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Clinical/Scientific Notes

No Association Between Paraoxonase 1 (*PON1*) Gene Polymorphisms and Susceptibility to Parkinson's Disease in a Chinese Population

The cause of Parkinson's disease (PD) remains unknown. Although twin, family, and case control studies provide overwhelming evidence of a genetic contribution PD,[1,2] and despite extensive genetic mapping studies in PD in the last decade, no susceptibility loci have yet been unequivocally identified. Several reasons for this relative lack of success include phenotypic uncertainty, clinical and genetic heterogeneity, and polygenetic inheritance. It is also possible that the genes of major effect are only responsible for a relatively small contribution to overall genetic risk and that the major contribution comes from genes of modest or minor effect. Indeed, association studies using candidate genes are useful and powerful methods for detecting genes of modest or even minor effect contributing to complex disorders, providing that it is possible to examine the functional variant itself or a polymorphic marker in strong linkage disequilibrium with the functional variant.

Human serum paraoxonase 1 (*PON1*) is involved in the metabolism of oxidized lipids and also plays a major role in the metabolism and detoxication of insecticides processed though the cytochrome P450/PON1 pathway. Two frequent polymorphisms present in the *PON1* gene are the methionine (M allele)–leucine (L allele) interchange at position 54 and the arginine (B allele)–glutamine (A allele) interchange at position 192.[3] Recently, a correlation between the Gln192Arg polymorphism in the *PON1* gene and PD was found in a Japanese population,[4] but it was not found in a Russian population.[5] We performed the current study to determine whether this polymorphism and another Met54Leu polymorphism in the *PON1* gene are associated with an increased risk for PD in a Chinese population.

Patients and Methods

Patients

One hundred eighty patients with PD (106 men and 74 women) were recruited from the outpatient clinic of neurology at the First Affiliated Hospital of the Sun Yat-sen University of Medical Sciences in Guangzhou, China. The ratio of men to women was 1.4 to 1. The study protocol was approved by the ethical committee of the Sun Yat-sen University of Medical Sciences. All patients with PD were diagnosed as having probable PD using the criteria of Gelb et al.[6] The age at onset and examination was 58.6 ± 12.6 years old (range, 28–80 years) and 66.9 ± 11.2 years (range, 32–86 years), respectively. Fifty patients with early-onset PD (age at onset, 28–50 years) and 130 patients with late-onset PD (age at onset, ≥51 years of age) were included in the study group. All patients were sporadic based on pedigree analysis. One hundred eighty healthy unrelated control subjects (106 men and 74 women; age range, 34–86 years; mean age, 64.9 ± 12.8 years) were randomly recruited from the same hospital. They were matched for age, gender, ethnic origin, and area of residence. A medical examination was performed to identify volunteers in good health.

Methods

High-molecular-weight genomic DNA was extracted from peripheral blood lymphocytes by standard methods. The amount of DNA was determined spectrophotometrically, and its purity was estimated by comparing absorbances at 260 and 280 nm. *PON1* genotypes were determined by the polymerase chain reaction according to previously published protocols.[3,7]

Subsequently, we compared the *PON1* genotypic and allelic frequencies of the patients with PD with those of the control subjects and searched for correlation between the *PON1* gene polymorphisms and the age at onset of PD. The distribution of genotypes and the allelic frequencies of the *PON1* gene were compared in the two populations by the χ^2 test. Odds ratios and 95% confidence intervals were computed to compare risk between levels of categorical variables by a Yates-corrected χ^2 test. A p value less than 0.05 was taken as the level of significance.

Results

The Hardy-Weinberg equilibrium test of the codon 54 and 192 polymorphisms of the *PON1* gene showed that all subgroups of patients were at equilibrium. The distribution of genotypes associated with the 54 and 192 polymorphisms corresponded to that observed in other Chinese populations.[8,9] The genotyping results for patients with PD subjects and control subjects are shown in Table 1. We did not find any significant differences between patients with PD, including early-onset and late-onset PD, and their respective control subjects regarding *PON1* 192 and 54 genotypic or allelic distribution (all $p > 0.05$).

Discussion

Paraoxonase is a serum enzyme whose precise physiologic role is unknown.[10] It hydrolyzes many substrates, including aromatic carboxylic acid and organophosphates such as paraoxon, a metabolic product of the widely used pesticides, and nerve gases, such as sarin. The hydrolytic products of paraoxon are relatively nontoxic, in contrast to paraoxon itself, a potent inhibitor of the cholinesterases that break down the neurotransmitter acetylcholine.[10] Thus, paraoxonase in the blood might help prevent paraoxon from reaching the nervous system, where the pesticide would cause acetylcholine to accumulate at

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Address correspondence and reprint requests to Jian Wang, MD, PhD, Room 504, Institute of Genetics, Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China.

TABLE 1. *PON1 192 genotypic and allelic frequencies in groups of patients with Parkinson's disease and control subjects*

Variables	Overall PD patients n (%)	Overall control subjects n (%)	Odds ratio (95% confidence interval)
PON1 192 genotype			
AA	25 (13.9)	26 (14.4)	1.0 (Ref)
AB	85 (47.2)	88 (48.9)	1.0 (0.5–2.0)
BB	70 (38.9)	66 (36.7)	1.1 (0.6–2.2)
Total	180 (100.0)	180 (100.0)	
Alleles			
A	135 (37.5)	140 (38.9)	1.0 (Ref.)
B	225 (62.5)	220 (61.1)	1.1 (0.8–1.4)
PON1 54 genotype			
LL	165 (91.7)	166 (92.2)	1.0 (Ref.)
LM	14 (7.8)	13 (7.2)	1.1 (0.5–2.5)
MM	1 (0.5)	1 (0.6)	1.0 (0.03–36.9)
Total	180 (100.0)	180 (100.0)	
Alleles			
L	344 (95.6)	345 (95.8)	1.0 (Ref.)
M	16 (4.4)	15 (4.2)	1.1 (0.5–2.3)

* No significant differences were found in either genotypic or allelic distributions between groups of patients with Parkinson's disease and control subjects (all $p > 0.05$).

PON1, paraoxonase 1.

cholinergic synaptic junctions and to overstimulate neurons. Serum levels of paraoxonase activity vary widely among individuals, which may partly account for differences in susceptibility to organophosphate poisoning.[11,12] The molecular basis for this difference has been attributed to the presence of DNA polymorphisms in the *PON1* gene at amino acid positions 54 and 192.[12–14]

Recently, Kondo and Yamamoto[4] found a correlation between the codon 192 polymorphism of the *PON1* gene and PD in a Japanese population. They determined that the odds ratio for developing PD in individual *PON1-BB* bearers was 1.60 ($p < 0.001$), as compared with the *PON1-AA* and *PON1-AB* genotypes. However, we find no evidence in our data to support the findings of the Japanese group. Similar negative findings were also reported in an association study from Russia.[5]

There are three primary reasons that this difference may have arisen. First, population admixture can result in apparent associations that are caused by differences in the frequencies of alleles in different ethnic groups. Second, the discrepancy may be caused by different environmental and lifestyle exposures, including different environmental neurotoxins, different exposures to protective factors, such as antioxidants in the diet or smoking, between the two races, as discussed by Leighton et al.[15] It is possible that certain patients with a possible genetic predisposition may have come in contact with the appropriate environmental stimulus required for phenotypic expression of the disease. Third, there may be more than one susceptible gene contributing to complex disorders such as PD. It is possible that interactions or combined actions of *PON1* with other genes play an important role in the susceptibility to PD. Therefore, complex gene–environment and gene–gene interactions or combined actions should also be investigated. Such studies have already been reported.[16–19]

In summary, our results suggest that the codon 54 and 192 polymorphisms of the *PON1* gene do not confer genetic susceptibility to PD in the Chinese population tested, even in patients with early-onset PD, in which genetic factors appear to be important.[20] To further clarify the association between the *PON1* gene polymorphisms and PD, promoter polymorphisms should also be investigated because they may exert an even stronger influence on concentrations and activity of serum *PON1*[21] and thus may increase risk for PD. The determination of *PON1* status in PD requires more than genotyping.[22] The enzyme activity analysis should also be required. This further study is currently underway in our laboratory.

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Jian Wang, MD, PhD
Zhuolin Liu, MD
Department of Neurology
The First Affiliated Hospital
Sun Yat-sen University of Medical Sciences
Guangzhou, People's Republic of China

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Lack of Association Between Cytochrome P450 2E1 Gene Polymorphisms and Parkinson's Disease in a Chinese Population

The etiology of Parkinson's disease (PD) remains unknown. A consensus shows that multiple etiologies may result in the clinical and pathologic abnormalities that are common to the majority of patients with sporadic PD. Genetic factors have displayed an importance in the cause of PD and in determining susceptibility.[1]

A susceptible factor for the development of PD may involve isoforms of cytochrome P450, some of which are found in the brain. CYP2E1, associated with free radical production[2,3] and the formation of endogenous toxins,[4] is specifically localized in the substantia nigra,[5] colocalizing with tyrosine hydroxylase.[6] CYP2E1 metabolizes n-hexane, leading to the formation of its neurotoxic metabolite 2,5-hexanedione, which may explain cases of solvent-induced parkinsonism.[7] Therefore, CYP2E1 is a plausible candidate gene for PD.[8]

Genetic polymorphism in the 5′-flanking region of the CYP2E1 and its ethnic variations have been reported.[9–13] Hayashi et al.[9] reported that genetic polymorphisms in the 5′-flanking region of the CYP2E1 affect its binding of the transacting factor and change its transcriptional regulation, which may lead to interindividual differences of microsomal drug oxidation activity. In this study, we investigated the association of this gene polymorphism with PD in a Chinese population.

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Address correspondence and reprint requests to Jian Wang, MD, PhD, Room 504, Institute of Genetics, Fudan University, 220 Handan Road, Shanghai 200433, P.R. China.

Subjects and Methods

Subjects

One hundred fifty patients with PD (84 men and 66 women) were recruited from the outpatient clinic of neurology at the First Affiliated Hospital of the Sun Yat-sen University of Medical Sciences, Guangzhou, P.R. China. All patients with PD were diagnosed as having probable PD using the criteria of Gelb et al.[14] The average age of onset was 59.5 ± 9.5 years (range, 30–86 yrs). Forty patients with early-onset PD (onset between 30 and 50 years of age) and 110 patients with late-onset PD (onset ≥51 years of age) were included in the study group. All patients with PD were sporadic based on pedigree analysis. One hundred fifty healthy control subjects were recruited from the same hospital. They were matched for age, gender, ethnic origin, and area of residence. A medical examination was performed to identify subjects in good health.

Methods

Genetic polymorphism assay genomic DNA was extracted from whole blood according to standard procedures. The *Rsa* I and *Pst* I polymorphisms of the CYP2E1 gene were determined according to Hayashi et al.[9] using primers J8 (5′-TTCATTCTGTCTTCTAACTGG-3′) and J9 (5′-CCAGTCGAGTCTACATTGTCA-3′). The PCR-amplified DNA fragment, which included the two polymorphic sites, was digested with *Rsa* I and *Pst* I, respectively. The presence of restriction sites yields two fragments of 120 and 290 base pairs for the *Pst* I restriction digest (allele C2) and 360 and 50 base pairs for the *Rsa* I restriction digest (allele C1).

Statistical Analysis

Statistical analysis was performed using the chi-square test with the WebStat 2.0 Beta (www.stat.sc.edu/west/webstat/version 2.0 beta/). Odds ratios and 95% confidence intervals were computed to compare risk between levels of categorical variables by a Yates-corrected chi-square test. $P < 0.05$ was taken as the level of significance.

Results

The Hardy-Weinberg equilibrium test of the *Rsa* I and *Pst* I polymorphisms of the CYP2E1 gene showed that all subgroups of both patients and control subjects were in equilibrium (all $p > 0.05$). The genotyping results for both patients with PD and control subjects are shown in Table 1. We did not find any significant differences between overall patients with PD, including patients with early-onset PD and those with late-onset PD, and their respective control subjects regarding CYP2E1 genotypic or allelic distribution (all $p > 0.1$).

Discussion

This study showed racial variations in CYP2E1 gene polymorphisms. Like what has been found in the dopamine transporter gene polymorphism,[15] the Chinese population shared similar allele frequencies with the Japanese population in CYP2E1.[9,10] In addition, the genotype distribution and allele

TABLE 1. *Genotypic and allelic frequencies of the* Rsa *I and* Pst *I polymorphisms of CYP2E1 gene in patients with Parkinson's disease and control subjects*

Genotypes	Early-onset PD patients n (%)	Younger control subjects n (%)	OR (95% CI)	Late-onset PD patients n (%)	Older control subjects n (%)	OR (95% CI)	Overall PD patients n (%)	Overall control subjects n (%)	OR (95% CI)
C1C1	27 (67.5)	43 (71.7)	1.0 (Ref.)	74 (67.3)	66 (73.3)	1.0 (Ref.)	101 (67.3)	109 (72.7)	1 (Ref.)
C1C2	10 (25.0)	15 (25.0)	1.1 (0.4–3.0)	34 (30.9)	23 (25.6)	1.3 (0.7–2.6)	44 (29.3)	38 (25.3)	1.3 (0.7–2.2)
C2C2	3 (7.5)	2 (3.3)	2.4 (0.3–22.1)	2 (1.8)	1 (1.1)	1.8 (0.1–50.3)	5 (3.4)	3 (2.0)	1.8 (0.4–9.8)
Total	40 (100.0)	60 (100.0)		110 (100.0)	90 (100.0)		150 (100.0)	150 (100.0)	
Alleles									
C1	64 (80.0)	101 (84.2)	1.0 (Ref.)	182 (82.7)	155 (86.1)	1.0 (Ref.)	246 (82.0)	256 (85.3)	1.0 (Ref.)
C2	16 (20.0)	19 (15.8)	1.3 (0.6–2.9)	38 (17.3)	25 (13.9)	1.3 (0.7–2.3)	54 (18.0)	44 (14.7)	1.3 (0.8–2.0)

PD, Parkinson's disease; CYP2E1, cytochrome P450 2E1; OR, odds ratio (95% confidence interval).
C1: *Pst* I−, *Rsa* I+.
C2: *Pst* I+, *Rsa* I−.
* No significant differences were found in either genotypic or allelic distributions between groups of patients with PD and their respective control subjects (all $p > 0.1$).

frequencies for the Chinese population were significantly different from either white or African-American populations.[11–13] These findings were consistent with previous studies.[13,16]

In this study, we found that the *Rsa* I and *Pst* I polymorphisms were completely linked in the Chinese population, as previously reported in white,[13,17,18] African-American,[13] Chinese,[13] and Japanese populations,[9,10] except for the study by Kato et al.[11] Therefore, it is probably true that these two polymorphisms of CYP2E1 are completely linked in different races unless there is a sequence study to provide results similar to those reported by Kato et al.[11]

PD is thought to be caused by some unknown endogenous or exogenous factors interacting with genetic dispositions.[19] An altered ability to metabolize toxins by P450 enzymes could underlie a genetic susceptibility to develop PD. Attention over the last 10 years has been focused mainly on CYP2D6 polymorphisms. The profound genetic studies initially indicated a link between CYP2D6B mutations and PD,[20–22] which did not get a confirmation from the critical analysis of the literature and recent studies emerging from independent laboratories.[23,24] Yet, because there is no conclusive evidence to suggest that CYP2D6 polymorphisms confer susceptibility to PD,[8] it is possible that polymorphisms in other P450s, such as CYP2E1 and CYP1A1, are implicated in PD.[8]

However, our results showed that the distribution frequencies of the CYP2E1 alleles and genotypes were not significantly different between groups of patients with PD and their respective control subjects. The indication is that, in this Chinese population, these two polymorphisms are not associated with the disease process, even in patients with early-onset PD (onset $\leq$50 years of age) in which genetic factors appear to be important.[25] Bandmann et al.[26] also reported negative results concerning CYP2E1 *Rsa* I polymorphism and PD in white patients. However, these findings did not necessarily exclude the CYP2E1 locus from playing a causative role for PD because other polymorphisms different from the two evaluated here may show some disease association. Therefore, it should be further studied.

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Jian Wang, MD, PhD
Zhuolin Liu, MD
Department of Neurology
The First Affiliated Hospital
Sun Yat-sen University of Medical Sciences
Guangzhou, China

Piu Chan, MD, PhD
The Parkinson's Institute
Sunnyvale, CA, U.S.A.

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Modafinil Treatment of Pramipexole-Associated Somnolence

Summary: We report the case of a 33-year-old woman with Parkinson's disease who experienced sudden waves of sleepiness on pramipexole that placed her at high risk of falling asleep while driving. Modafinil at a dosage of 200 mg per day essentially eliminated her somnolence and fatigue and allowed her to continue on pramipexole. **Key Words:** Modafinil—Pramipexole—Somnolence—Sleep—Parkinson's disease.

Pramipexole is a non-ergot dopamine agonist with strong D2/D3 receptor specificity.[1,2] It is effective as monotherapy in early Parkinson's disease (PD)[3,4] and as an adjunct to levodopa/carbidopa in advanced disease.[5] Somnolence is a common side effect of pramipexole. In a 10-week safety and efficacy study of pramipexole as monotherapy in early PD, somnolence was the most frequently reported adverse event, occurring in 30% to 31.5% of patients assigned to 3.0 to 6.0 mg pramipexole per day.[3] Frucht et al.[6] described sleep attacks causing motor vehicle accidents in eight patients with PD who were taking pramipexole and one who was taking ropinirole, thereby raising concern about driving safety. Additional cases of pramipexole-, ropinirole-, and pergolide-induced sleep attacks and sudden onset of sleep have since been reported.[7–10]

Modafinil acetamide is a wake-promoting agent effective in the treatment of excessive daytime sleepiness in patients with narcolepsy.[11] We successfully used modafinil to treat pramipexole-associated somnolence in a patient who reported sudden episodes of sleepiness and falling asleep while driving.

Case Report

A 33-year-old woman with a 4-year history of difficulty using her left arm and a 1-year history of left leg tremor was diagnosed with PD in January 1999. She was placed on 25/100 mg carbidopa/levodopa three times per day and reported approximately 90% improvement in parkinsonian symptoms. However, she also experienced moderate head dyskinesia that she found uncomfortable and embarrassing.

