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Clinical/Scientific Notes

Meta-analysis of Polymorphism of the Catechol-O-Methyltransferase Gene in Relation to the Etiology of Parkinson's Disease in Japan

Although the precise pathogenesis of Parkinson's disease (PD) remains unknown, free radicals could contribute to the selective loss of nigral dopaminergic neurons.[1] In dopamine metabolism, free radicals are formed by monoamine oxidase (MAO) and autooxidation, but not by catechol-O-methyltransferase (COMT).[2] Therefore, low-activity COMT might increase MAO and autooxidation rate, thereby acting as a risk factor for PD. COMT activity is determined by two codominant alleles; Val-108 (soluble)/158 (membrane-bound) allele and Met-108/158 allele are responsible for expression of thermostable high-activity allele (H) and thermolabile low-activity allele (L), respectively.[3–5] In whites, the distribution ratio of H/H, H/L, and L/L is approximately 25:50:25. This ratio does not differ between patients with PD and control subjects. Thus, the level of COMT activity does not seem to be a genetic risk factor for PD in whites.[6,7]

In contrast, a recent study in a Japanese population showed a significant increase in L/L genotype frequency in PD.[8] However, according to another Japanese study, it was H/H frequency that increases significantly in PD.[9] We evaluated these contradictory findings by power calculation. An odds ratio of 2.75 for PD with L/L shown by Kunugi et al.[8] was lower than the significant odds ratio of 3.3, which would yield 80% power in their center (Table 1). Similarly, an odds ratio of 1.66 for PD with H/H shown by Yoritaka et al.[9] was also lower than the significant odds ratio of 1.84 (Table 1). Therefore, the sample numbers might not be large enough to infer an increase of L/L or H/H in PD in the centers with a power of 80%. This weakness could be dissolved by the meta-analysis.

We have reexamined COMT polymorphism in 171 Japanese patients meeting the criteria for idiopathic PD[10] and 199 Japanese control subjects. The patients (aged 66.0 ± 8.0; onset, 58.0 ± 9.8 yrs; disease duration, 8.0 ± 4.9 yrs) had been under treatment at the neurological clinic of Utano National Hospital. Of the 199 control subjects (aged 67.5 ± 11.7 yrs), 73 subjects were volunteers enrolled at the Hyogo Institute for Aging Brain and Cognitive Disorders (HI-ABCD) for PET study from the community.[11] The remaining 126 control subjects were from the HI-ABCD-established population for the study of sex differences.[12] According to the informed consent, genomic DNA was extracted from whole blood and used for COMT genotyping by the PCR-RFLP method, as described previously.[6] No significant difference was found between patients with PD and control subjects in the COMT polymorphism distribution ($\chi^2 = 1.18$, df = 2, $p = 0.554$). Significant odds ratios for L/L (2.3) and H/H (1.82) were lower than the previous two studies, but no association between L/L or H/H and PD was found (Table 1).

In the meta-analysis, the cumulative frequency of the COMT polymorphism showed no significant difference between patients with PD and control subjects ($\chi^2 = 5.30$, df = 2, $p = 0.071$). Significant odds ratios for L/L and H/H were lower than all the previous studies. However, again cumulative odds ratios showed no association between L/L or H/H and PD (Table 1). Thus, the level of COMT activity does not seem to be a genetic

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TABLE 1. *The distribution of COMT polymorphism in patients with Parkinson's disease and control subjects in Japan*

	Genotype frequency (%)				Odds ratio (95% CI)		*Power calculation	
	No.	H/H	H/L	L/L	L/L	H/H	L/L	H/H
Kunugi et al.[8]								
Parkinson	109	46 (42)	47 (43)	16 (15)	2.75 (1.17–6.49)	0.78 (0.48–1.28)	3.3	2.13
Controls	153	74 (48)	70 (46)	9 (6)	p = 0.017	p = 0.324		
Yoritaka et al.[9]								
Parkinson	176	100 (56.8)	62 (35.2)	14 (8.0)	1.26 (0.54–2.93)	1.66 (1.08–2.56)	2.74	1.84
Controls	156	69 (44.2)	77 (49.4)	10 (6.4)	p = 0.588	p = 0.022		
Present study								
Parkinson	171	85 (49.7)	71 (41.5)	15 (8.8)	0.82 (0.41–1.64)	1.25 (0.83–1.88)	2.3	1.82
Controls	199	88 (44.2)	90 (45.2)	21 (10.6)	p = 0.564	p = 0.292		
Total								
Parkinson	456	231 (50.6)	180 (39.5)	45 (9.9)	1.28 (0.82–2.00)	1.13 (0.88–1.46)	1.82	1.45
Controls	508	231 (45.5)	237 (46.6)	40 (7.9)	p = 0.276	p = 0.329		

COMT, catechol-O-methyltransferase; CI, confidence interval.
H and L represent high (Val-108/158) and low (Met-108/158) activity allele of the COMT gene, respectively.
* Significant odds ratio which could be detected with 80% power and 95% confidence was calculated from sample numbers and control L/L or H/H frequency in each study.

risk factor for PD in the Japanese population, consistent with previous reports in whites[6,7] and the Chinese population.[13]

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Is There Addiction to Levodopa in Patients With Parkinson's Disease?

