviral drugs in the pathogenesis of this syndrome or in its treatment is still unclear.

Legends to the Videotape

Segment 1: Patient 1. This segment shows a very ill AIDS patient with marked muscle consumption and flaccid amyotrophic paraplegia resulting from peripheral neuropathy. There are bilateral involuntary flexion–extension movements of the toes, more prominent in the right foot.

Segment 2: Patient 2. This segment shows another AIDS patient presenting flexion–extension and adduction–abduction movements in both feet caused by HIV-related distal, predominantly sensory polyneuropathy.

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Sporadic Acetazolamide-Responsive Episodic Ataxia

Acetazolamide-responsive periodic ataxias are rare disorders, depicted as "often unrecognized" and mostly occurring as dominantly inherited "familial" conditions in which affected individuals experience attacks mainly consisting of gait ataxia and dysartria often brought on by physical or emotional stress, without neurologic abnormalities between attacks.[1,2]

Sporadic forms of periodic ataxia are rare and are mostly described as unresponsive to acetazolamide.[3] Symptoms were reduced by acetazolamide administration in only four patients affected by nonfamilial forms of periodic ataxia.[4,5]

We describe another patient affected by repeated attacks of ataxia and dysartria, which we could document on videotape, who responded to acetazolamide therapy and who had normal magnetic resonance imaging (MRI) scans, electroencephalograms (EEGs), and normal laboratory examinations, including genomic studies for spinocerebellar ataxia (SCA).

The patient is a 36-year-old man who was working as an expert automobile repairman. He had this disorder since the age of 29 years consisting of episodes of periodic ataxia described as vertigo, slurred and scanned speech, and an inability to write and perform skilled manual work. His family history, supported by interviews with all living relatives (grandparents, uncles), was negative.

There was no alteration in consciousness before, during, or after periodic attacks. The spells were apparently brought on by stress or fatigue or coffee ingestion, and recurred every month appearing in clusters of two to three episodes lasting throughout the morning, followed by a rejuvenating afternoon nap. The morning spells were heralded by a sensation of unsteadiness, without vertigo, and irritability.

Between attacks, neurologic examination was normal.

We could not precipitate attacks by coffee administration, but we could observe the patient during two attacks; both consisted of broad-based gait ataxia with prevalent left lateropulsion, without nystagmus and without any sensation of rotation, and of dysartria and scanned speech. During the attack, writing became tremulous and enlarged, almost illegible (see the videotape).

The EEG recorded between and during attacks by a video EEG technique consisted of 8–9 Hz alpha activity (in the slow range compared with normal age-matched control subjects) with normal reactivity. Electromyography of gastrocnemii and vastii mediales did not record any abnormality during attacks, thus excluding the coexistence of myokymia.[6,7]

Laboratory results, including blood count, glucose, electrolytes, levels of urea creatinine, calcium uric acid, vitamins E and B12, red cell folate, amino acids, serum piruvate and lactate, and plasma protein electrophoresis, were within normal limits between and during attacks. Brain stem and somatosensory evoked responses, audiograms, caloric tests, electroretinography, and rotational tests were normal. T1-, T2-weighted 1.5-T MRI of the brain was normal.

Genomic DNA was isolated from peripheral blood leukocytes; PCR analysis was used for detection of the SCA 1 locus mutation on chromosome 6p and SCA3 on chromosome 14 q. CAG repeats were 20 for SCA1 locus and 35 for SCA3 locus, thus excluding abnormal alleles.

Allelic comparison with parental genomic DNA resulted in a 99% certainty of paternity from the father.

This patient had been previously unsuccessfully treated with 50 mg thiethylperazine per day, 30 mg clobazam per day, 3 mg lorazepam per day, and 300 mg phenytoin per day all resulting only in severe somnolence. He was also treated with 80 mg pyridostigmine four times a day for 1 month resulting in no change in the recurrence of ataxia.

Acetazolamide was administered after all laboratory investigation had been completed following a patient-blind protocol: 60 unmarked tablets each containing 125 mg acetazolamide were administered by the hospital staff each month. Attacks ceased completely during the next 6 months.

Acetazolamide was then substituted with placebo tablets containing eccipients and 120 mg carnitine each. Three ataxic episodes recurred 15 days after the crossover and 15 days later. The new crossover to acetazolamide resulted in the disappearance of ataxic episodes during the following year.

Although the differential diagnosis includes paroxysmal choreoathetosis and dysartria, multiple sclerosis, basilar migraine, Labyrinth's disorders, and epilepsy, the evolution, the clinical and paraclinical evaluations, made the possibility of any of these disorders highly unlikely, and we conclude that the patient can be considered a typical example of acetazolamide-responsive periodic ataxia in nonfamilial presentation.

Furthermore, the EEG in this patient did not show the generalized or focal slowing, recently described in 20%–70% of patients affected by familial periodic ataxias and in the other four patients with sporadic forms.[3,8,9] MRI was also normal, whereas many reports of sporadic episodic ataxias describe minor cerebellar abnormalities.[10]

Legend to the Videotape

Segment 1 shows the patient during the ataxia attack while walking, tested for eye movements and writing, and repeating an Italian nonsense rhyme.

Segment 2 shows the same activities under acetazolamide therapy.

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A videotape accompanies this article.

Received March 13, 1999; revisions received March 19 and April 9, 1999. Accepted July 13, 1999.

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