In an effort to reduce dyskinesia, she was weaned off carbidopa/levodopa and was placed on pramipexole in April 1999 in doses escalating up to 1.5 mg three times per day over 6 weeks. Head dyskinesia was much improved but left upper extremity tremor increased. Beginning in July, after 2 months on a stable pramipexole dose (4.5 mg per day), she experienced sudden waves of somnolence approximately twice a week, usually while driving. She reported that she could avoid falling asleep while driving by turning up the radio or opening the car window. Her Epworth Sleepiness Scale (ESS) score at this time was 8 (normal $\leq$10; Table 1).[12]

Amantadine was introduced and escalated to a dose of 100 mg three times per day. She reported that this improved her parkinsonian symptoms. However, the intensity and frequency of episodes of sleepiness increased over the ensuing months.

By November 1999 she reported daily sudden waves of sleepiness. Her bed partner indicated that she was sleeping well through the night with no snoring or apparent breathing difficulties. The patient felt her background wakefulness was normal but noted that she had less energy and reported moderate fatigue. She had a 40-minute drive to and from work and would usually experience an episode of sleepiness each day while

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Address correspondence and reprint requests to Robert A. Hauser, MD, Parkinson's Disease and Movement Disorders Center, University of South Florida, 4 Columbia Drive, Suite 410, Tampa, FL 33606, U.S.A.

driving. The sleepiness would last approximately 30 minutes, and she was unable to determine any clear temporal relationship between onset of somnolence and medication intake during the day. She indicated that she had dozed off momentarily while driving on at least two occasions but did not cause a motor vehicle accident. She also noted episodes of falling asleep during periods of inactivity, but did not fall asleep in other inappropriate situations such as while talking to others. She reported that she consistently experienced subjective somnolence before falling asleep during the day. Her ESS at this time was 13 (Table 1).

She and her family members did not have known sleep disorders. No one in her family had excessive daytime sleepiness. She had no cataplexy, sleep paralysis, or hypnogogic or hypnopompic hallucinations.

The patient was treated with modafinil beginning in November 1999 in doses escalating to 200 mg each morning. She reported that her excessive daytime sleepiness resolved, and this benefit has been maintained through 7 months of observation. Her ESS score decreased (improved) to 3 (Table 1). She also noted that her energy level returned to normal and she has not experienced any side effects.

Discussion

Modafinil is effective in the treatment of excessive daytime sleepiness associated with narcolepsy.[13] At doses of 200 or 400 mg per day, modafinil reduced sleepiness in patients with narcolepsy as assessed by the ESS, Multiple Sleep Latency Test (MSLT), and the Maintenance of Wakefulness Test (MWT). Baseline ESS scores (mean ± standard deviation) improved from 17.9 ± 3.8 (200 mg) and 17.1 ± 4.27 (400 mg) to 14.4 ± 5.7 and 13.0 ± 5, respectively, at 9 weeks ($p < 0.001$). Mild headache and nausea were the most common side effects. Modafinil's mechanism of action is unknown.

Somnolence is a common side effect of pramipexole and may occur months after initiation of therapy. In a review of 37 patients treated with pramipexole in open-label extension studies, 21 (57%) reported somnolence as an adverse event and 11 (30%) reported moderate or severe somnolence.[10] For patients with moderate or severe somnolence, onset of worst-reported somnolence occurred after patients had been taking pramipexole for a mean (± standard error of mean) of 10.0 ± 1.5 months (range, .03–22 mos) and at their maximal dose for 6.7 ± 1.5 months (range, .03–20 mos). Three patients reported sudden episodes of sleepiness on a background of normal wakefulness. Two of these patients underwent polysomnography and MSLT while on 4.5 mg pramipexole per day and 2 weeks after pramipexole withdrawal.[10,14] Sleep latency was reduced during pramipexole therapy and normalized after pramipexole withdrawal. There were no sleep-onset rapid eye movements (REM).

Patients who experience somnolence may be at increased risk of motor vehicle accidents.[6,7,10] Somnolence usually resolves with medication dose reduction or discontinuation, and it is recommended that patients who experience somnolence should temporarily refrain from driving until this side effect is resolved.[10] Although our patient reported that she could initially avoid falling asleep while driving by opening the car window or turning up the radio, these maneuvers have been found to be only partially effective for short periods (approximately 15 mins).[15] The only safe countermeasures to sleepiness, particularly when the driver reaches the stage of fighting sleep, are to stop driving and to take a 30-minute break including a short nap (<15 mins) or coffee intake (150 mg caffeine), or both.[15] Whether these measures are effective against dopaminergic medication-induced sleepiness is not known.

Our patient experienced sudden waves of sleepiness on pramipexole that placed her at high risk of falling asleep while driving and causing a motor vehicle accident. Levodopa therapy had caused intolerable head dyskinesia. Modafinil at a dosage of 200 mg per day essentially eliminated her somnolence and fatigue and allowed her to continue on pramipexole. Her ESS score improved from 13 to 3.

We do not know if stimulants commonly used to treat narcolepsy would also be effective in this situation. Dextroamphetamines, methamphetamines, and methylphenidates are considered to have a high abuse potential and are Schedule II prescription drugs.[16] Pemoline has the least potential for abuse, but it is considered to be the least effective and is associated with potential hepatotoxicity. These agents often cause intolerable side effects at effective doses, including sympathomimetic effects such as headaches, irritability, nervousness or tremulousness, anorexia, insomnia, gastrointestinal disorders, dyskinesias, and palpitations. In addition, stimulants decrease both sleep time and REM sleep, whereas modafinil may not adversely affect nighttime sleep parameters.[16] Pemoline was

TABLE 1. *Epworth Sleepiness Scale (ESS) scores**

Date	7/19/99	11/29/99	2/28/00
Medications	4.5 mg pramipexole	4.5 mg pramipexole 300 mg amantadine	4.5 mg pramipexole 300 mg amantadine 200 mg modafinil
ESS scores†			
Sitting and reading	0	1	0
Watching TV	0	1	1
Sitting, inactive in a public place (for example, a theater or meeting)	1	2	0
As a passenger in a car for an hour without a break	3	3	1
Lying down to rest in the afternoon when circumstances permit	3	2	1
Sitting and talking to someone	0	0	0
Sitting quietly after a lunch without alcohol	1	1	0
In a car, while stopped for a few minutes in traffic	0	3	0
Total ESS score	8	13	3

* Total ESS score increased to 13 on 4.5 mg pramipexole per day and improved to 3 with the addition to 200 mg modafinil per day.
† ESS, Epworth Sleepiness Scale: 0 = would never doze; 1 = slight chance of dozing; 2 = moderate chance of dozing; 3 = high chance of dozing.

recently withdrawn from the Canadian market because of its association with life-threatening hepatic failure,[17] and in the United States it carries a black box warning delineating the need for rigorous liver function test monitoring and patient informed consent.

Modafinil may be a useful treatment for dopamine agonist and levodopa-induced somnolence and sudden episodes of sleepiness. Further study, including objective assessments of sleepiness (MSLT and MWT) before and during modafinil therapy, is warranted.

Robert A. Hauser, MD
Departments of Neurology, Pharmacology and Experimental Therapeutics, and Medicine
University of South Florida
Tampa General Hospital
Tampa, Florida, U.S.A.

Mervat N. Wahba, MD
Theresa A. Zesiewicz, MD
Department of Neurology
University of South Florida
Tampa General Hospital
Tampa, Florida, U.S.A.

W. McDowell Anderson, MD
Department of Medicine
University of South Florida
Tampa General Hospital
Tampa, Florida, U.S.A.

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Neuroacanthocytosis Presenting as Parkinsonism

Neuroacanthocytosis is an uncommon multisystem neurodegenerative disorder that is characterized by multiple movement disorders, seizures, cognitive and personality changes, and amyotrophy with areflexia.[1–4] Pertinent laboratory abnormalities include acanthocytosis and elevated creatine phosphokinase levels. Chorea, orolingual dystonia with tongue and lip biting, and tics are the most prominent movement disorders of neuroacanthocytosis but parkinsonism may also be present.[1–4] Parkinsonism is rarely a presenting feature, and it appears later when chorea and other hyperkinetic disorders subside.[1,2,5,6] We describe a patient with neuroacanthocytosis and parkinsonism as the presenting clinical manifestation of the disease.

Case Report

A 45-year-old man presented with a 5-year history of gradually progressive parkinsonism that did not respond to levodopa (L-dopa) treatment. His disease started insidiously with slurred speech, gait disturbances, and postural instability. The patient's cognitive abilities at that time were reported to be normal, and he was able to continue his work as a mechanical engineer despite his physical disability. He was initially treated with L-dopa/benserazide (450 mg/daily) and 6 mg of biperiden a day, but he showed no improvement and his symptoms gradually worsened. An increase of the L-dopa dose to 1000 mg a day provided mild benefit. Two years before admission to the hospital, cognitive slowing, loss of spontaneity, and apathy became apparent. Family history showed that his only brother had had parkinsonism of an unknown cause and died at an institution at the age of 47. His mother had died at the age of 45 from breast cancer, and until that time she had been neurologically healthy. His father is alive and free of any neurologic disorders. The patient has no children.

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Address correspondence and reprint requests to S. Bostantjopoulou, MD, 9 Navarinou Square, 54622 Thessaloniki, Greece.

On admission to the hospital, neurologic examination showed diminished facial expression, prominent hypophonia, and slurred speech. Voluntary eyelid movements were normal. Vertical and horizontal saccades were hypometric, and the patient could shift his gaze using a series of saccades. He had difficulty in opening his mouth fully and moving his tongue. Minimal drooling was also observed. Swallowing was normal. Rigidity was marked in his neck and legs and moderate in his arms. There was severe body bradykinesia and moderate bradykinesia of the upper and lower extremities, with the left side being worse. His posture was stooped and his gait was markedly impaired with shuffling steps and festination. The patient could walk alone for only a few meters and he needed assistance to go further. He was unstable and sometimes lost balance spontaneously, particularly during turning. No tremor or abnormal involuntary movements were observed or reported. Deep tendon reflexes were diminished bilaterally. Plantar reflexes were flexor. There was no muscle wasting or fasciculations. Cerebellar function and sensation were normal. Neuropsychological assessment of general cognitive ability showed mild cognitive impairment. The patient achieved a nonverbal IQ of 81 (10th percentile) on the Test of Nonverbal Intelligence-2 and a score of 121 on the Dementia Rating Scale. More specifically, the patient had a poor performance on the Wisconsin Card Sorting Test with many preservations, whereas his achievements in memory and visuospatial tasks were considerably better.

Laboratory Investigation

Routine blood test results were normal except for a high level of serum creative kinase 1,340 IU/L (normal range, 35–145 IU/L). Copper, ceruloplasmin, and vitamin E levels were normal. Repeated wet smears of peripheral blood showed more than 15% acanthocytes. Findings from a lipid profile examination were normal. Kell antigen typing excluded the McLeod phenotype. Genetic testing for Huntington's disease and dentato-rubral-pallido-luysian (DRPLA) was negative.

Findings from electrophysiologic studies (i.e., electroencephalography and electromyography) were normal. Magnetic resonance imaging scans showed ventricular dilatation with slight atrophy of the caudate bilaterally. Cerebral blood flow measured by ^{99}mTc hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomography was diminished in a multifocal pattern all over the hemispheres and subcortically, particularly in the basal ganglia and the thalamus.

Follow-up

Six months later the patient deteriorated markedly. He was wheelchair-bound and almost voiceless and had difficulty in swallowing. Video fluoroscopy showed impairment of the initial stage of swallowing because of incoordination of tongue movements. Food transit through the pharynx was slow without pooling or penetration into the airways. There was no cricopharyngeal achalasia, and peristalses of the esophagus was normal. Findings from a respiratory evaluation were within normal limits.

Discussion

We describe a patient with atypical familial parkinsonism accompanied by cognitive decline. No other movement disorders were reported or observed during the 5 years of the disease duration. Magnetic resonance imaging findings showing atrophy of the caudate provided no specific clues for the diagnosis, but areflexia and an increase in the creatine phosphokinase level without myopathy raised the suspicion of neuroacanthocytosis. The finding of more than 15% acanthocytes in the fresh blood smear provided a strong basis for the diagnosis of neuroacanthocytosis. This was further confirmed by normal lipoprotein levels, absence of the McLeod phenotype,[7] and genetic exclusion of Huntington's disease. Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP syndrome) seemed also an improbable diagnosis because of the lack of its most pertinent clinical and magnetic resonance imaging characteristics.[8]

Parkinsonism as a presenting feature of neuroacanthocytosis is unusual, and what makes our case noteworthy is that in our patient parkinsonism, besides being the initial clinical manifestation, remained the only movement disorder 5 years later.

Neuropathologic studies have shown that patients with neuroacanthocytosis and parkinsonism have a significant loss of neurons in the ventrolateral region of the substantia nigra.[9,10]

Some patients have been reported to respond to dopaminergic medication, whereas others are nonresponders.[1,6] Our patient had a poor response to L-dopa, which can be attributed to concomitant degeneration of the striatum as inferred by magnetic resonance imaging and single photon emission computed tomography findings showing abnormalities of basal ganglia structure and function.

Legend to the Videotape

This 45-year-old man has parkinsonism as the presenting symptom of neuroacanthocytosis.

S. Bostantjopoulou
Z. Katsarou
A. Kazis
Third Department of Neurology
University of Thessaloniki
Thessaloniki, Greece

C. Vadikolia
Department of Hematology
G. Papanikolaou Hospital
Thessaloniki, Greece

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Dopa-Resistant Parkinsonism, Oculomotor Disturbances, Chorea, Mirror Movements, Dyspraxia, and Dementia: The Expanding Clinical Spectrum of Hypoparathyroidism. A Case Report

Hypoparathyroidism usually presents with neuromuscular irritability, hypocalcemia, hyperphosphatemia, and low or absent circulating parathyroid hormone. With the current advances in surgical techniques, surgically induced hypoparathyroidism, once a common cause of hypoparathyroidism, is now rare. Basal ganglia calcifications resulting from surgically induced hypoparathyroidism are the consequence of long-standing untreated disease.[1,2] These calcifications cause a variety of neurologic signs and symptoms, including chorea, paroxysmal choreoathetosis, dystonia, myoclonus, cerebellar and pyramidal tract signs, tetany, and epilepsy.[1–7] Therefore, a high index of suspicion is required for early diagnosis. We report a case of progressive dementia with a dopa-resistant akinetic-rigid syndrome, oculomotor disturbances, foot resting tremor, chorea, hand movements with a stereotypic character, and apraxia.

Case Report

A 74-year-old woman came for neurological opinion regarding abnormal movements and progressive cognitive decline. She had a thyroidectomy for a thyroid adenoma 30 years earlier. Her immediate postoperative period was unremarkable. She began to be forgetful and through the ensuing years became withdrawn. The family described her as always being nervous but recently they noted increasing forgetfulness, untidiness, and increased "nervousness." She became "fidgety," moving her arms constantly, and developed a tremor of the left foot. Recently, she burned the stove, and at another time she could not find her way home. Once she urinated and defecated in the garage. Her medical history was otherwise unremarkable except for hypoparathyroidism treated with L-thyroxine. Her family history was negative for a movement disorder.

On examination (see the videotape) she had thickened facial skin and absent eyebrows bilaterally. There were no dysmorphic features or congenital ectodermal defects. She was unkempt and disheveled. She was disoriented with a short attention span and had difficulty with copying, calculation, and comprehension. She was unable to perform Luria's shifting, sequential and imaginary tasks with either hand. Symbolic gesture evocation and object use pantomime were impaired. She had facial hypomimia. Oculomotor function demonstrated a supranuclear gaze paresis, especially in the downward vertical plane, which was corrected using the oculogyric (doll's eye) maneuver, ocular inattention, saccadic pursuit, and dysmetria. Convergence was intact. No Kayser-Fleischer rings were noted. Fundoscopic and pupillary examinations were normal. Choreic movements of the fingers (piano playing sign), trunk, and toes were noted. Cogwheel rigidity was present in all limbs and she had a left foot rest tremor of 4 Hz. With repetitive motor tasks, she was slow and fatigued easily, and mirror movements were evident. Dyspraxia at times interrupted the flow of these repetitive movements. At rest, she had repetitive stereotypic-like hand movements, right greater than left. Her gait demonstrated slight stooped posturing, decreased left arm swing, and retropulsion on the pull test. She had no hepatosplenomegaly. The remainder of her neurologic and physical examination was normal.

Her routine blood cell count, sedimentation rate, renal and liver function values, T4-TSH, cholesterol and lipid profile, folate, antiphospholipid antibody, antinuclear antibodies, RPR, serum ceruloplasmin, copper and urine were normal. A fresh blood smear for acanthocytes was negative. Her serum calcium was 6.0 mg/dL (normal, 8.2–10.4 mg/dL), phosphorus 5.7 mg/dL (normal, 2.4–4.4 mg/dL), and her PTH level was 4 pg/mL (low). Her serum vitamin B12 was 141 pg/mL (normal, 200–900 pg/mL), serum homocysteine 15.9 nmol/mL (normal, 4.0–17.5 nmol/mL), and methyl malonic acid 564 nmol/L (normal, 79–376 nmol/L). Electroencephalogram, electromyogram, and autonomic testing were normal.

Magnetic resonance imaging of the brain demonstrated foci of increased T1 signal intensity in the basal ganglia (predominantly the lentiform nuclei) and thalamus (predominantly in the pulvinar nucleus) (Fig. 1) with a center of decrease signal intensity suggestive of ischemia. Mild cerebellar atrophy was observed. A brain computerized scan (Fig. 2) revealed extensive calcifications in the basal ganglia, pulvinar, dentate, cerebellar vermis, and centrum semiovale. Fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrated marked reduction of tracer utilization in the left frontal, anterior–parietal, and temporal lobes consistent with hypometabolic uptake in these regions. The patient began treatment with vitamin D and calcium supplementation. Fourteen months after increasing doses of levodopa, her neurologic examination was unchanged. The patient was then lost to follow up.

Discussion

Few conditions present with progressive dementia, dyspraxia, parkinsonism, oculomotor disturbances, and chorea. Huntington's disease, neuroacanthocytosis, antiphospholipid antibody syndrome, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Wilson's disease were considered. The extensive striato-dentate and white matter calcifications are the most likely cause of all of the clinical features

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Address correspondence and reprint requests to Néstor Gálvez-Jiménez, MD, Movement Disorders Program, Department of Neurology, The Cleveland Clinic Florida, 3000 W. Cypress Creek Rd., Fort Lauderdale, FL 33309, U.S.A.