In the advanced stages of Parkinson's disease (PD), many patients with response fluctuations are totally dependent on the success of single doses of levodopa for short-term regain of motor function.[1] Such patients have to take their levodopa at regular times. They impatiently wait for ignition of "on" after an oral dose of levodopa, feel the need to take the next dose when the effect of the previous one has worn off, and can no longer skip doses. Although such phenomena are reminiscent of addiction, patients with PD are generally not regarded as being addicted to levodopa. Their compulsive use of the drug is considered merely an urge to overcome their incapacitating motor signs and symptoms and not a psychologic craving phenomenon.

The following case strongly supports the possibility that there may be true addiction to levodopa in patients with PD.

Case Report

This 78-year-old patient had PD for 18 years. After an initial excellent response to levodopa lasting approximately 4 years, he developed dyskinesias and later motor response fluctuations, including "wearing off," "delayed on," and "no-on" phenomena, all of which became progressively worse and extremely disabling. When in "off," he was rigid and totally unable to move. When a dose of levodopa was successful, he regained free mobility but this was associated with violent dyskinesias involving the face, limbs, and trunk lasting almost throughout the "on" period. He was maintained on 0.5 to 1 tablet 250/25 mg levodopa/carbidopa given eight times per day, a tablet of controlled-release sinemet taken at night, and 5 mg jumex (deprenyl) once in the morning, with temporary additions of amantadine and various dopamine agonists. Approximately 15 days after a brief febrile illness, probably the result of a viral infection, the patient developed ascending paralysis that progressed in severity over a period of 72 hours. The neurologic findings on admission were complete flaccid quadriplegia, absent tendon reflexes, bilateral plantar extensor responses, loss of urinary sphincter control, and normal cognition, sensation, and cranial nerves. Based on the clinical phenomena, cerebrospinal fluid (increased protein levels, no cells), and electrophysiological findings, he was diagnosed as having acute in-

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flammatory demyelinating radiculoneuropathy (Guillain-Barré syndrome) with some myelopathic involvement. He was treated with a course of intravenous immunoglobulins and was maintained on his regular levodopa regimen. The other antiparkinsonian drugs were discontinued. There was no improvement in his neurologic condition and he remained incontinent, fully paralyzed in his upper and lower limbs, and bedridden. He could move his head, speak, chew, and swallow normally. The patient was transferred to a nursing home after 6 weeks of hospitalization.

Despite the fact that he was quadriplegic and permanently immobile, the patient continued to demand his levodopa doses regularly at 2-hour intervals during waking hours and claimed he could not do without them. During many observations carried out during hospitalization and later at the nursing home, after a levodopa dose was administered, there was no visible "on," that is, an effect on motor function in the trunk and limbs which remained paralyzed. There were dyskinesias involving only the facial muscles, indicating that the ingested levodopa dose reached its central nervous system target. When attempts were made to reduce the number of daily levodopa doses or totally skip occasional days of treatment with the drug, the patient was in extreme anguish associated with unexplained fear, agitation, palpitations, hyperventilation, excessive perspiration, lacrimation, and nose discharge. A prolonged similar reaction occurred in the nursing home when levodopa was discontinued for 48 hours as a result of visual hallucinations and paranoid delusions. These probable withdrawal phenomena readily disappeared after going back to the regular daily levodopa dosage schedule. There were, however, occasional daily doses, particularly in the afternoon, that failed to relieve these phenomena, probably representing "no-on" (dose failure) equivalents. The patient claimed that a successful dose of levodopa gave him "an internal relaxation and relief like a tranquilizer or a painkiller." This beneficial effect would typically start after approximately 30 minutes and last for 1.5 to 2 hours, similar to the time parameters of a levodopa dose-associated motor action that he typically had before his paralyzing illness. The patient remained paralyzed and continued to receive his regular levodopa treatment for an additional 3 years until his sudden death which was attributed to cardiac arrest.

Discussion

We think our patient was indeed addicted to levodopa. He had PD with motor fluctuations and depended on response to multiple daily levodopa doses to transiently overcome his incapacitating immobility. He continued to require his regular levodopa regimen and could not do without it, despite the fact that he became completely and irreversibly quadriplegic as a result of acute inflammatory radiculomyelopathy. Levodopa doses no longer produced an identifiable "on" (except for facial dyskinesias). Nevertheless, attempts to discontinue levodopa, or even to reduce the number of daily doses, were associated with psychologic as well as physical withdrawal phenomena. These included fear, anguish, agitation, palpitations, sweats, increased lacrimation, nose discharge, all of which rapidly abated when an oral dose of levodopa was successful. These phenomena were similar to panic attacks that are frequently experienced by patients with PD.[2] The causes of these attacks are not entirely clear. In fluctuating parkinsonians, many of these panic episodes are time-linked to their "off" periods. It is undetermined whether they exactly coincide with, follow, or even precede the "off" event.[3] In most patients, the "off"-linked panic attacks subside when a motor "on" is induced by a dose of levodopa. One possibility is that "off" panic simply occurs in reaction to PD symptoms taking over. Another explanation is that there is a decline in dopamine produced from levodopa not only in the striatum, but also in other structures, for example, the limbic system. Alternatively, panic attacks may represent withdrawal phenomena resulting from recurrent depletions of levodopa and the formed dopamine in mesolimbic regions such as the nucleus accumbens. There are several additional phenomena suggesting addiction to levodopa in patients with fluctuating PD. They feel the need to take doses of levodopa regularly, are unable to skip doses, and cannot tolerate long "drug holidays."[4] In addition, some patients increase their daily levodopa dose to achieve euphoria and do not mind the resultant side effects such as enhanced dyskinesias.[5] There are few additional case descriptions of levodopa and apomorphine dependence or abuse.[6–9] It is our experience that occasional patients give exaggerated descriptions of their poor motor status to get their neurologists to prescribe more levodopa.

Dopamine plays a key role in reward signaling and addiction.[10] In particular, the nigromesolimbic dopaminergic pathway has been implicated in the addictive properties of many drugs of abuse, including cocaine, heroin, amphetamine, alcohol, and nicotine.[11] These agents are known to increase extracellular dopamine levels in the nucleus accumbens, in part through blockade of the specific dopamine reuptake channels.[12] Levodopa works in PD by being decarboxylated to dopamine in the striatum, thus replenishing the reduced neurotransmitter levels.[13] Exogenous levodopa also increases dopamine levels in mesolimbic regions such as the nucleus accumbens.[14] This may be one of the mechanisms responsible for addiction to, and dependence on, levodopa in some patients with PD. This phenomenon may not be uncommon, and studies should be conducted to estimate its prevalence in PD.

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The Use of NMDA Antagonist Memantine in Drug-Resistant Dyskinesias Resulting From L-Dopa

The mechanism of L-dopa-induced dyskinesias is still unclear. An overactivity of NMDA-mediated glutamatergic transmission in the striatum was implicated in the pathophysiology.[1]

Memantine is an amandatine derivative which acts as a noncompetitive NMDA receptor antagonist.[2,3] Memantine has been described to enhance the efficacy of L-dopa in Parkinson's disease and was shown to reduce parkinsonian symptoms including motor fluctuations.[4,5]

We report the significant response to memantine in a young patient with Parkinson's disease and severe dyskinesias resistant to other pharmacologic interventions.

Case Report

This 35-year-old man had young-onset Parkinson's disease for 14 years. Treatment with L-dopa was effective for the first 8 years, but the efficacy decreased gradually despite high doses. Wearing-off phenomenon developed, followed by peak-dose dyskinesias and fluctuations. A right-sided pallidotomy was performed 2 years before, improving dyskinesias and fluctuations on the left side, but off-phase dystonia of both feet soon developed and right-sided as well as axial dyskinesias continued. The peak-dose dyskinesias were ballistic and so violent that activities of daily living were almost impossible. During on-phase, total Unified Parkinson's Disease Rating Scale (UPDRS) score (parts 1, 2, and 3) was 60, motor score (part 3) was 41, on-phase dyskinesia score (items 32, 33, and 34 of UPDRS part 4) was 8, and off-phase Hoehn-Yahr[6] score was 5. Eating was difficult and the patient was losing weight. L-Dopa was reduced to 150 mg per day, treatment with high-dose (60 mg per day) bromocriptine was introduced with limited success and clozapine was added. There was again limited improvement, but this did not ameliorate activities of daily living significantly. One and half years after the beginning of treatment with clozapine, NMDA antagonist memantine (3 × 10 mg per day) was initiated, and significant improvement was observed with substantial decrease of on-phase dyskinesias and motor fluctuations. Off-phase dystonias did not change to a notable extent. The total UPDRS on-phase score (parts 1, 2, and 3) decreased to 48, on-phase motor score (part 3) to 31, on-phase dyskinesia score (items 32, 33, and 34 of UPDRS part 4) to 1, and off-phase Hoehn-Yahr score to 4. At that time he was receiving 150 mg L-dopa per day), 60 mg bromocriptine per day, 175 mg clozapine per day, and no MAO-B or COMT inhibitors. The dose of memantine was increased to 3 × 20 mg per day to further improve the motor performance, but no additional benefit was obtained. The patient tolerated memantine well and no side affects were observed. Following the decrease in dyskinesias, L-dopa was increased to 500 mg per day to improve off-phase disability without causing an increase in dyskinesias. The improvement observed lasted more than 1.5 years, albeit with some return of dyskinesias (items 32, 33, and 34 of UPDRS part 4: 4) but not to the extent as before treatment.