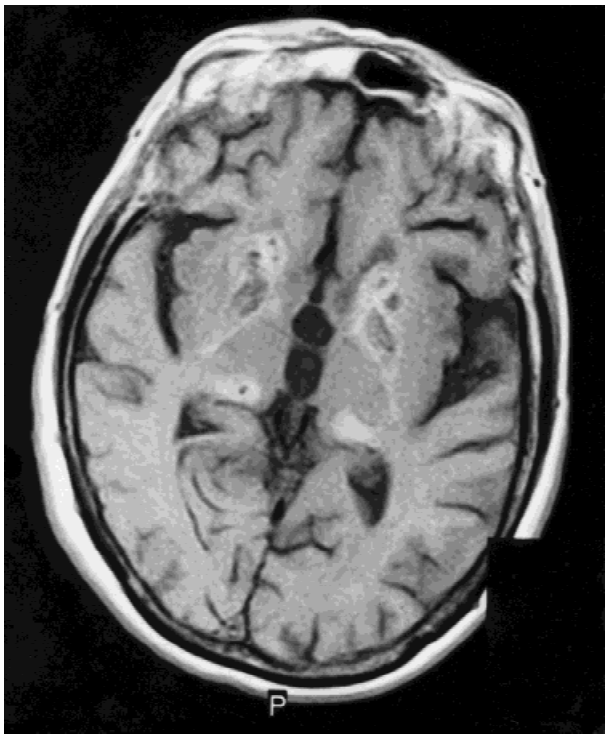

FIG. 1. Initial T1W brain MRI demonstrated foci of increase signal intensity in the basal ganglia and pulvinar nuclei with a center of decrease signal intensity suggestive of small vessel ischemia.

in this patient. We cannot completely exclude the role that vitamin B12 deficiency had in her cognitive decline, but the extensive basal ganglia pathology and diffuse alterations in the corticostriatal afferents suggest the behavioral alterations and ideomotor apraxia were the result of this pathology rather than vitamin B12 deficiency. Furthermore, she had no signs of myelopathy, peripheral neuropathy, and a normal hemoglobin and mean corpuscular volume. Vitamin B12 replacement therapy resulted in no clinical changes.

Idiopathic hypoparathyroidism resulting in bilateral basal ganglia calcifications may present with chorea, kinesigenic choreoathetosis, dystonia, neuroleptic-induced acute dystonic reactions, L-dopa resistant parkinsonism, epilepsy, myoclonus, hand tremor, spasticity, ataxia, depression, psychotic reactions, and dementia.[4–7,9–13,15,16,18–22] Our patient had a clearly documented history of thyroid gland resection and lack of surgical follow up. Postoperative hypoparathyroidism has been specifically associated with choreoathetosis, seizures and epilepsy, papilledema, increased intracranial pressure, levodopa-resistant parkinsonism, oromandibular dyskinesias, and ataxia.[1–3,14,20]

The combination of stereotypic-like movements, oculomotor disturbances, and ideomotor apraxia, with progressive dementia, parkinsonism, mirror movements, and chorea resulting from hypoparathyroidism has not been previously described in the same patient. Parkinsonism and chorea as a manifestation of post-thyroidectomy hypoparathyroidism is now a rare observation. Chorea, which is the most common movement disorder reported in basal ganglia calcifications,[4,6,11,13,14] was present involving predominantly the fingers, trunk, and toes.

Dopa-resistant parkinsonism has been described by Klawans et al. and others.[2,3,18,22] Most likely, alterations in the down-

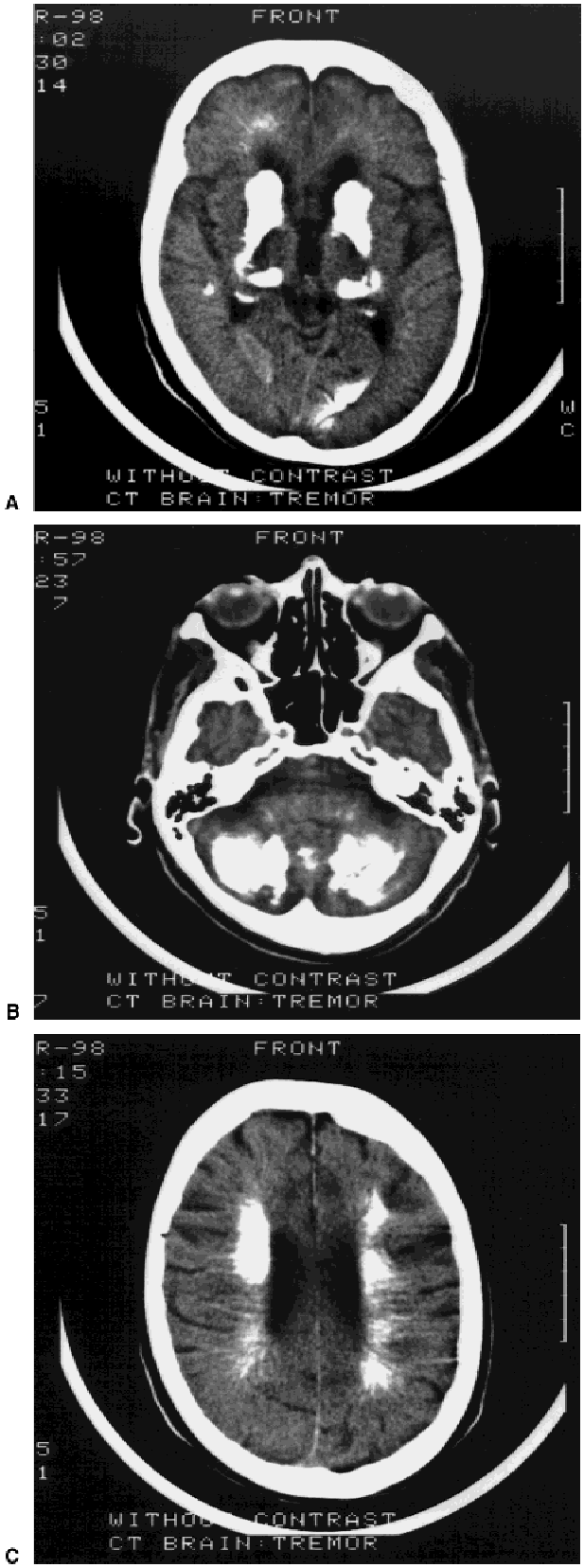

FIG. 2. Follow-up computerized tomography of the brain revealed extensive striatopallidal and pulvinar **(A)**, dentate nuclei and cerebellar hemispheres **(B)**, and centrum semiovale **(C)**.

stream pathways or postsynaptic dopamine receptors may account for the lack of response to levodopa. We found hypoactivity in the left frontal, anteroparietal, and temporal lobes using FDG-PET. Similar FDG-PET findings in patients with Parkinson's disease have been reported by others.[25,26] In the cases reported by Tambyah et al. and Rubinstein et al.,[2,22] the parkinsonian symptomatology improved by treating the underlying hypoparathyroidism. In contrast, our experience has been similar to that of Friedman et al.[6] with persistent neurologic deficits at last follow up.

The precise mechanism of calcium deposition is not fully understood. Asymptomatic basal ganglia calcifications may be seen at autopsy, especially in the elderly, located in the globus pallidus, putamen, caudate, thalamus, dentate nuclei, and internal capsule.[24] In severe cases, such as our patient, these calcifications form concretions or "brain stones" which may be dislodged during brain cutting. The calcium deposits may be present along capillary vessels on the walls of small to medium-sized arteries.[4]

In conclusion, we have presented a patient with nontreated surgically induced hypoparathyroidism of 30 years duration complicated by oculomotor disturbances and ideomotor or limb kinetic apraxia in combination with an akinetic-rigid syndrome and chorea. To our knowledge, this combination of findings has not been previously encountered with hypoparathyroidism or other disorders causing basal ganglia calcifications.

Legend to the Videotape

Chorea is demonstrated by the presence of the piano playing sign while the patient holds the hands outstretched. A left foot rest tremor is present. The patient has some difficulty with the finger to nose testing as a result of limb dyspraxia. After a few attempts, she is able to carry out the task. Limb kinetic or ideomotor apraxia is observed when the patient is asked to pretend that she is holding scissors with the left hand and to cut a piece of paper. Similarly, buccolingual dyspraxia is noted when asked to blow a kiss.

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Néstor Gálvez-Jiménez, MD
Maurice R. Hanson, MD
Movement Disorders Program
The Department of Neurology

José Cabral, MD
Endocrinology Section
Division of Medicine
The Cleveland Clinic Florida
Fort Lauderdale, Florida, U.S.A.

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Nicotine-Sensitive Writer's Cramp

It is suggested that primary dystonia results from a functional disturbance of the basal ganglia, particularly of the striatal control of the globus pallidus and substantia nigra pars reticulata.[1] Beneficial clinical effects of haloperidol, trihexyphenydil, and baclofen propose the involvement of the dopaminergic, muscarinic acetylcholinergic, and GABAergic systems, all of which play important roles in the basal ganglia. By contrast, the role of the nicotinic cholinergic system has been implicated only in a few reports of symptomatic hemidystonia of childhood in which nicotine was effective in relieving symptoms.[2,3]

We treated two patients with writer's cramp whose symptoms significantly improved after they stopped smoking cigarettes and deteriorated by resuming smoking or by using nicotine gum. These cases prompted us to survey the patients with writer's cramp in our clinic. We found that those who stopped smoking had significantly improved dystonic symptoms. Cessation of smoking might be a helpful strategy for patients with writer's cramp if other therapeutic measures prove unsatisfactory.

Case Reports

Case No. 1

A 42-year-old, right-handed salesman came to our clinic because of difficulty in writing and using chopsticks for 4 years. He did not have a history of major illnesses or a family history of dystonia. He had smoked approximately 20 cigarettes a day for 20 years.

Physical examination revealed excessive contraction of the right extensor carpi radialis (ECR) and extensor digitorum communis (EDC) muscles when writing. Gripping a pen induced involuntary activation of the wrist extensor muscles with subsequent contractions of the wrist extensor and flexor muscles. These co-contractions sometimes turned into alternative contractions of these muscles causing wrist tremor, which was most prominent when using chopsticks. Other physical findings and basic laboratory tests were normal.

After his first visit to our clinic, he incidentally stopped smoking because of his concern about its harm. Ten days later, he found his writing improved and he could use chopsticks with his right hand without difficulty. On the next visit to us 6 months later, the abnormal contractions of the ECR and EDC muscles during writing were diminished markedly, and wrist tremor was reduced even when using chopsticks. The symptoms remained stable over the next 3 months. We then compared his writing before and after smoking a cigarette, after obtaining informed consent (Fig. 1). One minute after finishing the cigarette, he had difficulty gripping a pen and writing. Two minutes later when he tried to write, involuntary wrist extension developed even before gripping the pen, and co-contraction of the wrist flexor and extensor muscles interfered with his writing. Muscle contractions were not induced by smoking in a control subject (44-year-old man) with a history of smoking (Fig. 1). The clinical benefit in this patient remained unchanged after 1 year.

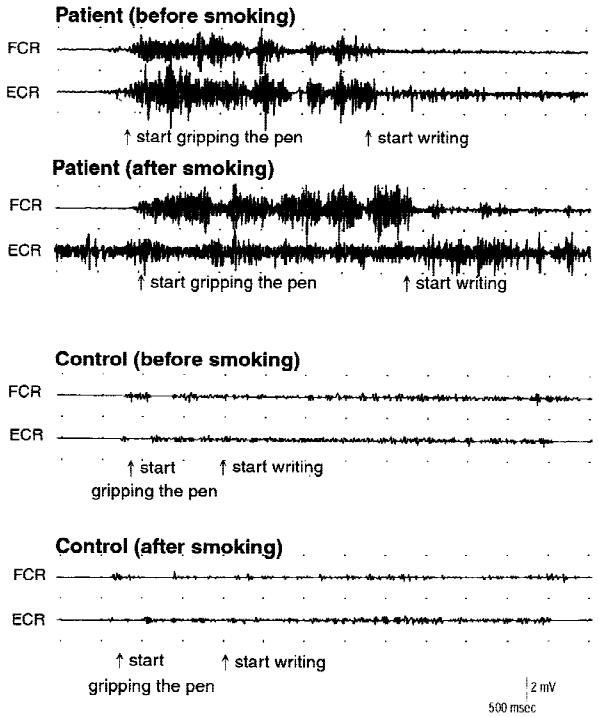

FIG. 1. Surface electromyogram of flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles during writing before and 2 minutes after smoking a cigarette in case no. 1 and in a healthy control subject. It is evident that smoking induced contraction of the ECR muscle starting even before gripping a pen. By contrast, the control subject showed no abnormal muscle activation induced by smoking.

Case No. 2

A 55-year-old man who had a history of smoking 30 cigarettes a day for 26 years developed writer's cramp at the age of 46. His right flexor carpi ulnaris (FCU), flexor digitorum profundus (FDP), and triceps muscles showed abnormal contractions during writing, and co-contractions of ECR and FCU muscles sometimes made him totally unable to write. He incidentally stopped smoking, and 2 weeks later he noticed that his symptoms improved. On his visit 4 weeks after smoking cessation, his writing was better. He resumed smoking because of his long-term habit resulting in no intercurrent stress or anxiety. He again smoked 10 to 15 cigarettes a day and after a week his symptoms relapsed.

He wanted to stop smoking so we recommended a nicotine gum, a tobacco antabuse. We then studied the effect of nicotine on his symptoms by challenging him with nicotine gum, after obtaining informed consent. He stopped smoking for 24 hours before the test and he chewed two sheets of 4 mg nicotine gum

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Address correspondence and reprint requests to Ryuji Kaji, MD, PhD, Department of Neurology, Kyoto University Faculty of Medicine, Kyoto University Hospital, 54 Shogoin Kawahara-cho, Sakyou-ku, Kyoto city 606-8397, Japan.

for 1 hour. His dystonic symptoms were markedly aggravated after 1 hour subjectively and objectively (Fig. 2).

Methods

Smoking Survey

We surveyed the frequency of smokers among 22 consecutive patients with writer's cramp (18 men and 4 women, aged 23–70 yrs, mean age 50.4 yrs) who were seen in our clinic.

Effect of Smoking Cessation

To evaluate the effect of smoking cessation, we used subjective and objective measures in eight patients (7 men and 1 woman, aged 23–70 yrs, mean age 50.1 yrs) who followed our advice to stop smoking. Although the patients were not informed of the effect of smoking for dystonic symptoms without general harmful effect of nicotine when they start smoking cessation, this was not a blinded study. The patients rated the subjective change in symptoms on scores of five grades (0: no change from the baseline, +1: slightly better, −1: slightly worse, +2: definitely better, −2: definitely worse).

As an objective measure, four raters who were blinded as to whether the testing was done on subjects before or after smoking cessation compared a pair of handwritings for each patient using five grades (0: no difference, +1: slightly better, −1: slightly worse, +2: definitely better, −2: definitely worse).

Results

Smoking Survey

Of 22 patients (18 men and 4 women) with writer's cramp, 16 (72.7%) had a history of smoking (15 men [83.3%] and 1 woman). Fourteen (63.6%) were already smokers at the onset of disease (13 men [72.2%] and 1 woman [25%]). These outnumbered the prevalence rate of smoking among the Japanese population who are older than 20 years of age (57.5% in men and 14.2% in women; the Japan Monopoly Corp, the Japan Tobacco Industry, Japan, 1996). Among those 16 patients who had a history of smoking, dystonic tremor was seen in nine (56.2%). The mean duration between starting smoking and onset of dystonia was 19.0 ± 10.4 years (mean ± standard deviation) and mean daily cigarette number was 27.8 ± 10.6. There was no difference in clinical symptoms among the patients between smokers and nonsmokers.

Effect of Smoking Cessation

We examined eight patients at 4 weeks of abstinence out of 14 smokers (Table 1). Patient no. 8 began smoking after the onset of dystonia and his symptoms gradually deteriorated. One patient participated in the study of smoking cessation but resumed smoking, and the other five smokers did not participate. Clinical symptoms in these six patients did not change for 4 weeks.

Cessation of smoking ameliorated subjective symptoms in seven patients, and their scores significantly increased by 1.4 ± 0.7 points (mean ± standard deviation; $p = 0.023$, nonparametric paired sign test; Table 1).

Objective scores by four raters also improved significantly after smoking was stopped (0.9 ± 1.0 points, mean ± standard deviation; $p = 0.00052$, nonparametric paired sign test; Table 1).

Of the eight patients examined as above, we could reexamine seven patients after 1 year; four patients were still nonsmokers.

FIG. 2. The posture of the right hand and Chinese characters written before and after chewing nicotine gum in case no. 2. Extension of the upper arm and flexion of the wrist appeared after administration of 4 mg nicotine gum when his blood nicotine level reached 21 ng/mL. The Chinese characters became more distorted parallel to the dystonic posture.

TABLE 1. *Effect of smoking cessation*

Patient no.	Age/sex	Duration (yrs)	Smoking (cigarettes*years)	Subjective score	Objective score†
1	70/M	5	20*48	1	−1, 0, 0, 1
2	65/M	11	30*40	1	0, 0, 0, 1
3	57/M	13	40*36	2	0, −1, 0, −1
4	56/M	7	20*30	2	2, 2, 2, 2
5	55/M	9	20*35	1	2, 2, 2, 2
6	38/F	3	20*10	2	0, −1, 0,−1
7	32/M	2	20*10	0	1, 0, 0, 1
8	23/M	4	30*3	1	0, 1, 0, 1

† Objective scores show the values by each of four raters.dard deviation; EMG, electromyography.

Clinical symptoms in three of them remained stable, and those in the other patient further gradually improved. One patient, who resumed smoking but at a reduced number of cigarettes per day, and the remaining two patients failed to stop smoking. Symptoms in two of these three remained unchanged and those in the other deteriorated gradually.

Discussion

The clinical observations reported here indicate that smoking may aggravate the symptoms of writer's cramp. Dystonic movements were aggravated by the chewing of nicotine gum, indicating that nicotine is responsible for these clinical effects. The high incidence of smokers at disease onset strengthens the case for a possible link between nicotine intake and the development or aggravation of writer's cramp.

Previous reports showed that nicotine relieves the symptoms of hemidystonia in childhood.[2,3] Dystonia in these cases may have been caused by a pathomechanism distinct from that of writer's cramp, which is an idiopathic focal dystonia of late onset characterized by task specificity. This assumption is supported by the study of cerebral blood flow[4]; the activation pattern in acquired symptomatic hemidystonia caused by lesions in the basal ganglia or thalamus was subtly different from that in idiopathic focal dystonia.