Discussion

This observation is in line with previous experimental and clinical findings that NMDA antagonists can reduce L-dopa-induced dyskinesias. The mechanism of L-dopa dyskinesias is still unclear. An increase in NMDA-mediated glutamatergic transmission in striatum resulting from upregulation of NMDA receptors as a consequence of chronic intermittent L-dopa therapy was implicated as the underlying pathophysiological mechanism.[1]

In MPTP monkeys, NMDA antagonists have been shown to decrease L-dopa-induced dyskinesias.[1] Drugs that antagonize NMDA receptors, like amantadine,[7,8] dextromethorphan,[9] and its metabolite dextrorphan,[10] have been previously reported to be beneficial in the treatment of L-dopa-induced dyskinesias. Memantine has recently been recognized as an NMDA antagonist, and its antiparkinsonian effect was suggested to be mediated through NMDA receptor antagonism,[2,3] although the drug has also been reported to enhance dopaminergic activity[11] and exert some anticholinergic activity, which may contribute to its antiparkinsonian effects.[12]

In the earliest reports of memantine treatment in Parkinson's disease, 12 patients were intravenously administered memantine resulting in a decrease in tremor and rigidity.[13] Rabey et al. reported the use of oral memantine in 14 cases with L-dopa-induced motor fluctuations.[5] Ten patients showed improvement and memantine was discontinued in four cases as a result of side effects like abdominal pain, psychomotor agitation, confusion, and dizziness. Schneider et al. reported a multicenter, placebo-controlled trial using memantine in 67 patients with Parkinson's disease. Memantine was shown to be effective in decreasing tremor and was suggested as monotherapy or adjunct therapy in mild and early cases.[4] The potential neuroprotective effects of memantine have been shown to be more pronounced than those of amantadine in in vitro studies.[14–16] In

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animals, memantine is also better tolerated compared with amantadine or other NMDA receptor antagonists.[15]

An important aspect of the case presented here was the significant improvement in life-threatening dyskinesias along with a decrease in on–off fluctuations. Considering its additional dopaminergic effect, putative neuroprotective potential, and low side effect profile, we suggest that memantine may be an important potential drug for the symptomatic treatment of PD and treatment of L-dopa-induced complications.

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Cerebrotendinous Xanthomatosis With Predominant Parkinsonian Syndrome: Further Confirmation of the Clinical Heterogeneity

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal-recessive neurometabolic disorder with wide clinical and molecular heterogeneity. The phenotype includes juvenile cataract, usually the presenting symptom, Achilles tendon xanthomas, mental deterioration leading to dementia, pyramidal signs, cerebellar ataxia, peripheral neuropathy, and premature atherosclerosis.[1] Subclinical muscle involvement has also been reported.[2] CTX is associated with mutations of the CYP27 gene which encodes for mitochondrial sterol 27-hydroxylase, an enzyme that catalyzes the oxidation of sterol intermediates during bile acid synthesis.[3–8] As a result of the enzymatic defect, patients with CTX have a reduced synthesis of bile acids, in particular chenodeoxycholic acid, and excessive formation and accumulation of cholestanol in plasma and tissues.[9] An early diagnosis of CTX is crucial because long-term therapy with chenodeoxycholic acid (CDCA) reverses biochemical abnormalities and prevents neurologic deterioration.[1]

We present the case of a 52-year-old Italian patient with an unusual neurologic presentation of parkinsonism and evidence of a missense mutation of the CYP27 gene.

Case Report

The patient is a 52-year-old man, the son of unrelated parents. His younger sister, who died at the age of 48 years, is reported to have had CTX with predominant cerebellar manifestations. Since childhood the patient was noted to have mild mental retardation with poor school performance. At the age of 10, he underwent bilateral cataract extraction. At the age of 35 years, gait disturbances with slowness of movements and frequent falls were noted as well as swelling of the Achilles tendons. A few years later, tremor of the right hand developed. Parkinson's disease was diagnosed and the patient was treated with L-dopa. Slight clinical improvement for a few years was followed by progressive deterioration of motor disability and cognitive functions. CTX was not diagnosed until the age of 45 years, and was confirmed by elevated serum cholestanol levels

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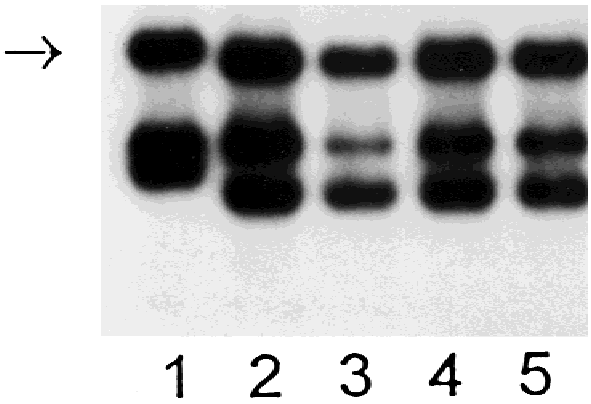

FIG. 1. SSCP analysis of exon 2 of CYP27 gene. Lane 1: the proband; lanes 2–5: control subjects. The arrow indicates the abnormal migration pattern.

(2.0 mg/100 mL; normal value ≤0.1). Treatment with 750 mg chenodeoxycholic acid per day was recommended.

The patient first presented to us at the age of 52 years. Clinical examination revealed a poorly expressive, seborrheic face, and xanthomas of the Achilles tendons. Neurologic evaluation showed monotonous and dysarthric speech, occasional dysphagia, bradykinesia, rigidity, prominent right arm resting tremor, hyperactive deep tendon reflexes (more prominent on the right side), and extensor plantar response. Gait was slow and spastic with small steps. Psychologic examination revealed a global impairment of attention, memory, and intelligence.

Laboratory evaluation included lactic acid (1.5 mmoles/L; normal 0.3–1.3), pyruvic acid (0.09 mmoles/L; normal 0.03–0.08), and cholestanol (0.58 mg/100 mL, under CDCA therapy). Serum cholesterol, carnitine, vitamin E, and thyroid enzymes were in the normal range. Electrocardiography was normal. Transthoracic echocardiography showed the presence of lipomatous hypertrophy of the interatrial septum. Electromyography and nerve conduction velocities were normal. Moderately prolonged I–III and I–V interpeak latencies of brainstem auditory evoked potentials (EPs) and delayed N9 to N13 interpeak latencies for arm somatosensosry EPs were found. Visual EPs were delayed and temporally dispersed. Electroencephalogram showed irregular, diffuse slow activity. Brain magnetic resonance image (MRI) showed diffuse cerebral, cerebellar, and callosal atrophy. T2-weighted sequences showed a focal hyperintense lesion in the right cerebellar hemisphere, near the dentate nuclei, probably the result of demyelination. No signal alterations of the basal nuclei were observed.

Molecular Genetic Analysis

Southern Blot Analysis

Genomic DNA extracted from peripheral leukocytes was digested using 5–10 U/μg DNA of several restriction enzymes (BamHI, EcoRI, SacI, HindIII, and KnpI), separated by agarose gel electrophoresis, transferred to nylon membranes, and hybridized with sterol 27-hydroxylase cDNA probe, as previously described.[7]

Single-Strand Conformation Polymorphism (SSCP)

SSCP was performed according to Orita et al.[10] The promoter region and all exons of CYP27 gene were amplified by PCR from genomic DNA using the primers reported previously by Leitersdorf et al.[11] PCR conditions were as previously described.[7]

Sequencing of Genomic DNA

The sequence of exon 2 (SSCP-positive PCR fragment) was performed using the following oligonucleotide: 5′ TGG CCC AGT TAT TCA GTT TTG ATT G 3′ (2A).[11]

Results

After Southern blotting and hybridization with the full-size sterol 27-hydroxylase cDNA, no major rearrangement of the CYP27 gene was detected. However, SSCP analysis revealed an abnormal migration pattern of exon 2, indicating a mutation in this exon (Fig. 1). Direct sequencing revealed that the patient was homozygote for a G→A transition in exon 2 (nucleotide 401 of the cDNA), a mutation causing a glutamine for arginine substitution (R94Q; Fig. 2). No additional sequence changes were found in the other exons of the gene.

Discussion

The CTX patient reported here had peculiar clinical and molecular genetic features. The neurologic presentation was atypical because of the predominance of extrapyramidal manifestations. This led to misdiagnosis and a delay in starting treatment with CDCA, which prevents neurologic deterioration. The clinical presentation was not really that of typical idiopathic Parkinson's disease, but rather a "parkinsonism-plus" syndrome with early age of onset, gait disturbances, corticospinal tract signs, cognitive abnormalities, and suboptimal response to levodopa. To our knowledge, a female Japanese patient has been the only case in which parkinsonism was reported as presenting neurologic symptoms, but no molecular characterization was performed.[12] Like in our patient, MRI did not detect any basal ganglia or midbrain abnormalities. Minor extrapyramidal signs have also been reported by Rogelet et

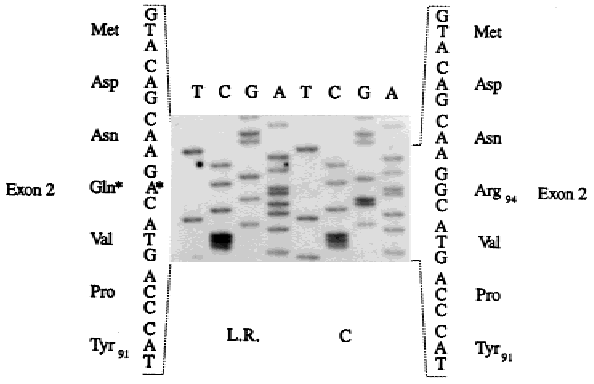

FIG. 2. Nucleotide sequence of exon 2 of CYP27 gene in the proband (L.R.) and in a control subject (C). The proband is homozygous for a G←A transition at nucleotide 125 of exon 2 (R94Q).

al.[13] and Fiorelli et al.[14] The latter also found MRI abnormalities in the basal nuclei. Another unusual finding in this CTX phenotype was the presence of lipomatous hypertrophy of the atrial septum, a rare cardiologic abnormality recently described in several CTX patients,[15] probably resulting from cholestanol accumulation in the interatrial septum. The mild increase in serum lactic and pyruvic acid levels we found pointed to abnormalities of mitochondrial metabolism, already described in other CTX cases and partially reversed by CDCA therapy.[2,16]