Nicotine stimulates nicotinic acetylcholine receptors in the central as well as peripheral nervous systems and cardiovascular system.[5] Our findings suggest that the nicotinic acetylcholine receptors play a role in the pathophysiology of focal dystonia. On the other hand, anticholinergics, such as trihexyphenydil as a muscarinic receptor blocker, are also used to treat patients with focal dystonia,[6] pointing to the excess of acetylcholine in the basal ganglia of these patients. Nicotine may aggravate dystonic symptoms by facilitating the acetylcholine release, because it is known to enhance the release of acetylcholine.[7] Nicotine may act as a general stimulator of the release of neurotransmitters like norepinephrine, dopamine, serotonin, and others,[7,8] which deteriorate clinical symptoms of dystonia.

Cigarette smoking has a protective effect against idiopathic Parkinson's disease.[9] This was ascribed to the facilitation of dopamine release by nicotine through nigrostriatal neurons. By contrast, dystonic symptoms may be relieved by reserpine,[10] which depletes the dopamine and norepinephrine vesicules. Thus, the harmful effect of nicotine demonstrated in this study may also be associated with the abnormal activation of the dopaminergic system.

In conclusion, cessation of smoking may be a helpful strategy for patients with writer's cramp if other therapeutic measures prove to be unsatisfactory.

Nagako Murase, MD
Ryuji Kaji, MD, PhD
Takashi Sakamoto, MD
Hineki Shimazu, MD
Shinnichi Matumoto, MD
Nobuo Kohar, MD, PhD
Hiroshi Shibasaki, MD, PhD
Department of Neurology
Kyoto University Faculty of Medicine
Kyoto, Japan

Jun Kimura, MD
Department of Neurology
University of Iowa Hospitals and Clinics
Iowa City, Iowa, U.S.A.

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Can Intravenous Immunoglobulin Improve Antibody-Mediated Botulinum Toxin Therapy Failure?

Recurrent intramuscular injections of small doses of botulinum toxin type A (BT) have been used with remarkable success for several years for symptomatic treatment of various muscle hyperactivity disorders, such as dystonia, spasticity, and tremor.[1] In a small number of patients, formation of neutralizing antibodies against BT (BT-AB) can occur.[2] Those BT-AB terminate the therapeutic effect of BT, possibly permanently, and render patients with conventional treatment strategies that are often ineffective, accompanied by intolerable side effects, or both. One possible strategy in these situations is to eliminate the neutralizing BT-AB. Recently, plasma exchange and consecutive repeated immunoadsorptions applied during a period of more than 1 year were tried successfully in one patient for this purpose.[3] Complexities and costs involved with this procedure, however, make this approach impractical. Intravenous immunoglobulin (IVIg) application introduced some years ago as a therapeutic agent to treat autoimmune disorders[4] has been shown to decrease autoimmune antibody titers within a few days in various conditions, such as myasthenia gravis,[5] Lambert-Eaton myasthenic syndrome,[6] paraproteinemic polyneuropathy,[7,8] and multifocal motor neuropathy,[9,10] without inducing major side effects, possibly by means of antibodies against disease-related antibodies.[11–13] We therefore sought whether IVIg application can decrease BT-AB and resensitize patients for BT therapy.

Case Report

A 41-year-old man had a 12-year history of tonic-clonic idiopathic cervical dystonia with retrocollis (25°), left laterocollis (20°), and right torticollis (50°) with some minor involvement of both distal arm muscles. The severity of his symptoms measured 21 on the Toronto Western Spasmodic Torticollis Rating Scale.[14] Despite the prolonged persistence of his symptoms, there was no pain, and passive neck and head mobility was unrestricted besides a slight deficit of 15° on left rotation. Various previous medical treatments remained unsuccessful. Three years before the current admission, BT therapy with Dysport (Ipsen Ltd, Maidenhead, Berks, United Kingdom) was initiated in another hospital. After substantial initial improvement, the therapeutic effect started to vanish. The last two injection series ceased to produce any therapeutic effect at all. According to a recently introduced classification,[15] the situation was diagnosed as complete permanent secondary BT therapy failure. The mouse diaphragma assay[16] showed a BT-AB titer of 0.011 mU/L, and sternocleidomastoid testing,[17] extensor digitorum brevis testing,[18] and clinical evaluation did not detect a BT effect.

Intravenous immunoglobulin (Venimmun N, Centeon Pharma, Marburg, Germany) was given in five single doses of 35 g, equivalent to approximately 4.5 g/kg body weight every second day. BT therapy was performed on the day after the third IVIg application with BT (Dysport; reconstitution: 500 mouse units in 2.5 mL of 0.9% $NaCl/H_2O$) according to the following dosage scheme: left sternocleidomastoid muscle: 240 mouse units (three injection sites); right splenius capitis muscle: 240 mouse units (three injection sites); left splenius capitis muscle: 120 mouse units (two injection sites); right trapezius and semispinalis capitis muscles: 180 mouse units (three injection sites); left trapezius and semispinalis capitis muscles: 180 mouse units (three injection sites); and left extensor digitorum brevis muscle: 200 mouse units (one injection site).

Figure 1 shows that the patient's response to the BT application was monitored by daily self assessments, daily neurologic examinations, video documentations, and Toronto Western Spasmodic Torticollis Rating Scale evaluations 1 week before and 2 weeks after BT application, sternocleidomastoid testing, and extensor digitorum brevis testing, initiated on the third day after the BT application and read 5 and 10 days later, and mouse diaphragma assay testing on the day after the IVIg application was finished and 6 weeks after it was started. Compared with the baseline before the BT application, neither of these parameters showed any significant change that could be attributed to the BT application. The neurologic examinations did not show muscle paresis or muscle atrophy of the target muscles. During the monitoring period, side effects did not occur that were attributable to neither BT nor IVIg.

Discussion

Data collected in this study show that BT therapy combined with IVIg did not reduce BT-AB titers and did not resensitize a patient with BT-AB–mediated, complete secondary BT therapy failure. Because in other antibody-mediated disorders, antibody activity could be reduced and clinical improvement could be achieved, possible reasons for IVIg failure in our study must be discussed.

Intravenous immunoglobulin could fail to improve the BT response if BT therapy failure was not mediated by BT-AB. As recently summarized,[15] failure of therapy not mediated by BT-AB can be caused by suboptimal target muscle selection and BT dosages, secondary alterations, such as contractures, radiculopathies, and arthrosis, and dystonia subtypes with primary reduced BT efficacy, such as antecollis or tremor dominant cervical dystonia. None of these causes, however, could be identified in our patient. Instead, a BT-AB titer of 0.01 mU/L was found, which is in itself fully sufficient to explain BT therapy failure.[21] IVIg could also fail to improve the BT response if the BT-AB titer reduction occurred too late in relationship to the BT application. This possibility seems unlikely, however, because IVIg-induced BT-AB reduction usually occurs within the time window that was used in this study. In addition, this possibility is unlikely because even 6 weeks after the IVIg application, BT-AB titer reduction could not be seen. IVIg could fail to reduce the BT-AB titer if there was a gross imbalance between the amount of BT-AB and the amount of

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Address correspondence and reprint requests to Dirk Dressler, MD, Department of Neurology, University of Rostock, D-18147 Rostock, Germany.

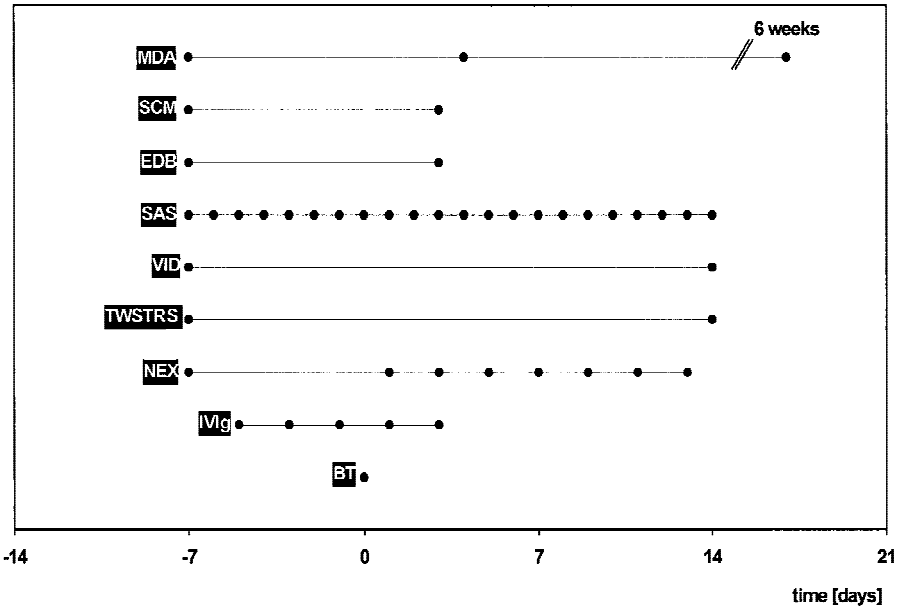

FIG. 1. Schematic synopsis of the monitoring parameters and the therapeutic interventions. None of the monitoring parameters changed significantly after the combined application of botulinum toxin and intravenous immunoglobulin. BT, botulinum toxin; EDB, extensor digitorum brevis test; IVIg, intravenous immunoglobulin; MDA, mouse diaphragm assay; NEX, neurologic examination; SAS, self-assessment scale; SCM, sternocleidomastoid test; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; VID, video monitoring.

IVIg. Because the IVIg dose used was maximal as compared with other IVIg indications and BT-AB titers were generally low,[21] this does not seem to be the case. IVIg could also fail to reduce the BT-AB if the IVIg antibody pool of the particular IVIg preparation would not contain antibodies against BT-AB. This possibility cannot be excluded and seems to be the most likely explanation. Whether IVIg preparations using different donor pools would contain antibodies against BT-AB cannot yet be determined. Extraction of BT-AB from the serum of patients with BT-AB–mediated BT therapy failure remains a challenging task but seems to require means other than IVIg administration.

Dirk Dressler, MD
Uwe Zettl, MD
Reiner Benecke, MD
Department of Neurology
University of Rostock
Rostock, Germany

Hans Bigalke, MD
Department of Toxicology
Medizinische Hochschule
Hannover, Germany

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Treatment of Persistent Hemiballism With Botulinum Toxin Type A

Hemiballism, irregular vigorous proximal limb movements that are highly disabling, exhausting, and socially stigmatizing, occurs with approximately 0.5% of strokes[1] and in other conditions, including nonketotic hyperglycemia, multiple sclerosis, and systemic lupus erythematosus,[2,3] affecting the subthalamic nucleus and other basal ganglia structures, such as the thalamus, caudate nucleus, and putamen. Probably because of compensation mechanisms, remission usually occurs within 6 months. In some patients, however, hemiballism is persistent and requires treatment. Medical treatment with antidopaminergic drugs,[4] including clozapine,[5] and surgical treatment with stereotactic interventions[6] are often ineffective or bear the risk of serious side effects. Recurrent intramuscular injections of small doses of botulinum toxin type A (BT) have now been used for several years for symptomatic treatment of various muscle hyperactivity disorders.[7] We report its use to treat hemiballism.

Case Report

A 93-year-old woman complained of involuntary right-sided arm movements that started suddenly 7 years earlier. At that time, in another hospital, the diagnosis of hemiballism was made and a vascular cause was suspected. Treatment with haloperidol was unsuccessful and produced tardive perioral dyskinesia. The severity of hemiballism fluctuated with time but never improved substantially. Recently, the patient was admitted to our service because of an additional acute right middle cerebral artery stroke with left hemiparesis.

On neurologic examination (video segment 1), there were right-sided irregular vigorous proximal movements in the arm and, to a minor extent, also in the leg. Proximal arm movements mainly consisted of shoulder elevations, arm adductions and inward rotations, and some forearm extensions. There was only minimal involvement of the hand and fingers. Trunk muscles were spared entirely. The involuntary movements could not be suppressed voluntarily but improved slightly when the patient tried to use the affected arm. Physical activity elsewhere in the body facilitated the symptoms slightly. During sleep, all involuntary movements disappeared. In the affected limb, there were chronic painful hematomas predominantly over the extensor parts of the arm that could not be avoided by protective pads. Sensory functions, including vibration sense and joint position sense, and motor functions were entirely normal in the affected limb. Because of the superimposed proximal involuntary movements, fine movements of the right hand and fingers were impossible, and the use of tools or objects was grossly impaired. This situation was worsened by the current additional contralateral hemiparesis that deprived the patient from almost all her upper extremity motor functions and interfered with her walking, standing, and sitting so that she was rendered bedridden. Magnetic resonance imaging showed multiple microangiopathic lesions in the periventricular white matter and the basal ganglia bilaterally.

After the diagnosis of probable vascular hemiballism was made, BT (Dysport, Ipsen Ltd, Maidenhead, Berks, United Kingdom; reconstitution: 500 mouse units in 2.5 mL of 0.9% $NaCl/H_2O$) was injected into the right levator scapulae (180 mouse units), right scalenii (120 mouse units), horizontal part of the right trapezius (480 mouse units), right pectoralis major (240 mouse units), right pectoralis minor (200 mouse units), right biceps brachii (120 mouse units), and right triceps brachii (360 mouse units) in a total dose of 1700 mouse units.

Under this treatment (video segment 2), the first beneficial effects were noted after 5 days, and full therapeutic effect was seen after approximately 2 weeks. Involuntary proximal arm movements were reduced substantially. As measured with surface electromyography, amplitudes of hemiballism activity of the target muscles were reduced substantially. The patient became able to use tools and objects, although with some remaining clumsiness. The chronic hematomas vanished with time, and the associated pain ceased. Because of the reduced involuntary movements, the patient gained postural stability and could be positioned in an armchair for several hours each day which improved her social contacts and her general well-being. There was some expected mild paresis of arm elevation, shoulder elevation, arm adduction and inward rotation, and forearm extension not exceeding Medical Research Council grade 4.[8] With the exception of reduced arm elevation, which slightly impaired the patient's ability to reach out, none of these limitations were functionally significant. Systemic side effects of BT therapy did not occur. Active hand and finger mobility was not reduced but, instead, improved because of reduced interference with involuntary movements. Negative effects on the contralateral hemiparesis could not be detected. After approximately 3 months, the patient had returned to her original condition.

Discussion

This case shows that BT therapy can be used to treat persistent hemiballism efficiently and safely. With conventional treatment strategies often being ineffective, risky, or both, BT therapy seems to be a valuable addition to therapy options in hemiballism. As compared with other indications for BT therapy, hemiballism has features favoring the therapeutic use of BT. With its predominance in proximal muscles, BT injections of distal muscles with narrow therapeutic windows

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Address correspondence and reprint requests to Dirk Dressler, MD, Department of Neurology, University of Rostock, D-18147 Rostock, Germany.

can be avoided and thus minimize the risk of paresis frequently seen in BT therapy of writer's cramps with its distal predominance. With its lack of paresis, BT therapy has a broader therapeutic window in hemiballism than in conditions with obligatory association of paresis, such as spastic syndromes. With its limited duration of action, BT must be reinjected in persistent hemiballism but should correspond to the time course of transient hemiballism when given as a single dose.

Legends to the Videotape

Segment 1: Before treatment with botulinum toxin, the patient shows vigorous involuntary shoulder elevations, arm adductions and inward rotations, and some forearm elevation. The patient is unable to sit because of the involuntary movements. There is only minimal involvement of the hand and fingers. The patient suffers from chronic painful hematoma.

Segment 2: Three weeks after treatment with botulinum toxin, the involuntary proximal arm movements are reduced substantially. The patient is able to sit and use objects, although with some remaining clumsiness. The chronic hematomas vanished with time, and the associated pain ceased.

D. Dressler, MD
M. Wittstock, MD
R. Benecke, MD
Department of Neurology
Rostock University
Rostock, Germany

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McLeod Syndrome and Neuroacanthocytosis With a Novel Mutation in the XK Gene

McLeod syndrome is an X-linked multisystem disorder characterized by the association of neurologic manifestations with abnormalities of red blood cell morphology. Abnormally shaped erythrocytes, known as acanthocytes, occur in a few heterogeneous neurologic conditions grouped under the common term "neuroacanthocytosis," namely, McLeod syndrome, chorea-acanthocytosis, and abeta-lipoproteinemia.[1,2] McLeod syndrome is a rare condition defined by weak expression of the Kell blood group antigens and absence of a red blood cell surface antigen known as Kx.[3] The neurologic symptoms have an insidious late onset, usually in the fourth decade of life. These include peripheral and central nervous system involvement with neuropathy, areflexia, seizures, and progressive choreic and dystonic movements, the latter being the predominant clinical feature. Cognitive impairment and psychological disturbances, sometimes manifesting as personality changes, have also been reported.[4–7] The clinical syndrome may also include myopathy cardiomyopathy and elevated levels of serum creatine kinase.

Different point mutations, linked to disease, have been reported in the XK gene, which codes for a novel membrane transport protein corresponding to the Kx antigen, which is absent in McLeod syndrome.[8–11] We report a 56-year-old man with progressive choreic and dystonic movements, neuromuscular involvement, and psychological disturbances who is carrying a novel mutation in the XK gene.

Case Report

The patient was a 56-year-old man from an Italian family with no known history of consanguinity. He was married without any offspring had a brother and three sisters who were in good health. A first cousin, aged 50 years (son of his mother's sister), was reported to have had psychiatric disturbances and multiple "tics" for 10 years. The patient had been healthy until age 42, when mild involuntary movements of the legs were first noticed. Some years later the psychological disturbances began with neurologic symptoms spreading slowly to involve the neck, face, and trunk. At age 50, worsening involuntary movements and weakness resulted in frequent falls causing the patient to stop working as a postal carrier. He was first admitted to our department at age 54. Neurologic examination showed generalized choreic and dystonic movements, hypotonia, and areflexia. Psychiatric evaluation revealed anxiety, mild depression, and obsessive-compulsive behavior. Funduscopic examination was normal. Neuropsychological assessment, including Wechsler Adult Intelligence Scale and the Wisconsin Card Sorting Test, was normal. Routine blood tests showed increased creatine kinase (CK, 1020 U/L, normal <190), LDH (787 U/L, normal <460), glutamic oxalo-acetic transaminase (GOT, 70 U/L, normal <40), and glutamic pyruvic transaminase (GPT, 98 U/L, normal <40). During 3 years of observation CK was elevated variably between 260 U/L and 1350 U/L. Serum levels of ceruloplasmin, copper, apoprotein A and B, lysosomal enzymes, thyroid hormones, and vitamin E were normal. Huntington's disease was ruled out by molecular genetic analysis.

In the peripheral blood, approximately 8% acanthocytes were detected. Kell serology was as follows: sample 1 (proband) K: −1, w2, −3, w4, −6, w7 (McLeod phenotype, in which w = weak reaction); sample 2 (control) K: −1, 2, −3, 4, −6, 7 (negative phenotype). Electrocardiography showed left axis deviation and the echocardiogram was normal. Electromyography showed mild, chronic neurogenic changes, and nerve conduction velocity studies suggested mild sensory motor neuropathy. Brain magnetic resonance imaging indicated mild, diffuse ce-

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Address correspondence and reprint requests to Prof. Antonio Federico, U.O. of Neurometabolic Diseases, Institute of Neurological Sciences, Policlinico "Le Scotte," V.le Bracci, 2-53100 Siena, Italy.

rebral atrophy and areas of bilateral high signal intensity in the caudate and putamen nuclei, and in the posterior periventricular white matter on T2-weighted images. A single photon emission computed tomography (SPECT) using 123I-IBZM showed diffuse and heterogeneous reduction of IBZM distribution in cortical and subcortical regions without accumulation in the striatum. Positron emission tomography (PET), using 18F-FDG, suggested absent metabolism in the basal ganglia and hypometabolism in the frontal and parietal cortex.

Sural nerve biopsy revealed a normal number of myelinated fibers. However, in some fibers, thin myelin sheaths were seen and teasing showed demyelination signs in 5% fibers. Rare axonal degeneration and complex onion bulb formations were also observed (Fig. 1A, B). On quadriceps muscle biopsy there was a slight variation in fiber size with 12% nuclear centralization. Several basophilic fibers and small clusters of necrotic fibers were observed (Fig. 1C). There were rare hypotrophic angulated fibers and slight fiber-type grouping. Immunocytochemical analysis gave normal results.

During the last year, movement disorders continued to worsen despite therapy with different neuroleptic drugs and more recently with tetrabenazine. Moreover, he began to experience untreatable insomnia, sudden hypersalivation, and excessive sweating. The patient died in his sleep at home and an autopsy was not performed.

DNA Sequencing Methods

Exons of the McLeod gene, *XK*, were PCR-amplified, as described by Ho et al.,[8] from 40 ng of genomic DNA. PCR products were purified for direct sequencing using a Qiaquick PCR purification kit (Qiagen, Hilden, Germany). Sequencing was carried out with fluorescence-based technology on an ABI 377 sequencer using Big Dye chemistry (Applied Biosystems, Foster City, CA, USA). Additional sequencing primers as those published[8] were designed for mutation analysis of *XK* exon3 (xkseq3.3 [forward]: 5′ATCTCTGGATGACTGTAGATCTTC3′, xkseq3.4 [reverse]: 5′GAACATAGAGAAGGCCCTCAGTAG3′). DNA sequence was analyzed for both strands using the Sequence Analysis program (ABI, Foster City, CA, USA) and mutation analysis, DNA sequence alignments, and sequence contig assembly was achieved using Sequence Navigator (ABI) and the BESTFIT and GELSTART programs from the Wisconsin GCG package (version 9.1).

Results of *XK* Mutation Analysis

Initially, the patient and his first-degree relatives (mother and three unaffected siblings) were tested for genetic linkage to chromosome 9q21, which harbors the gene for chorea-acanthocytosis (CHAC).[12] No linkage was found to this region. To test for the X-linked recessive form of neuroacanthocytosis, McLeod syndrome, the *XK* gene was sequenced in the proband. A nonsense mutation at nucleotide position 479 of the *XK* coding sequence (exon 2) was found that resulted from a C→T transition (CGA→TGA) and a corresponding amino acid change of an arginine residue to a stop codon (R133X).

Discussion

Neuroacanthocytosis syndromes (NA) have to be considered in the differential diagnosis of hereditary, late-onset, slowly progressive dystonic and choreiform movements. The clinical features of NA are similar and consist of movement disorders, neuropathy, myopathy, epilepsy, and possible abnormalities in neuropsychological or psychopathologic symptoms.[1] In chorea-acanthocytosis, peripheral nerves are sometimes severely affected with biopsy findings of axonal damage.[1,13] In McLeod syndrome, elevated serum CK and cardiomyopathy are important features for which a primary or secondary "myopathic" origin of the muscular pathology are still a matter for debate.[3,4,14] Recently, a McLeod patient with unusually severe muscular symptoms and pathology was described.[15] Our patient shows the typical presentation and evolution of the neurologic manifestations without cardiomyopathy and atrophy of the caudate nuclei, usually listed as classic signs of McLeod syndrome. Moreover, in his last year of life, he manifested autonomic symptoms, which have not yet been reported in this neurologic disorder, but which are commonly observed in other degenerative diseases involving the extrapyramidal system. Biopsy findings were consistent with primary myopathic changes and concomitant signs of neurogenic atrophy secondary to a moderate mainly demyelinating neuropathy.

Molecular genetic analysis identified a novel point mutation in the XK gene that would result in translation of a truncated

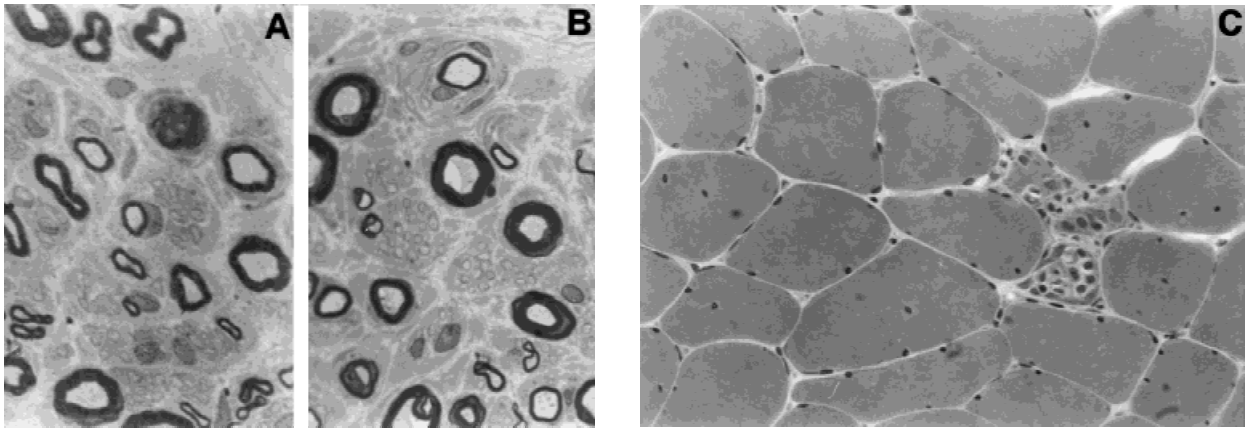

FIG. 1. Sural nerve biopsy ×1000: semithin sections showing an axonal degeneration (**A**) and a complex onion bulb (**B**). (**C**) Muscle biopsy hematoxylin and eosin, ×500: small cluster of necrotic fibers. Note the nuclear centralization.

Kx protein less than one third the size of the full-length predicted protein. Given that the truncated Kx protein would possess just three of the 10 predicted transmembrane regions of the wild-type protein, it is unlikely that this mutant product would be able to carry out the normal function of Kx. Nonsense mutations producing premature stop codons can also lead to rapid degradation of mRNA so that truncated proteins are not even made or are at low levels.

The patient reported here and others previously described have relatively severe neurologic disease, clinically and pathologically indistinguishable from NA without McLeod serology. Thus, investigation of red blood cell morphology, serology, and molecular genetic analyses should be performed in patients with unexplained chorea.

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Maria Teresa Dotti, MD
Carla Battisti, MD
Alessandro Malandrini, MD
Antonio Federico, MD
Unit of Metabolic Diseases
Institute of Neurological Sciences
University of Siena
Siena, Italy

Justin P. Rubio, PhD
The Walter and Eliza Hall Institute of Medical Research
The Royal Melbourne Hospital
Victoria, Australia

Giuseppe Circiarello, MD
Servizio di Immunoematologia e Medicina Trasfusionale
Ospedale S. Maria Annunziata
Firenze, Italy

Anthony P. Monaco, PhD, MD
Wellcome Trust Centre for Human Genetics
University of Oxford
Oxford, U.K.

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Chorea in New Variant Creutzfeldt-Jakob Disease

Since the initial reports[1,2] of new variant Creutzfeldt-Jakob disease (NVCJD), well-defined clinical features have been established.[3,4] A psychiatric presentation with painful, distal, sensory symptoms, ataxia, and cognitive decline represents the usual picture. Movement disorders, either chorea or myoclonus, dystonia, chorea, or combinations thereof may occur, particularly in the later stages. This report describes a patient with NVCJD who developed florid generalized chorea early in the course of the disease with videotape of the case.

Case Report

A 28-year-old woman had a 10-month history of behavioral disturbances and cognitive decline. After an initial diagnosis of depression, antidepressant medication (i.e., selective serotonin reuptake inhibitors [SSRIs]) was prescribed but produced no benefit. Additional therapy with a tricyclic antidepressant, a thioxanthine (for 2 weeks), and a norepinephrine and serotonin uptake inhibitor failed to improve her symptoms. Four months into the illness, generalized writhing movements and imbalance were noted with secondary amenorrhea. As cognition and imbalance deteriorated, the chorea became more florid and interfered with activities of daily living. On direct questioning, the

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Address correspondence and reprint requests to Dr. John Bowen, Department of Neurology, Royal Hospital Haslar, Gosport, HANTS.PO12 2AA, U.K.

patient described two brief day-long episodes of tingling confined to one limb. No relevant personal or family history was elicited. Physical examination showed florid, generalized chorea with superimposed dysarthria and predominantly axial ataxia. Hyperesthesia, consistently manifested as an apparent fear of sensory and tendon reflex examination, was also prominent although no objective sensory loss was found. Eye movements were full with broken pursuit but normal saccadic velocity. An increased jaw jerk but no other pyramidal signs or primitive reflexes were found. Neuropsychological examination showed marked intellectual decline with a predominantly frontal emphasis.

Results of hematologic, biochemical, pregnancy, and endocrine tests, autoantibody, lupus anticoagulant, and anticardiolipin antibody screenings, copper studies, blood films for acanthocytes, and testing for Huntington's disease and dentatorubropallidoluysian atrophy were normal or negative. Electroencephalography showed profound asymmetric widespread abnormalities without periodic complexes. Brain magnetic resonance imaging showed subtle bilateral high signal changes in the posterior thalamus on T2-weighted sequences.

Cerebrospinal fluid was acellular and had a mildly increased protein level of 0.74 g/L and a normal lactate level. Oligoclonal bands were absent from the cerebrospinal fluid and serum. Elevated levels of neuron-specific enolase and S100b protein, a positive assay for 14-3-3 protein, and tonsil biopsy[5] confirmed the diagnosis of NVCJD.

Discussion

This case shows a clinical presentation with early psychiatric, psychological, and cerebellar features coupled with gross chorea within 4 months of symptom onset. Although extrapyramidal reactions attributed to SSRIs are well described,[6] in addition to a toxic syndrome associated with SSRIs with various movement disorders,[7] chorea is rare and accounts for only 3 of 246 suspected SSRI-induced extrapyramidal reactions.[8] Furthermore, reported cases of SSRI-related chorea have occurred after 7 months of SSRI ingestion, resolving within 1 month,[9] and after 2 years of continual SSRI use with rhythmic palatal movements, myoclonus, and possibly dystonia, resolving within 1 week of drug withdrawal[10] and occurring and resolving within 1 day of a single dose.[8] Tricyclic and antidepressant antidepressants and thioxanthines were prescribed for a brief period, and despite withdrawal, the chorea in this patient worsened progressively during the following months. To our knowledge, chorea has not been reported with norepinephrine and serotonin reuptake inhibitors. Therefore, drug-induced chorea seems unlikely.

Alternative diagnoses pursued in this case included Huntington's disease, dentatorubropallidoluysian atrophy, neuroacanthocytosis, Wilson's disease, anticardiolipin antibody syndrome, vasculitides, and endocrinopathies. The diagnosis of NVCJD was confirmed by showing an abnormal isoform of cellular prion protein in tonsillar tissue. This abnormal isoform was found in tonsillar biopsies from three patients all found to have neuropathologically confirmed NVCJD at necropsy and is reported to be diagnostic in the appropriate clinical context.[5] Chorea and myoclonus are well described in NVCJD, although more usually as later features in the course of the disease.[3]

This case clearly shows that chorea may occur as an early and prominent feature of NVCJD, which should now be considered in the differential diagnosis of rapidly progressive chorea with dementia and ataxia.

Legend to the Videotape

The patient's behavior and demeanor are child-like. Generalized chorea is evident. Eye movements appear full although pursuit is fragmented. Axial ataxia predominantly coexists.

John Bowen, MRCP(UK)
Tejal Mitchell, MRCP(UK)
Ronald Pearce, MRCP(UK)
National Hospital for Neurology and Neurosurgery

Niall Quinn, FRCP
Institute of Neurology
Queen Square
London, U.K.

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Primary Anticholinergic-Responsive Pisa Syndrome

Pisa syndrome is a form of dystonia characterized by truncal rotation and lateral flexion and was first described in 1972 by Ekbom and Lindholm.[1] It occurs almost exclusively in the context of chronic neuroleptic therapy rather than acute

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Address correspondence and reprint requests to K. F. Bhattacharya, MRCP, Movement Disorders Unit, King's College Hospital, Mapother House, De Crespigny Park Road, London SE5 8AZ, U.K.

neuroleptic-induced dystonic reaction after therapy initiation.[2,3] It has also been described, although less frequently, in the context of Alzheimer's disease[4] and multiple system atrophy.[5] Primary dystonia resembling Pisa syndrome is rare and may be underrecognized. In a recently reported series of 18 patients with axial predominant adult-onset primary dystonia, three patients had lordotic and scoliotic deviation similar to that seen in Pisa syndrome.[6] We report a case of sporadic adult-onset truncal dystonia with head, neck, and shoulder involvement, reminiscent of Pisa syndrome, with complete resolution on high doses of anticholinergic therapy.

Case Report

A 38-year-old white woman was referred to our movement disorders unit. Four months earlier she had experienced sciatic pain down one leg while carrying a heavy load. On vacation that same month, she noted that she was tilting to the left, which interfered with walking and swimming. During the next few weeks, her head began to pull toward the right, and her left shoulder pulled upward. The symptoms were alleviated when lying down and disappeared when asleep. Her medical history included sciatica and low back pain for a number of years. The patient was taking depot contraception only. There was no history of neuroleptic, vestibular, sedative, or antiemetic medication at any time. There was no family history of extrapyramidal disorder.

On examination there was dystonic spasm of the left sternocleidomastoid and left splenius capitis muscles, with marked torticollis and retrocollis. Overactivity of the left paraspinal muscles resulted in truncal twisting toward the left (video segment 1). The patient used stretching of the left arm as a trick maneuver to attenuate the truncal dystonia. The rest of the neurologic examination was unremarkable.

The following test results and levels were negative or normal: copper studies, detailed biochemical and hematologic profiles, autoimmune profile, white cell and lysosomal enzymes, acanthocytes, serum angiotensin-converting enzyme, and urinary amino acids. Findings from magnetic resonance imaging of the brain and spinal cord were normal. Genetic testing for dentatorubralpallidoluysian atrophy, Huntington's disease, spinocerebellar ataxia type III, DYT1 gene, and dopa-responsive dystonia were negative.

Treatment included targeting therapy with botulinum toxin A injections to the right sternocleidomastoid, left splenius capitis, and left trapezius muscles for torticollis. Anticholinergic therapy with benzhexol, using a dose-escalating regimen, was started at 1 mg a day. The dose of benzhexol was slowly increased to 20 mg a day for 6 months, and the patient noted virtually complete dissolution of the dystonia (video segment 2). After 1 year, she was discharged from the clinic and the use of anticholinergic drugs was tapered off. Recurrence of the truncal dystonia, retrocollis, and torticollis occurred 6 months later and required reinstatement of anticholinergic therapy. Currently, the patient remains free of symptoms and is treated with a maintenance dose of 20 mg benzhexol a day.

Discussion

We report a case of adult-onset, sporadic, segmental dystonia resembling Pisa syndrome. Striking features of this case are the lack of previous exposure to neuroleptic medication, a nearly complete resolution of the dystonia with anticholinergic therapy, and recurrence of the syndrome on withdrawal of anticholinergic drugs.

Pisa syndrome is a descriptive term for a twisting truncal dystonia causing patients to veer to one side while walking.[7] The cases originally described did not have concomitant dystonic symptoms,[1,3,7,8] but the head and neck may be involved. Pisa syndrome is most frequently seen after chronic neuroleptic therapy,[2,3,8] with or without concurrent antidepressant medication. In the context of chronic neuroleptic exposure and antidepressant therapy, Pisa syndrome is thought to arise secondary to a complex interaction between several neurotransmitters, including serotonin, noradrenaline, dopamine, and acetylcholine.[9] Association with structural brain lesions (e.g., chronic subdural hygroma and cerebral cortical atrophy) has been described in some cases.[1,7,9]

Our patient had sporadic truncal and craniocervical dystonia. The only possible, but unlikely, causal association is the protracted history of sciatica and low back pain. Peripheral injury, often in association with reflex sympathetic dystrophy, has been documented as a cause of focal and segmental dystonia and posttraumatic hemidystonia.[10]

The response to high doses of anticholinergic therapy in our patient was virtually complete, with recurrence of the original presentation in its entirety after medication withdrawal and milder breakthrough symptoms on lower dosage. Open-labeled and double-masked trials have substantiated the benefits of anticholinergic therapy in focal, segmental, and generalized dystonia, quoted as 40% and 50% in adults and children, respectively.[11] It has been observed that the greatest benefit is obtained with treatment initiation within the first 5 years of dystonia onset. There is no evidence that anticholinergic drugs modify the course of the disease. Anticholinergic drugs are often given before neuroleptic therapy to prevent acute dystonic reactions and during neuroleptic treatment to treat tardive dystonia. They may increase the incidence of tardive dyskinesias. Therefore, recognition of each condition is important.[12,13] The exact mode of anticholinergic action in dystonia is uncertain, but restoration of the acetylcholine–dopamine balance probably plays a role, particularly in the context of neuroleptic-induced dopamine blockade.

In conclusion, we have described a rare phenotype of adult-onset, sporadic, segmental dystonia resembling Pisa syndrome, with virtually complete resolution of symptoms with high doses of anticholinergic medication.

Legends to the Videotape

Segment 1: Before treatment, dominant left laterocollis with lateral bending of the trunk, scoliosis to the right, and retrocollic spasms are seen.