Molecular genetic study showed that our patient was homozygote for a G→A transition in exon 2, a mutation causing a glutamine for arginine substitution. The same mutation R94Q has been previously reported, only in one allele, in a CTX patient who was a compound heterozygote.[17] We have not found other molecular changes in the CYP27 gene of our patient. This is a further indication of the possible role of R94Q as the cause of CTX. By replacing a positively charged amino acid with a neutral one of a smaller size, this mutation may alter the proper folding of the protein and affect either its intracellular translocation or its biologic activity. Arginine in position 94 is located within a stretch of amino acids which is 100% conserved in human, rabbit, and rat CYP27 cDNA.[18–20] It is close to arginine in position 104, which is thought to interact with a heme propionate group.[21] The mutation found in this patient involves a CpG dinucleotide, which is regarded as a hot spot for mutations in several human genetic diseases.[22] It is of interest that of the 26 mutations reported up to now in CTX patients, 12 involve CpG dinucleotides, with a frequency of 46% that appears to be higher than that reported in the literature (35%).[22]

In conclusion, this new case confirms the wide clinical and molecular heterogeneity of CTX and suggests that atypical early-onset parkinsonism should be checked as a possible manifestation of this rare neurometabolic disorder.

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Clinical and Genetic Study of Familial Essential Tremor in an Isolate of Northern Tajikistan

Essential tremor (ET) is the most common adult movement disorder with an age-specific prevalence ranging between 0.4% and 6.7% among people over 40 years of age and reaching the peak of as high as 8% to 13% in the eighth and ninth decades.[1–3] The disease is characterized primarily by bilateral postural tremor of the arms that may be present also during action; less frequently, tremor of the head, lips, voice, trunk, and legs may be observed.[4,5] A slow progression and generalization of tremor may result in significant disability in a proportion of patients with ET, especially with advancing age and increasing duration of the disease.[5]

Genetic studies of ET are highly complicated because of the existence of numerous phenocopies and difficulties in establishing strict diagnostic criteria for this condition. Familial forms are thought to represent approximately half of all cases of ET,[4,6,7] and a model of autosomal-dominant inheritance with a high age-dependent penetrance has been generally accepted for familial ET.[3,5] The occasional occurrence of ET in families with Parkinson's disease, dystonia, and peripheral neuropathy,[8–11] as well as the presence of anticipation in some families with "pure" ET,[5] further complicate the problem of genetic mechanisms of familial ET. Linkage of families with ET to the idiopathic torsion dystonia locus on chromosome 9q32-34 was definitely excluded by several groups.[12,13] Recently, two genetic loci for "pure" familial ET have been reported. In one study, a locus on chromosome 3q13 (designated as FET1) was identified through a genome-wide scan of a group of families from Iceland.[14] Another locus, ETM, was mapped to chromosome 2p22-25 in four large American families,[15,16] and a repeat expansion detection analysis in one of these families suggested the presence of an expanded CAG repeat in affected individuals.[15] We report the results of genetic studies of ET in a set of families from an isolate of Northern Tajikistan and demonstrate further genetic heterogeneity of familial ET with the existence of at least one more, as yet unidentified, locus in a single large pedigree.

Methods

Family Studies

We examined five families with ET residing in a relatively isolated mountainous village of Northern Tajikistan. Visual inspection of the pedigrees (Fig. 1) suggests a clear autosomal-dominant mode of transmission of the trait. The severity of tremor in family members was assessed as mild (<2-cm excursions), moderate (2- to 4-cm excursions), or coarse (>4 cm, disabling); the additional assessment of hand tremor was performed using the drawing of the "Archimed spiral." The criteria for "definite" ET in family members were as follows:

1. Presence of persistent bilateral postural tremor, with or without a kinetic component, involving the hands and the forearms. In the case of isolated hand tremor, only patients with coarse or moderate tremor were considered affected. Alternatively, patients exhibiting mild postural hand tremor in combination with tremor in other part of the body (that is, head tremor, voice tremor) were also considered affected.
2. Slowly progressive course of the disease.
3. Absence of muscle tone abnormalities (such as rigidity, dystonia), postural disturbances, dementia, or other signs of multiple system involvement.
4. Absence of recent exposure to tremorigenic agents (endocrine abnormalities, alcohol, and so on).

The present conservative criteria are consistent with those used by other researchers[3,15] and provide, in our opinion, a reliable tool for selecting patients with "definite" ET for the purpose of linkage studies. According to these diagnostic criteria, 19 patients from the families under study were considered affected.