Segment 2: After treatment, mild laterocollis to the right and some anticholinergic-induced chorea of the fingers in both hands are seen.

K. F. Bhattacharya, MRCP
I. Giannakikou, MBBS
N. Munroe, MRCP
K. Ray Chaudhuri, FRCP
Movement Disorders Unit
King's College Hospital/Guy's, King's, a
and St. Thomas's Medical School
London, U.K.

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Radiation-Induced 'Meige Syndrome'

The effects of ionizing radiation on the nervous system may appear years after exposure.[1] Five years after radiotherapy for nasopharyngeal carcinoma, a patient experienced bilateral spasm of the periorbital and jaw muscles. The clinical presentation resembled that of craniocervical dystonia.

Case Report

A 77-year-old man was examined in June 1998 for painful jaw spasms. The spasms made eating difficult. He often could not keep food in his mouth. During the previous 4 years he had experienced persistent eye blinking, with the left eye affected more. He also complained of a constant dry mouth. His eye and jaw symptoms had worsened during the 6 weeks before consultation. In 1993 the patient had received a total of 70 Gy of radiotherapy in 35 fractions to a 1.2-cm malignant squamous cell carcinoma on the left side of the roof of his nasopharynx. Radiation was administered in a three-field, two-phase technique. Twenty Gy was directed at the anterior neck, and 50 Gy to the upper neck, primary tumor, and bilateral lymph nodes.

Neurologic examination showed spontaneous bilateral irregular contraction of the periorbital muscles that was worse on the left side. Eye movements were normal. There were irregular spasms of forced jaw clenching that at times were painful. The patient could open his jaw to a limited degree, and jaw opening or chewing food occasionally would precipitate spasms. He had difficulty protruding his tongue without precipitating spasms. His speech was normal between spasms. Facial muscle strength was mildly reduced on the left and markedly reduced on the right side in a lower motor neuron distribution. Fine undulating spontaneous contractions, consistent with myokymia, could be seen in the right periorbital and cheek muscles. The rest of the neurologic examination was unremarkable.

Findings from a magnetic resonance imaging scan of the brain and brainstem with gadolinium were normal. Median and tibial somatosensory evoked responses showed normal central conduction time. Brainstem auditory evoked potentials were also normal. Nerve conduction studies of the facial nerve showed normal latencies and action potential amplitudes on the left, but the compound muscle action potential amplitude was markedly reduced on the right, to 0.1 mV. Blink responses after right supraorbital nerve stimulation showed delayed R1 (latency, 20.7 milliseconds) and ipsilateral R2 (44.5 milliseconds) blink responses, but a normal latency for the contralateral R2 (35.8 milliseconds) blink response. After left supraorbital nerve stimulation, the R1 (10.5 milliseconds) and R2 (34.4 milliseconds) blink responses were of normal latency, but the contralateral R2 blink response was delayed (43.9 milliseconds).

Electromyography of the facial muscles showed recruitment and motor unit morphology consistent with chronic denervation. This was particularly so in the right facial muscles, in which sparse fibrillation potentials were also seen. Spontaneous grouped discharges, some myokymic and neuromyotonic, were present bilaterally in the orbicularis oculi, orbicularis oris, and masseter muscles. Electromyography of the left orbicularis oculi muscle during some episodes of periorbital muscle spasm showed neuromyotonic discharges.

The patient was prescribed carbamazepine, which was poorly tolerated. His prescription was then changed to phenytoin. This medication resolved his jaw spasms and significantly improved his periorbital muscle spasm.

Discussion

Cranial nerve damage secondary to radiation is rare.[1] This patient presented 5 years after head and neck irradiation with clinical features resembling craniocervical dystonia or Meige syndrome.[2]When his electromyogram showed myokymic and neuromyotonic discharges, the diagnosis became clear. The normal magnetic resonance image, the normal central conduction time on evoked potential studies, and the blink response latencies suggest that the myokymic and neuromyotonic electromyographic discharges originated from the motor branches of the fifth and seventh cranial nerves rather than from the brainstem. These results also suggest that the patient's periorbital and jaw spasms were of a peripheral nerve origin and related to previous radiotherapy.

Myokymic discharges are spontaneously generated ectopic bursts of individual motor unit potentials occurring as doublets,

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Address correspondence and reprint requests to Paul D. Clouston, MB, BS, PhD, FRACP, Department of Neurology, Westmead Hospital, Sydney 2145, Australia.

triplets, or multiplets. The firing frequency of the potentials within a burst is 5 to 60 Hz. Neuromyotonic discharges are prolonged bursts of motor unit potentials firing at 150 to 300 Hz for a few seconds. Multiple motor units may be involved. The bursts begin and end abruptly, and the potential amplitude may wane. Bursts may be initiated by needle movement, voluntary effort, or nerve percussion.[3]Some of our patient's discharges were of an intermediate frequency for these definitions.

The pathophysiology of myokymic and neuromyotonic discharges is unknown but most likely involves a biochemical alteration in the microenvironment of the axon membrane with or without associated nerve demyelination. In our patient, there was marked axonal loss of right facial nerve fibers, as evidenced by the reduced right-sided compound muscle action potential amplitude and the presence of fibrillations on the electromyogram of the right facial muscles. The long latency of the R1 and ipsilateral R2 blink responses after right-sided stimulation is suggestive of demyelination of remaining seventh nerve fibers proximal to the stylomastoid foramen. Spontaneous ectopic excitation, ephaptic transmission from axon to axon, and autoexcitation at ectopic generators are mechanisms thought to play a role in the generation of neuromyotonic and myokymic discharges. These abnormal mechanisms of nerve excitation can occur in the altered axon microenvironment that occurs after irradiation.[1]Spontaneous and contraction-induced neuromyotonia presumably explained this patient's episodes of spontaneous orbital and painful masseter contraction.

Shults et al.[4]and Lessell et al.[5] each described four cases of ocular neuromyotonia after radiation therapy. Their patients had paroxysmal monocular deviations with associated transient visual disturbances attributable to involuntary contraction of the muscles supplied by the third, fourth, and sixth cranial nerves. There was no involvement of the perioral or periorbital muscles. This condition is distinct from that seen in our patient.

Diaz et al.[6]and Marti-Fabregas et al.[7]have described patients with neuromyotonia of the facial and trigeminal nerves after radiotherapy. The patients were described as having involuntary contractions of the masticatory and lower facial muscles, which were painful at times. The movements interfered with speaking and eating. Marti-Fabregas et al. reported myokymic and neuromyotonic discharges on electromyography, but electromyographic findings were not mentioned in the report by Diaz et al. Our patient's lower facial movements resembled the neuromyotonia in the distribution of the facial and trigeminal nerves as described by Marti-Fabregas et al. and Diaz et al. All previous cases have reported a good response to anticonvulsant drugs.

This case emphasizes the importance of using electrophysiology as an extension of the neurologic examination. If the tests had not been performed, the patient may have received an incorrect diagnosis.

Legends to the Videotape

Segment 1: Mild right lower motor neuron facial weakness is visible. The left eye is partially closed, with irregular contraction of periorbital muscles. The movements of the tongue and lips related to the patient's postradiation sicca syndrome are seen. At no time had the patient taken neuroleptic drugs.

Segment 2: During involuntary contraction of the left orbicularis oculi muscle, electromyographic discharges are present. Spontaneous discharges are present in the right orbicularis oculi, right orbicularis oris, and right masseter muscles.

Stacey K. Jankelowitz, MBBCh
Paul D. Clouston, MB, BS, PhD, FRACP
Department of Neurology
Westmead Hospital
Department of Medicine
University of Sydney
Sydney, Australia

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Pseudoathetosis in a Patient With Cervical Myelitis: Neurophysiologic and Functional MRI Studies

Pseudoathetotic movements, defined as involuntary slow, writhing, vermicular, sinuous movements, can occur in patients with loss of proprioception caused by lesions at various parts of the sensory pathways, including the spinal cord and peripheral nerves.[1,2] Abnormal postures and focal dystonia have been associated with peripheral nerve lesions or trauma,[3,4] and dystonia and athetosis of the upper limb have been recently reported in patients with syringomyelia.[5,6]

Abnormal movements such as tremor, myoclonus, or dystonia can occur in multiple sclerosis.[7] In contrast, pseudoathetosis has been reported scarcely in this disease.[8,9] We report the observation of striking pseudoathetotic movements, with an impulsive behavior to manipulate objects with the right hand, in a woman with clinical criteria of definite multiple sclerosis,[10] who had a single lesion, compatible with demyelination, in the right posterior quadrant of the cervical spinal cord. Functional magnetic resonance imaging (MRI) provided an interpretation

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Address correspondence and reprint requests Josep Valls-Sole, Unitat d'EMG. Servei de Neurologia, Hospital Clinic, Villarroel, 170, Barcelona, 08036. Spain.

for the abnormal movements and utilization behavior in this case.

Case Report

Clinical Aspects

The patient was a 61-year-old woman with a subacute onset of difficulties with performing voluntary movements with her right hand, in which she reported a burning sensation and other paresthesia. Mild pain irradiated from the cervical spine to the axilla and occasionally also to the hand. She had earlier experienced two episodes of optic neuritis (one in each eye), with documented abnormalities in the visual evoked potentials performed 1 and 2 years before, and a transient episode of cramps and paresis of the right lower limb.

Physical examination, performed with a conventional Snellen chart, showed a visual acuity of 0.9 in her right eye and 0.5 in her left eye (decimal scale), with no restriction of the visual fields. Both pupils were pale. No other cranial nerve abnormalities were found. Strength was normal in upper and lower limbs. The tendon jerks of the biceps and brachioradialis muscles were absent on the right side, whereas those of the right triceps and of the left upper limb were normal. Plantar reflexes were flexor on both sides. Vibration and positional joint sensation were severely reduced on the right side, whereas temperature and pain sensation were normal. There were slow, repetitive, flexion–extension and abduction–adduction involuntary movements of the right fingers and wrist at rest. These movements increased slightly when the patient was asked to close her eyes, do mental tasks, or maintain postural activity, and more strikingly when she performed voluntary movements with her contralateral upper limb, which gave rise to dystonic postures (video segment 1). Motor abilities were severely impaired in the right hand. The patient had difficulty in performing simple voluntary movements of the fingers and wrist, such as opening and closing the fist, or more complex movements, such as buttoning, opposing the thumb to the fingers, and writing. When asked to perform one of these tasks, the patient persisted for a long time in doing repeated attempts or related movements with her right hand. For instance, after several unsuccessful attempts to write or draw a figure on a paper, the patient tried repeatedly to cover up the pen that she was alternately leaving on the top of the table and holding it up again with great difficulties (video segment 2). When a simple object was put inadvertently close to her right hand and within her visual field, the patient manipulated it even if she had the instructions to remain quiet. However, she left the object when we told her specifically to do so. When we asked why she touched and manipulated the objects, her usual answer was that she wanted to exercise her right hand.

Laboratory Data

Serum analysis was normal regarding levels of vitamin B_{12} and folic acid. Serologic results against syphilis, borrelia, and HIV were also normal. Titers of antibodies against rheumatoid factor, antinuclear antibodies, anti-DNA antibodies, anti-neutrophil-cytoplasmatic antibodies (ANCA), and antibodies against extractable nuclear antigens derived from serum of patients with Sjogren's syndrome (anti-Ro/SSA and anti-La/SSB) were all negative. The cerebrospinal fluid showed a slight increase in proteins (70 mg/dL) and lymphocytes (11/mm^3). No oligoclonal bands were found.

Neurophysiologic Studies

The somatosensory evoked potentials (SEPs) to the right median nerve stimulation showed normal responses at Erb's point (latency, 9.6 milliseconds; amplitude, 3.0 μV), but absent responses in the cervical spinal cord (C2) and contralateral parietal sites. Left median nerve stimulation elicited normal SEPs (latencies at Erb's point, C2, and parietal sites, 9.7, 12.3, and 17.9 milliseconds, respectively; amplitudes at Erb's point, C2, and parietal sites, 3.5, 1.2, and 4.0 μV, respectively). Visual evoked potentials to monocular pattern stimulation showed normal amplitude but marked latency increase of the P100 on both sides (135 milliseconds on the right side and 146 milliseconds on the left side). Cortical and cervical magnetic stimulation, performed with a figure-eight coil and a Novametrix 200 magnetic stimulator (Oxford Medical Instruments, Surrey, UK), elicited well-synchronized motor evoked potentials of normal amplitude and latency in thenar muscles with a central motor conduction time of 8.7 milliseconds in both sides. Responses to cortical stimulation were limited to the contralateral limb and had similar duration and shape on both sides.

Magnetic Resonance Imaging

Magnetic resonance imaging showed a predominantly right posterior hyperintense lesion in the cervical spinal cord, extending from C2 to C6 (Fig. 1) compatible with a demyelinating lesion or myelitis. No lesions were seen in cranial MRI.

Follow-up

The patient's disorder was diagnosed as multiple sclerosis, based on the clinical findings, exclusion of other possible causes, and laboratory support from the results of the MRI and neurophysiologic studies.[10]

The patient was treated with cortisone and experienced subjective improvement, with less paresthesia or burning sensation and pain, but no changes regarding her abnormalities in motor control of her right hand.

Functional MRI

A functional MRI study was carried out using a 1.5 T Signa system (General Electric, Milwaukee, WI, USA) equipped with echo-speed gradients and single-shot echoplanar imaging (EPI) software. The functional sequence consisted of gradient recalled acquisition in the steady state (time of repetition [TR], 3000 milliseconds; time of echo [TE], 50 milliseconds; pulse angle, 90°) with a 96 × 64-pixel matrix, within a field of view of 24 cm, and with a section thickness of 5 mm. Six interleaved slices, parallel to the anteroposterior commissure line, were obtained for each functional sequence to cover the upper cortical motor system (four slices) and the basal ganglia opercular region (two slices).

The functional time series consisted of 60 consecutive images obtained in 3 minutes, in which 30-second periods of rest and activation were alternated. The patient was instructed to perform two different unilateral repetitive self-paced tasks with each hand.[11] The simple task involved the opening and closing of the hand at an approximate rate of one per second. In the complex motor task, the patient was asked to oppose individu-

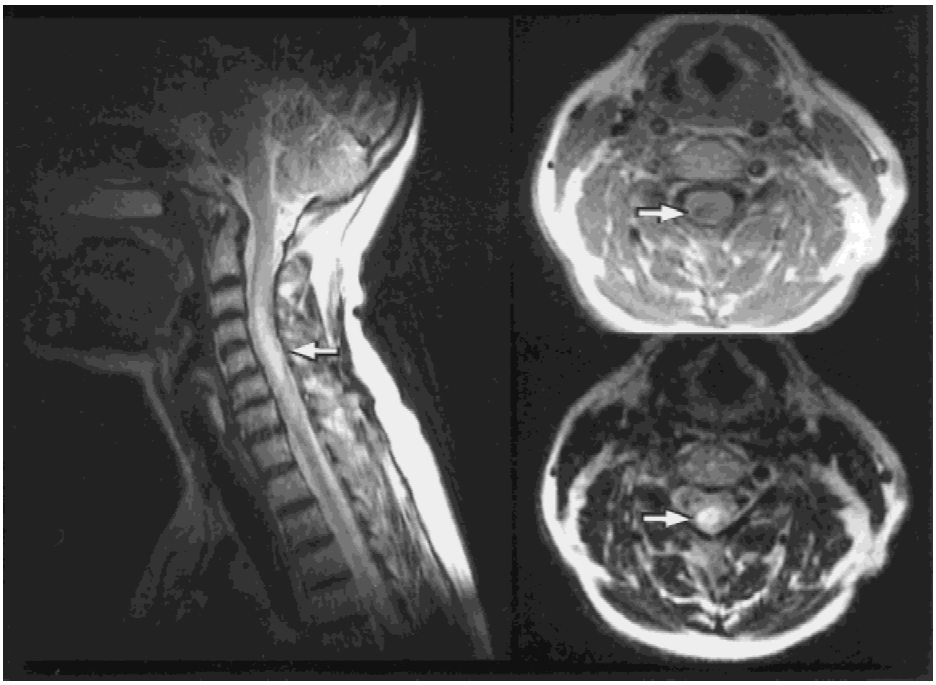

FIG. 1. Magnetic resonance imaging of the cervical segment of the spinal cord in our patient. The sagittal view (left) shows the location of the lesion in the central portion of the spinal cord. The axial T1- and T2-weighted images (right) show the predominant involvement of the right posterior spinal cord quadrant.

ally the thumb to the fingers following a sequence of little finger, middle finger, ring finger, index finger.

Functional sequences were analyzed using an auxiliary workstation (SPARCstation 20, Sun Microsystems, Mountain View, CA, USA) and specific image analysis software (FuncTool, GE Medical Systems, Buc, France). Parametric statistical maps were obtained using Student's *t* statistics and adopting previously described procedures.[12,13] Activation images were displayed in pseudo color, scaled according to significance, and superimposed on corresponding anatomic images. The activation threshold was empirically assessed as in a previous report.[13] A total of 200 stimulus-lacking (identical procedures, but with no task) functional images (50 four-slice sequences) were acquired in control subjects to estimate the probability of obtaining activations by chance and stimulus unrelated artifacts. The resulting images produced only four (2%) pixel clusters greater than 3.75×3.75 mm^2 at the p value level of 0.0001 within the brain contour. Thus, because of functional changes above this cluster size and significance level, the probability of including task unrelated activations is low. An activation threshold reference is provided in Figures 2 and 3.

Simple right-hand movements induced activation of the contralateral left precentral region, involving motor and premotor cortices, together with functional activity in the supplementary motor area. Activation of the primary motor cortex was large and extended from the brain vertex to the opercular region (Fig. 2). In contrast, simple movements performed with the left hand induced striking functional changes in both hemispheres, with larger activation of the area roughly corresponding to the ipsilateral primary motor and premotor areas. The left precentral region and basal ganglia, specially the putamen, were consistently activated (Fig. 3). Right precentral (primary motor) functional changes were less evident than those of the left hemisphere or those of the postcentral (primary somatosensory) region. Left hand motor task enhanced right hand involuntary movements, inducing predominantly dystonic postures.

Complex movements of the right hand similarly induced extensive contralateral prerrolandic activation, and those of the left hand induced bilateral functional activity in frontal areas. In addition, the complex task involved premotor, prefrontal, and supplementary motor areas bilaterally during left and right hand tasks.