Genotyping and Linkage Analyses

Blood samples were collected with informed consent from 38 individuals, including 19 affected persons. Genomic DNA was isolated by standard procedures.[17] The five families were first typed for markers D2S131 and D2S224 on chromosome 2p22-25 and for markers D3S3529, D3S3620, and D3S1267 on chromosome 3q13; seven additional markers on chromosome 3q13 (D3S3652, D3S1278, D3S1558, D3S1303, D3S3515, D3S3576, and D3S3720) were subsequently analyzed in all families except *ET-1*. Genotyping was performed using an automated ABI Prism 377 DNA Sequencer and the GeneScan Analysis Software (Applied Biosystems, Foster City, CA, USA). Pairwise and multipoint linkage analyses were performed using, respectively, the MLINK and LINKMAP programs of the FASTLINK package (version 2.2). In the linkage calculations, we used a model of autosomal-dominant inheritance with age-dependent penetrance (four liability classes were established through analysis of the cumulative age at onset curve in the affected persons). A mutant gene frequency of 0.005, a phenocopy rate of 0.01, and equal marker allele frequencies were assumed. Alternative models for linkage analysis with variable disease allele frequencies (0.01–0.02) and phenocopy rates (0.001–0.03) modified only slightly the maximum LOD score values.

Results

The age of patients with "definite" ET at examination was 39.3 ± 14.8 years (mean ± standard deviation), varying from 20 to 72 years, and the age at onset of the disease was 20.0 ± 13.8 years (7–55 yrs). In family *ET-1*, there was marked anticipation with strikingly younger onset of tremor in generation III (10–20 yrs) compared with generation II (40–55 yrs). Interestingly, in this same family we observed unusually severe and highly disabling hand tremor in patients II-2 and II-3 from the older generation, so that both patients needed permanent and significant assistance in their daily activities. The ages at onset of tremor in different generations did not differ significantly in families *ET-2*, *ET-3*, *ET-4*, and *ET-5*.

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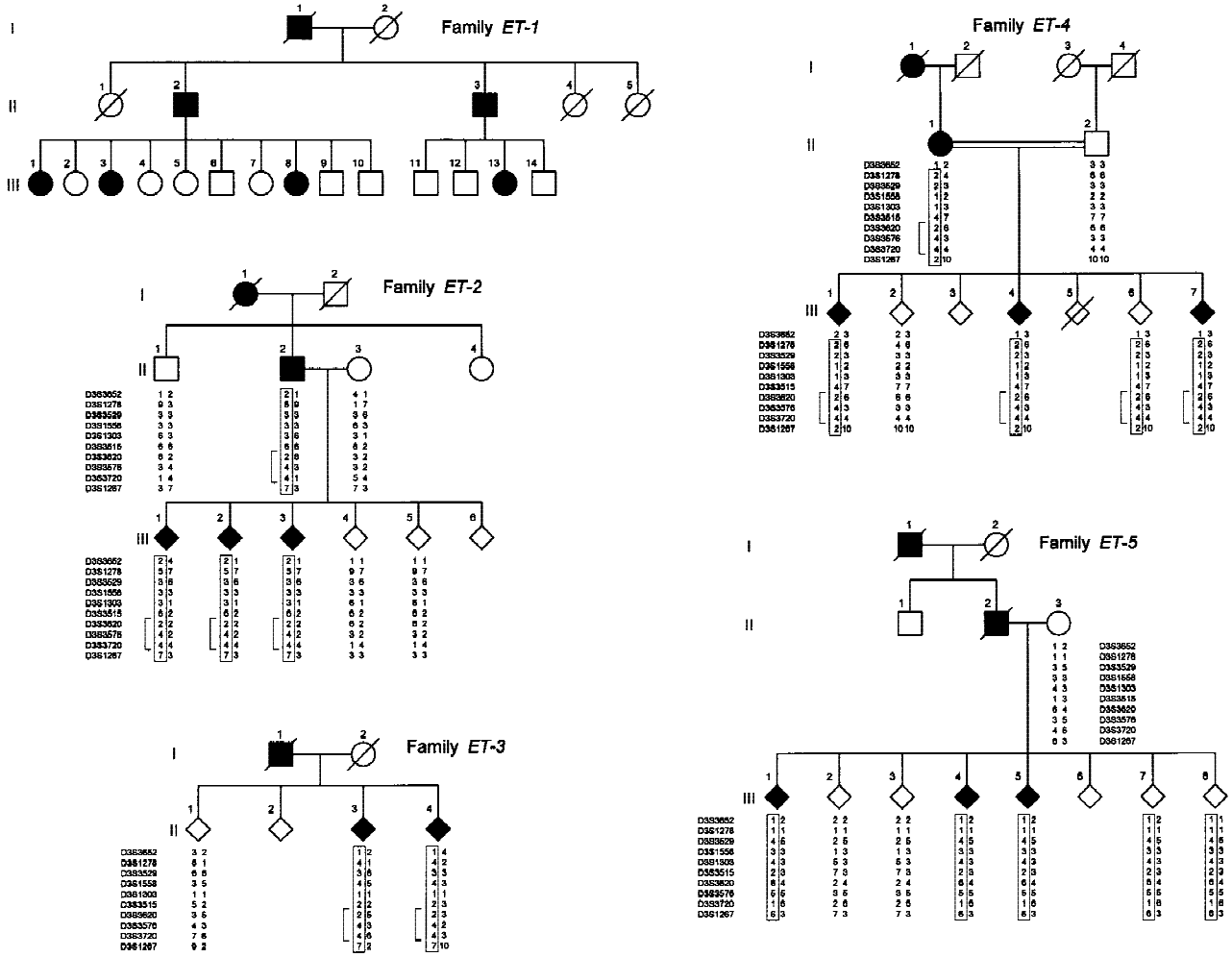