Discussion

Our patient showed abnormal movements of the right hand with sensory loss and absence of cervical cord and cortical SEPs to stimulation of the right median nerve in the presence of a demyelinating lesion of the cervical spinal cord. The case should be recognized as one of pseudoathetosis and dystonia caused by a spinal lesion, similar to other previously reported cases.[1,9,14] Pseudoathetotic movements have been associated with a loss of proprioception in the area in which the movements occur.[2] Sensory loss alone, however, cannot explain the occurrence of a movement. From the analysis of seven cases of pseudoathetosis in patients with lesions along the sensory pathway, Sharp et al.[2] suggested that pseudoathetotic movements originate in an abnormal integration of sensory and motor inputs at the level of the striatum. This theory assumes that true athetosis, with no sensory loss, and pseudoathetosis, with sensory loss, occur as a defect in the sensorimotor inhibition at the level of the striatum.[15] Abnormal sensorimotor integration can occur at other levels of the central nervous system. There is a net of propriospinal interneurons with sensorimotor integrative capabilities at the cervical C3–C4 level.[16–18] Loss of inhibitory inputs from these interneurons to the cervical motor neurons may have contributed to the generation of pseudoathetotic movements in our patient. Additional possible explanations for the origin of pseudoathetotic movements in patients with lesions in the cervical segment of the spinal cord include ectopic generation of impulses in descending motor fibers[19–21] and connectivity or plasticity changes induced by the disorganized

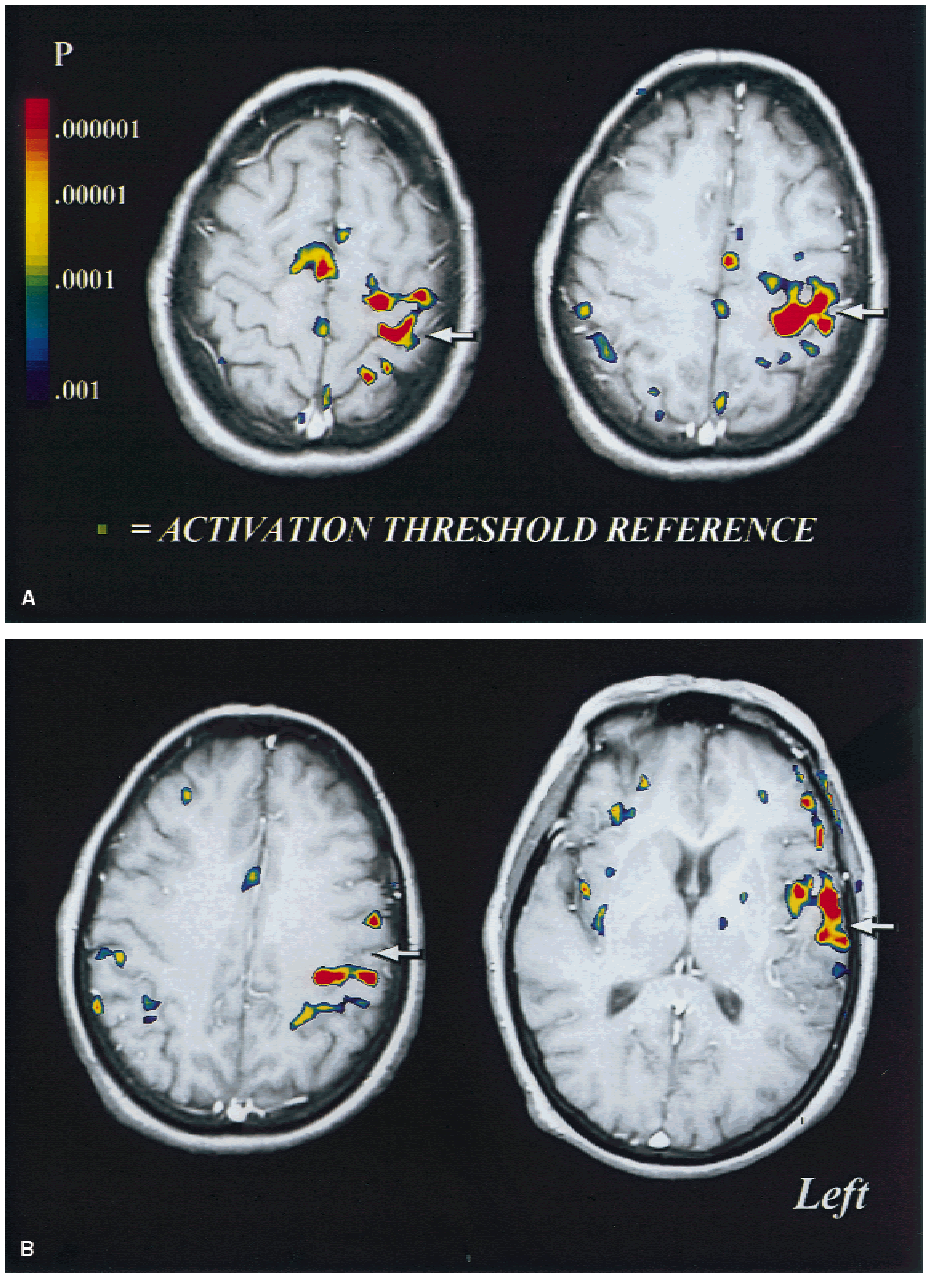

FIG. 2. Functional activation pattern observed during simple opening and closing of the abnormal right hand. Functional changes were contralateral and involved mainly precentral areas from the brain vertex to the opercular region. Color is proportional to the *t* value in our statistical parametric maps. Reference p values are provided in the nonlinear color scale. The activation threshold reference, a 3.75×3.75 mm^2 pixel cluster at p value of 0.0001, was empirically determined (see *Methods*). Functional changes larger than this reference are considered to be significant. Arrows indicate the central sulcus.

sensory volley[22,23] in various levels of the central nervous system, including the frontoparietal cortex.

The functional MRI scan obtained in our patient showed two different expressions of the abnormal cortical control of the right hand movements: an enhancement of the contralateral primary and premotor cortex activation with movements of the right hand and an excessive activation of the ipsilateral precentral cortex and putamen with movements of the left hand. Both findings can be the result of a loss of the normal tonic inhibitory influence of sensory inputs on the motor system. Such defective inhibition can be the consequence of the lesion our patient showed in the ascending tracts of the cervical cord. Release of motor system activity may lead to pseudoathetotic movements, which would become more evident during nonselective activation of the brain, such as with stress, mental tasks, or preparation for performing voluntary movements.

In our patient, manipulative movements of objects could be a behavioral consequence of severe deafferentation. This behavior is similar to that shown by patients with frontal lobe lesions and is thought to be an extension of the grasping response. Monkeys with frontal cortical lesions show facilitation of tactile and visually directed palpatory reactions in the hands and lips, such as instinctive grasping and sucking reactions.[24] L'hermitte[25] proposed that utilization behavior is the result of an imbalance between impaired frontal and intact parietal lobe processes. In our patient, the functional MRI scan showed an

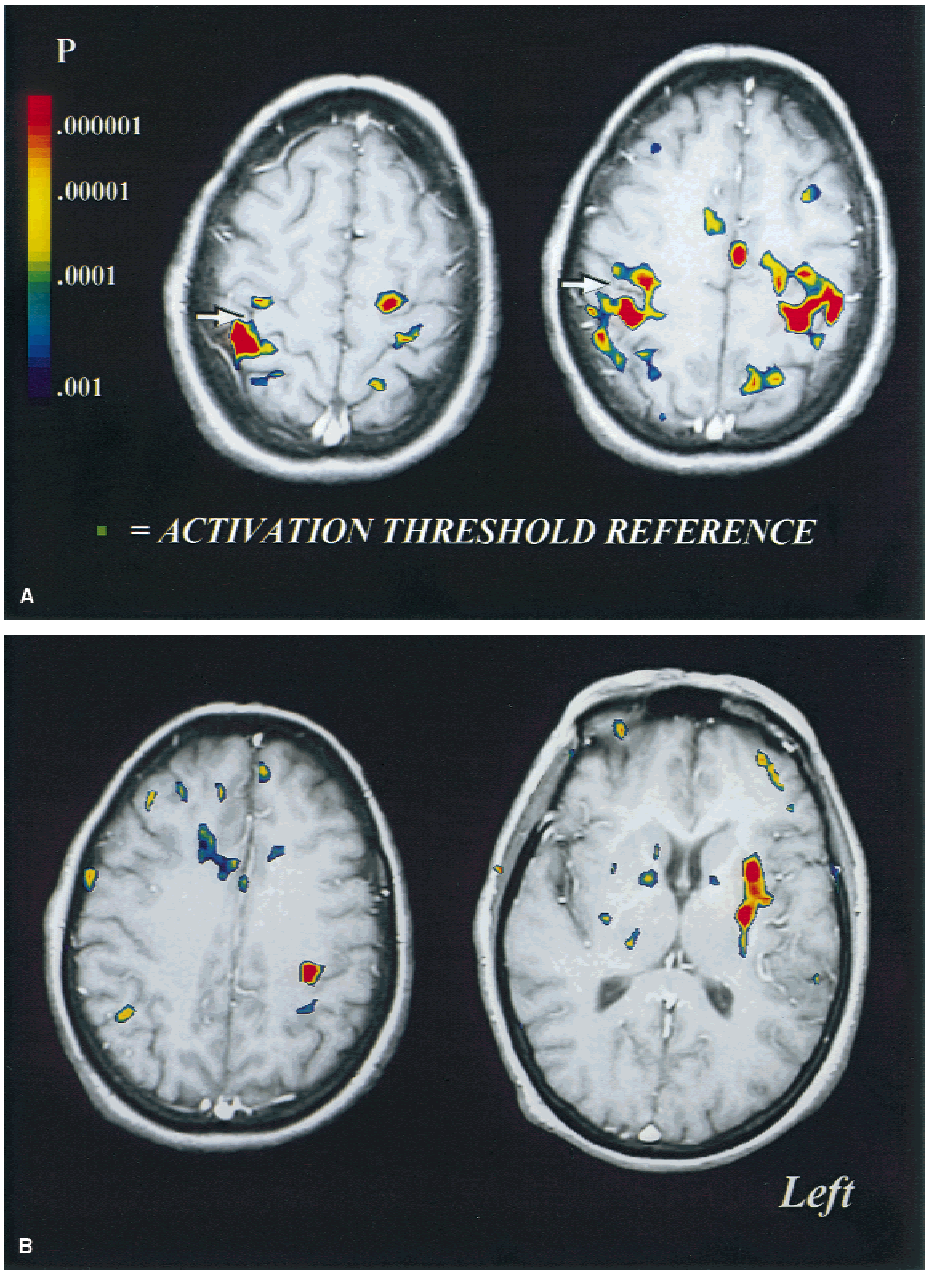

FIG. 3. Functional changes observed during the simple motor task done with the normal left hand, a situation that notably increased right hand pseudoathetosis. Bilateral activation was observed, although changes contralateral to the dyskinetic movement were more evident than changes contralateral to the voluntarily activated left hand. Functional images are *t* test statistical maps. Reference p values are attached to the color-coded scale. The activation threshold reference was empirically determined (see *Methods*). Arrows indicate the central sulcus.

abnormal hyperactivity of the frontal lobe, suggesting frontal lobe disinhibition. We interpret that, in our patient, a parallelism can be assumed between athetotic dyskinesia and utilization behavior and that this phenomenon can be better explained as a release of stimulus-driven frontal behavior, normally modulated by subcortical structures and inputs from the parietal and inferomesial frontal cortices. Abnormal spontaneous movements and exploratory behavior have been reported in association with frontal lobe disinhibition in parietal lobe lesions,[26] thalamic infarcts,[27] and lesions of the frontal–subcortical circuits.[28] Release of frontal lobe activity, as a consequence of severe sensory loss in patients with lesions at different levels of the sensory pathway, may contribute to the clinical presentation of certain abnormal movements and motor behavior.

Legends to the Videotape

Segment 1: The patient is shown in two sessions with pseudoathetotic movements at rest. In the first session, the patient is seated and shows spontaneous movements in her right hand. The patient is asked to close her eyes, count backwards, and perform movements of the thumb to finger opposition. The movements performed with the right hand are clumsy and performing simple movements with her left hand induced a dys-

tonic posture in the right hand. In the second session, the patient first lies with her hands over her belly and shows clear spontaneous movements of which she is unaware. The patient has difficulty in buttoning and unbuttoning and shows increased involuntary movements with postural activity.

Segment 2: In the first session, the patient is seated in front of a table with four objects on it. She is instructed to hold one of them and return it to the same place, which is done with great difficulty; the object falls to the floor twice. She is asked to take a specific key from a bunch and imitate opening a lock. She does this once with her left hand and several times with her right hand. In the second session, the patient is seated in front of a desk while holding a pen with her right hand and trying to write. She was instructed to write her name, and she did so with great difficulty, spontaneously repeating the maneuver three times. She then took off and put on the top of the pen several times while holding the pen with her right hand. When she was finished with the pen, she took a measuring tape placed inadvertently in her visual field and played with it for a while.

Jesús Pujol, MD
CETIR
Centro de Resonancia Magnética de Barcelona

Joan Monells, MD
Department of Neurophysiology
Centre Hospitalari de Manresa

Eduard Tolosa, MD
Department of Neurology
Hospital Clinic de Barcelona
Barcelona, Spain

Josep M. Soler-Insa, MD
Department of Neurology
Centre Hospitalari de Manresa

Josep Valls-Solé, MD
Department of Neurology
Hospital Clinic de Barcelona
Barcelona, Spain

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Hyperekplexia in the First Year of Life

Hyperekplexia, or startle disease, is a rare autosomal-dominant neurologic disorder characterized by generalized

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Address correspondence and reprint requests to Marina A. J. de Koning-Tijssen, MD, PhD, Department of Neurology H2-222, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands.

stiffness during the first years of life, excessive startle with unexpected stimuli from birth, and short periods of generalized stiffness after the startle reflex. This momentary stiffness causes severe falls during standing and walking because it is impossible to stretch out the arms.[1] Tapping on the nose induces an exaggerated head retraction reflex in most patients.[1] Tendon reflexes are normal or slightly increased without clear evidence of a pyramidal syndrome.[1] Clonazepam may provide symptomatic relief.[2] The syndrome was described in detail in a large Dutch family in 1966,[1] and several reports have subsequently been published.[2–11]

Genetic studies identified mutations in the gene encoding the α1 subunit of the glycine receptor (*GLRA1*) on chromosome 5 in patients with the autosomal dominant form of hyperekplexia.[12–17] Occasionally, an autosomal recessive inheritance pattern or compound heterozygosity have been described.[18–20] Besides families with the hereditary form of hyperekplexia, several sporadic cases have been described.[3,6,9,10,21–25] Frequently, in the sporadic patients, no mutation can be detected in the *GLRA1* gene.[13,15,16,24] Most of these patients had additional abnormalities not encountered in or essential for the diagnosis hereditary hyperekplexia. Several associated features have been mentioned in newborns and adults with hyperekplexia that are not essential for the diagnosis. They include periodic limb movements in sleep and hypnagogic myoclonus,[3–5] inguinal, umbilical or epigastric herniations,[1,26,27] congenital dislocations of the hip,[9] epilepsy,[1,6] feeding and breathing problems,[10,28] and sudden infant death.[1,28] The most striking features of hyperekplexia in adulthood are the excessive startle responses and the stiffness related to the startle response. The intensity of these phenomena may increase because of emotional tension, nervousness, fatigue, and even the expectation of being frightened.[1] Conversely, holding objects or drinking alcohol may reduce the occurrence of the startle responses.[1] The frequency of startle responses varies considerably, not only between subjects, but also over the course of time.

The aim of this report is to show the clinical features typical of hereditary hyperekplexia in infancy. Hyperekplexia is a rare disorder, and the knowledge of the clinical picture probably restricts the number of sporadic patients. The video recordings show the development of these features in two children from a large Dutch pedigree in the first 14 months of life.[1,14]

Case Reports

Patient 1

A 6-week-old girl was born at term. Directly after birth, she showed continuous generalized stiffness. The degree of stiffness increased markedly when the girl was handled and decreased during sleep. The parents described a temporary increase of muscle tone with unexpected loud noises. Occasionally, generalized jerks occurred when falling asleep.

The family history showed that her 7-year-old sister also showed remarkable startle responses and had generalized stiffness directly after birth. The mother had the same symptoms as a baby. The generalized stiffness disappeared during the first years of life, but excessive startle responses remained in the sister and mother. A short-lasting generalized stiffness occurred directly after the startle responses. This was severe enough to render the mother and sister unable to stretch out their arms to break a fall. Both fell regularly during childhood, and the mother fell occasionally during adulthood. They were both taking clonazepam. In the mother and other family members, genetic screening showed a point mutation in the *GLRA1* gene.[14]

On neurologic examination at the age of 6 weeks, the girl showed few spontaneous movements. She was stiff, and the stiffness increased with handling. It was difficult to elicit a startle response. Tapping on the nose induced an exaggerated head retraction reflex. Eliciting the Moro reflex resulted in a slight abduction of the arms immediately followed by flexion of the arms (video segment 1).

Patient 2

A girl was recorded at the ages of 2, 5, 10, and 14 months (video segments 2–5). She was born at term after an unremarkable pregnancy. Directly after birth, she was stiff. This stiffness increased with handling and disappeared during sleep. She did not have many startle responses, but when she did, they were pronounced and increased the stiffness. Her parents noted marked jerks mainly when falling asleep. When the patient grew older, the stiffness gradually decreased. Motor development proceeded normally, and she was able to sit at the age of 7 months and stood at the age of 9 months. She started walking with support at 10 months of age, and at 14 months, she was able to walk with her mother's assistance. She was not taking medication. Her parents felt no need to start medication because they were familiar with the disorder and were cautious of the side effects of clonazepam.

The family history showed that her father showed increased startle responses and had generalized stiffness directly after birth. The generalized stiffness disappeared in the first years of life, but excessive startle responses remained. A short-lasting generalized stiffness occurred directly after the startle responses. This was severe enough to render him unable to stretch out his arms to break a fall. He fell regularly during childhood, but rarely during adulthood. He was not taking medication. The father and other family members showed a point mutation in the *GLRA1* gene.[14]

On neurologic examination at the age of 2 months, the girl showed marked hypokinesia. The tone increased when handling and was mainly axial. If she was turned horizontally, she was as "stiff as a stick." It was difficult to elicit a startle response on examination. Eliciting the Moro reflex resulted in a minimal abduction directly followed by flexion of the arms. Her head retraction reflex was exaggerated and could be elicited several times. At the age of 5 months, she showed more spontaneous movement, although there was still hypokinesia and bradykinesia. The stiffness and excessive head retraction reflex were still noticeable. At 10 months of age, she was able to sit without support and showed increasingly more spontaneous movements. If both hands were held, she was able to make a few stiff-legged steps. When she was turned horizontally, the stiffness was less than that seen in previous visits. Her head retraction reflex was still exaggerated and could be elicited repetitively. At 14 months of age, she could walk with her mother's assistance. Her walking was slightly stiff-legged, as was her crawling. The tone was almost normal on examination. The head retraction reflex was still exaggerated.

Discussion

The most striking features of the two children with hereditary hyperekplexia are the generalized stiffness, marked hypokinesia, and exaggerated head retraction reflex. The stiffness is

illustrated by holding the child horizontal; she was "stiff as a stick." The stiffness increases with handling and disappears in sleep. As shown on the video, it gradually decreases during the first 14 months of life. The main differential diagnosis of a stiff newborn is postanoxic encephalopathy. In patients with hyperekplexia, however, no other signs of irritability are apparent. The hypokinesia is probably induced by the stiffness and decreases with a similar time course. Motor development was normal in the two patients. Delayed milestones have been described in hyperekplexia but catch up when the patients start walking.[1] The head retraction reflex was exaggerated in both children. In most patients, this reflex remains easy to elicit throughout life,[1] and it has been mentioned as a hallmark of hyperekplexia.[10] The video illustrates that startle reflexes are not the most impressive feature in newborns, and it is often difficult to elicit a startle response in a clinical situation.

Although generalized stiffness in newborns with hyperekplexia has been frequently observed, the pathophysiology has not been studied extensively. A good model for studying the stiffness is the spasmodic mouse (*spd*), which has a good phenotypical resemblance to human hyperekplexia and a similar genetic background with a recessive point mutation in the gene encoding the α1 subunit of the glycine receptor (*Glra1*) on chromosome 11.[29,30] Clinically, these mice have an exaggerated acoustic startle reflex, fine motor tremor, leg clasping, prolonged righting reflex, and stiffness. These *spd* mice are normal in the first 2 weeks of life and are most severely affected by the third to fifth weeks, with fewer symptoms in adulthood.[31,32] The appearance of symptoms in *spd* mice 2 or 3 weeks after birth are supposed to be related to the replacement of a neonatal type glycine receptor (two β subunits and three α2 subunits) with the adult type (two β subunits and three α1 subunits).[31,33–35] In contrast to mice, the stiffness in humans with hyperekplexia is apparent directly after birth. The expression of the α1 subunit glycine receptor (*GLRA1*) in humans probably starts before birth.

During the first years of life, the stiffness gradually decreases in humans with hyperekplexia and *spd* mice. This might be the result of a changed expression of isoforms of the α subunits of the glycine receptor but is more likely to be related to development of the central nervous system. The pyramidal tract projects largely to the la inhibitory interneurons in the spinal cord.[36] These interneurons are involved in reciprocal inhibition and prevent co-contraction of antagonistic muscles. During the first years of life, the influence of the pyramidal tract on the reciprocal inhibition is limited because myelination of the corticospinal tract in humans starts in late gestation and is complete at approximately 2 years of age.[37] In adult patients with hyperekplexia, impaired transmission in glycinergic reciprocal inhibitory pathways in the spinal cord has been detected.[38] This lack of inhibition of co-contraction may account for the generalized stiffness in newborns. We hypothesize that the gradual diminution of stiffness in patients with hyperekplexia during the first years of life is related to the gradually increasing amount of corticospinal influence caused by myelination of the spinal tract.

In conclusion, although hyperekplexia is derived from the Greek word Εκ-ληω (i.e., to startle excessively),[1] the generalized stiffness, hypokinesia, and excessive head retraction reflexes are more reliable features to make the diagnosis in newborns.

Legends to the Videotape

Segment 1: Patient 1, at 6 weeks of age, shows marked hypokinesia and a generalized stiffness. The head retraction reflex is exaggerated. The Moro reflex results in a slight abduction of the arms immediately followed by flexion of the arms.

Segment 2: Patient 2, at 2 months of age, shows hypokinesia. When turned horizontally she is as "stiff as a stick." The Moro reflex is similar to patient 1 (segment 1). Her head retraction reflex is exaggerated.

Segment 3: Patient 2, at 5 months of age, shows more spontaneous movement as compared with her condition at the age of 2 months, but the generalized stiffness is still noticeable. The head retraction reflex remains excessive.

Segment 4: Patient 2, at 10 months of age, sits without support. She shows more spontaneous movements, and she makes a few stiff-legged steps with support. Turned horizontally, she is no longer as "stiff as a stick." Her head retraction reflex is still exaggerated.

Segment 5: Patient 2, at 14 months of age, walks slightly stiff-legged with support. The crawling is almost normal. The head retraction reflex is exaggerated.

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Marina A. J. Koning-Tijssen, MD, PhD
Department of Neurology
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

O. F. Brouwer, MD, PhD
Department of Child Neurology
Leiden University Medical Center
Leiden, The Netherlands

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Persistence of Rhythmic Movement Disorder Beyond Childhood: A Videotape Demonstration

Rhythmic movement disorder (RMD) is a sleep-wake transition parasomnia and includes head banging, head rolling, body rocking, and, less frequently, body rolling, leg banging, and leg rolling. It is defined as a group of stereotyped, repetitive movements of 0.5 to 2 Hz involving the head and neck, or large muscle groups, that usually occur immediately before sleep onset and are sustained in all sleep stages.[1–5] Its onset is typically within the first 2 years of life and ends spontaneously at the age of 2 to 5, with the prevalence being 6% by 5 years of age.[1,2] The etiology is still unknown. Numerous treatments have been proposed: drug therapy with clonazepam, benzodiazepines, tricyclic antidepressants, and L-dopa, or relaxation techniques and psychotherapy. In one case, hypnosis has been reported as effective.[6–8] There have been anecdotal reports of RMD disappearing after changing from a conventional bed to a waterbed.[9] Usually there is no need for treatment except reassurance. There are only a few reports on RMD persisting until adulthood.[4–8,10] The presentation of RMD is mostly seen just by chance as a result of observations by the bed partners.

We report two healthy boys aged 15 and 18 years and another 59-year-old woman with RMD at sleep onset. The two boys came to our sleep laboratory for exclusion of nocturnal epileptic seizures. In the other case, the RMD was perceived by chance as a result of observations by the bed partner. A videopolysomnography was carried out in all three cases. In all three patients no psychiatric disease was present. No patient had parasomnia and treatment was not requested.

A videotape accompanies this article.

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Address correspondence and reprint requests to Svenja Happe, MD, Department of Neurology, University of Münster, 48129 Münster, Germany.

Case Reports

Case No. 1

A 15-year-old healthy boy was admitted to our sleep laboratory for exclusion of epilepsy. He suffered from head banging while lying in bed in the prone position with repeatedly striking his forehead against the pillow until he fell asleep. This happened almost nightly since early childhood. The boy grew up in a children's home. When presenting to our sleep laboratory his educators thought he might have epilepsy. Magnetic resonance imaging (MRI) scan of the brain, psychiatric exploration, and electroencephalography (EEG) were normal. Video-polysomnography showed typical RMD with head banging and rhythmic vocalizations in the prone position. The episode lasted approximately 1 minute during presleep drowsiness; he then entered sleep stage 1. He was happy to learn that he did not have epilepsy and no therapy was required.

Case No. 2

An 18-year-old healthy young man was admitted to our sleep laboratory for exclusion of nocturnal epileptic seizures. Since early childhood, he reported "rolling" in bed for up to 1 hour before falling asleep. Clinical examination, MRI scan of the brain, and EEG were all normal. A psychiatric consultation excluded a severe psychiatric disease; only a mild form of neuroticism was seen. In the video-polysomnography, a 45-minute period of body rolling during presleep drowsiness and sleep stages 1 and 2 could be seen. Movements consisted of lateral rotations of approximately 90° with rolling along the medial axis of the body. One arm was folded around the neck and seemed to drive the body motion while the other arm was stretched perpendicular to the body, resting on the bed. Again, no other treatment was required other than reassurance of the disorder's harmlessness.

Case No. 3

A 59-year-old woman came to the hospital because of residual cognitive impairment and vertigo after having herpes simplex-encephalitis 1 year earlier. The roommates observed her "rolling" in bed during the night. MRI scan of the brain showed bilateral temporal lesions secondary to previous herpes simplex-encephalitis. Clinical and psychiatric examination and EEG were normal; neuropsychologic evaluation revealed cognitive impairment and attention deficit. Cerebrospinal fluid showed local IgG synthesis and positive oligoclonal bands; otherwise it was normal, including PCR of HSV-DNA. Video-polysomnography showed body rolling for approximately 15 minutes during presleep drowsiness and approximately 4 minutes during a period of nocturnal wakefulness almost identical to the pattern in case no. 2. The patient told us that she was unaware of the movements while falling asleep but that her relatives told her about having had them when she was a young girl. Actually, she did not complain about the rhythmic movements and no treatment was requested.

Discussion

Three cases of a RMD parasomnia are described. All of our patients presented at an older age than usually seen in this disorder. Typically, the onset of RMD is within the first 2 years of life. It stops spontaneously at the age of 2 to 5.[1,2] When the disorder persists into adolescence or adulthood, it has mostly been reported to be associated with autism, mental retardation, or other significant pathology.[1,5] Although one of our patients (case no. 3) has had herpes simplex-encephalitis, the RMD was already known before, when she was a young girl. Therefore, in this patient persisting RMD since early childhood seems to be the correct diagnosis. On no occasion was an EEG abnormality appreciated immediately before, after, or during an event in all three cases, as epilepsy is seen to be one of the differential diagnoses.

During the last 2 years, we examined two other persons with suspicion of RMD in our sleep laboratory. The first one was a 28-year-old healthy man showing rhythmic rolling of the right leg stretched perpendicular to the body lying in the left position during presleep drowsiness and sleep stages 1 to 3. Because this leg rolling might have been a form of periodic leg movement disorder, the diagnosis of RMD could not be established. The other case was a 30-year-old man with HIV infection and additional neuroborreliosis. He showed intermittent RMD with body rolling. Because his bed partner had told him about having it before the diagnosis of HIV infection and neuroborreliosis, he might represent another example of persistent RMD.

We think RMD is a form of NREM-parasomnia persisting into adulthood without significant psychiatric or neurologic pathology more often than previously recognized. To our knowledge, this is the first videotape demonstration of two healthy adolescents and one adult with persistence of RMD beyond childhood. In most cases, persons with RMD do not have any complaints, and the presentation is observed by chance or not at all. Generally treatment is unnecessary because the affected individuals are not impaired by their parasomnia. For exclusion of epilepsy in the two boys and for evaluation of the herpes simplex-encephalitis in the 59-year-old woman, we carried out various non-polysomnographic evaluations. However, no expensive evaluation (such as computed tomography, MRI, PET, or SPECT) is indicated in uncomplicated cases as video-polysomnography is the only practical technique to diagnose RMD.[3]

Legends to the Videotape

Segment 1, Case no. 1: Typical head banging with rhythmic vocalizations while lying in bed in the prone position with repeatedly striking his forehead against the pillow. The shown episode lasted for approximately 1 minute during presleep drowsiness. He then entered sleep stage 1.

Segment 2, Case no. 2: Sequence of a 45-minute period of body rolling during presleep drowsiness and sleep stages 1 and 2. Movements consisted of lateral rotations of approximately 90° with rolling along the medial axis of the body. One arm was folded around the neck and seemed to drive the body motion while the other arm was stretched perpendicular to the body, resting on the bed.

Segment 3, Case no. 3: Sequence of body rolling for approximately 4 minutes during a period of nocturnal wakefulness almost identical to the pattern in case no. 2.

Svenja Happe, MD
Peter Lüdemann, MD
E. Bernd Ringelstein, MD
Department of Neurology
University of Münster
Münster, Germany

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Friedreich Ataxia Associated With Dystonic Head Tremor Provoked by Prolonged Exercise

The association of dystonia with Friedreich ataxia is uncommon.[1] This report describes a young man with clinically proven Friedreich ataxia who had fixed rotational torticollis with a superimposed dystonic head tremor that could be induced by prolonged exercise in the form of cycling. These unusual features have been documented by video. This case may represent a link between the heredo-familial spinocerebellar ataxias and paroxysmal exercise-induced dystonia. There has been only one previous case report of similar nature.[2]

Case Report

This 28-year-old man is one of the two brothers affected by Friedreich ataxia. He experienced paroxysmal jerky head tremor induced by cycling. The patient was first seen approximately 8 years ago with a 2-year history of gait ataxia. Detailed clinical and laboratory investigations confirmed the diagnosis of Friedreich ataxia. He had gait ataxia, limb uncoordination, dysarthria, Rombergism, generalized areflexia, and extensor plantar responses with mild rotational torticollis toward the right side. He was found to have cardiomyopathy on echocardiography and frank diabetes mellitus. Nerve conduction studies showed an absence of sensory nerve action potentials in the sural nerves. An axial computed tomography scan of the head showed mild cerebellar atrophy. Results of a radiologic examination of the cervical spine were normal. Genetic testing of the Friedreich ataxia gene was not performed.

Because the gait ataxia was disabling, the patient took to cycling to attend his work. This required approximately 15 minutes of pedalling in each direction daily. He experienced jerky head tremor that would appear after approximately 5 minutes of pedalling. It would subside approximately 5 minutes after alighting from the cycle. Thus, he experienced such paroxysms lasting approximately 15 minutes two or three times a day. They were not precipitated by sudden movement, loud noise, mental strain, tea, coffee, eating after a period of fasting, or exposure to cold. They did not occur in sleep. The patient never drank alcohol and had no history of neuroleptic drug intake.

Such paroxysms could be precipitated during his hospital stay by making him pedal a stationary bicycle. The abnormal movements were documented by video. They consisted of jerky "no-no" tremor of the head dominantly toward the right side (see *Videotape*). He experienced no pain and could speak easily. Surface electromyographic studies using the left sternocleidomastoid and right splenius capitis showed bursts of muscle activity lasting 250 to 300 milliseconds with a frequency of 2.0 to 2.5 Hz. Results of ictal and interictal electroencephalography were normal. Such movements could not be suppressed by touching or pressing the occipital region, neck, or chin. They could not be precipitated by passive movement of any part of the body or by application of a 128-Hz vibrator to the neck. There was no concomitant worsening of the ataxia. The patient's brother, who is also affected by Friedreich ataxia, did not show such movement disorders on examination.

Trial of treatment was given using levodopa–carbidopa (125 mg three times a day), trihexyphenidyl (up to 20 mg a day), and propranolol (80 mg a day) with no improvement. Each drug was tried separately for a minimum of 4 weeks.

Discussion

This young man had clinical and electrophysiologic findings diagnostic of Friedreich ataxia. They confirm the criteria suggested by Geoffroy et al.[3] and Harding.[4] He also had cardiomyopathy and diabetes mellitus, which are less common but well-recognized accompaniments of this disorder. The unusual features in this patient included the presence of a fixed rotational torticollis and a superimposed head tremor that appeared only after cycling for approximately 5 minutes (see *Videotape*). Further discussion is focused on this unusual observation.

The fixed rotational torticollis observed in our patient is obviously a secondary torticollis in view of its association with the ataxic syndrome. Clinical and radiologic evaluation ruled out craniovertebral anomalies, spinal cord disorders such as syringomyelia and tumor, posterior fossa tumors, vestibular and ocular disorders as causes for the torticollis. The patient had no history of neuroleptic drug intake or features of psychogenic torticollis. The association of torticollis with Friedreich ataxia is extremely uncommon. A Medline search for this combination covering a period of 15 years (1984–1998) did not show any such published association. Anecdotal evidence and sketchy reports of the occurrence of dystonia musculoram deformans associated with Friedreich ataxia are mentioned in the early literature.[1]

A videotape accompanies this article.

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Address correspondence and reprint requests to G. M. Wali, Department of Neurology, K.L.E. Society's Hospital and Medical Research Centre, Belgaum 590 010, Karnataka State, India.

The occurrence of tremor in association with dystonia is not uncommon. The tremor in such cases could be of the dystonic type or essential type. Deuschl and Krack[5] suggested the following criteria for the diagnosis of dystonic tremor: tremor in an extremity or body part affected by dystonia, focal tremor with an irregular amplitude and variable frequency mostly less than 7 Hz, and postural and kinetic tremor usually not seen with complete rest. With these criteria, our patient can be considered to have dystonic tremor of the head. In a related study, Rivest and Marsden[6] recognized that trunk and head tremor could occur as isolated manifestations of idiopathic dystonia.

The other notable feature in our patient is the appearance of the dystonic head tremor only after prolonged exercise in the form of cycling. Such paroxysmal behavior is a feature of paroxysmal dystonias.[7] This group of dystonias is further classified based on the nature of the provoking factors and includes paroxysmal dystonic choreoathetosis, paroxysmal kinesigenic choreoathetosis, and paroxysmal exercise-induced dystonias. Rare cases of paroxysmal dystonic head tremor have also been described.[8,9] The patient cannot be considered as having a case of paroxysmal dystonia because he had a fixed rotational tortocollis in between the attacks of dystonic head tremor. This patient may represent a link between the heredo-familial spinocerebellar ataxias and paroxysmal exercise induced dystonia. A similar case has been reported by Mayeux and Fahn.[2] Their patient had paroxysmal dystonic choreoathetosis-associated familial ataxia. His brother was similarly affected but had rare paroxysmal episodes. Genetic linkage studies of such cases may help clear such relationships.

The pathophysiology of dystonic head tremors is not clear. In reference to spasmodic torticollis, the studies of Berardelli et al.[10] and Tolosa et al.[11] using blink reflex studies have shown that there is increased brainstem interneuron hyperexcitability. The cause of this abnormality is interpreted as excessive drive, possibly from the basal ganglia, on the polysynaptic pathways in the lateral reticular formation. A similar mechanism may be operative in our patient.

Legend to the Videotape

This 28-year-old man with clinically diagnosed Friedreich ataxia has mild fixed rotational torticollis to the right side. There are no involuntary movements at rest. The involuntary movements of the head appear after approximately 5 minutes of cycling. They are characterized as a jerky slow-frequency dystonic tremor of the head in the "no-no" direction. The movement subsides spontaneously within 5 minutes of concluding the exercise.

Dr. G. M. Wali
Department of Neurology
Jawaharlal Nehru Medical College
K.L.E. Society's Hospital and Medical Research Centre
Belgaum, India

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