FIG. 1. Pedigrees of the families with ET and results of haplotype analysis in the 3q-linked families. In the lower generation of each of the 3q-linked families, changes have been made in the birth order to protect the identity of the haplotyped individuals. Squares indicate males; circles, females; diamonds, sex not declared. Black symbols indicate affected individuals; open symbols, clinically unaffected; slashed symbols, deceased. "Affected" haplotype in each family is boxed; a common haplotype segregating with the disease in the three families is indicated by brackets.

Results of pairwise linkage analysis with the marker loci from the candidate regions on chromosomes 2p22-25 and 3q13 in the largest pedigree *ET-1* are shown in Table 1. We obtained significantly negative pairwise LOD scores for markers from both candidate regions. These findings allow exclusion of linkage between a disease-causing gene and both loci for ET studied in family *ET-1*.

In the other four families, we observed consistently negative LOD scores for loci at 2p22-25 (data not shown), whereas the data for loci at 3q13 were suggestive of linkage to chromosome 3. Detailed results of linkage analysis with 10 polymorphic markers spanning the 20-cM candidate region at 3q13 are shown in Table 2. Because the LOD scores for particular markers depend to some extent on their informativity in each family, we used the entire haplotypes as single markers in the linkage calculations (see Fig. 1 and Table 2). Such an approach gave a maximum combined LOD score of 2.46 at a recombination fraction (δ) of 0.00. Results of multipoint linkage analysis confirmed the likely placement of a mutant gene at 3q13 with a maximum combined LOD score of 3.35 achieved at the position of marker D3S3515 (data not shown).

In families *ET-2*, *ET-3*, and *ET-4* we observed a common haplotype encompassing three markers (D3S3620, D3S3576, and D3S3720) and co-segregating with the disease in affected members (see Fig. 1).

TABLE 1. *Pairwise LOD scores in family* ET-1

Marker locus	Recombination fraction					
	0.00	0.01	0.05	0.10	0.20	0.30
D3S3529	−6.31	−2.50	−1.16	−0.60	−0.15	0.00
D3S3620	−4.82	−2.88	−1.52	−0.92	−0.38	−0.14
D3S1267	−6.78	−3.08	−1.66	−1.03	−0.43	−0.16
D2S131	−1.34	−1.11	−0.68	−0.42	−0.16	−0.06
D2S224	−6.67	−3.10	−1.68	−1.05	−0.44	−0.16

LOD, logarithm of the odds.

TABLE 2. *Pairwise LOD scores in families* ET-2, ET-3, ET-4, *and* ET-5 *for chromosome 3q markers*

		Recombination fraction							
Locus	Family	0.00	0.01	0.05	0.10	0.20	0.30	Z_{max}	θ_{max}
D3S3652	ET-2	0.51	0.51	0.50	0.47	0.36	0.22		
	ET-3	−1.36	−1.08	−0.64	−0.41	−0.18	−0.07		
	ET-4	−0.22	−0.21	−0.16	−0.11	−0.04	−0.01		
	ET-5	0.29	0.28	0.25	0.20	0.13	0.06		
	Combined	−0.78	−0.50	−0.05	0.15	0.27	0.20	0.27	0.20
D3S1278	ET-2	1.12	1.09	0.99	0.85	0.58	0.31		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.05	0.05	0.04	0.03	0.01	0.00		
	ET-5	0.29	0.28	0.25	0.20	0.13	0.06		
	Combined	2.05	2.00	1.81	1.55	1.05	0.55	2.05	0.00
D3S3529	ET-2	−0.50	−0.46	−0.35	−0.25	−0.12	−0.05		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.07	0.09	0.16	0.21	0.21	0.15		
	ET-5	0.29	0.28	0.25	0.20	0.13	0.06		
	Combined	0.45	0.49	0.59	0.63	0.55	0.34	0.63	0.00
D3S1558	ET-2	−0.50	−0.46	−0.35	−0.25	−0.12	−0.05		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.18	0.19	0.23	0.26	0.24	0.16		
	ET-5	0.12	0.11	0.10	0.08	0.05	0.02		
	Combined	0.39	0.42	0.51	0.56	0.50	0.31	0.56	0.10
D3S1303	ET-2	0.37	0.38	0.41	0.41	0.34	0.21		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.41	0.41	0.41	0.38	0.30	0.19		
	ET-5	0.00	0.00	0.00	0.00	0.00	0.00		
	Combined	1.37	1.37	1.35	1.26	0.97	0.58	1.37	0.00
D3S3515	ET-2	−0.52	−0.48	−0.36	−0.26	−0.13	−0.05		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.46	0.46	0.44	0.41	0.32	0.19		
	ET-5	0.29	0.28	0.25	0.20	0.13	0.06		
	Combined	0.82	0.84	0.86	0.82	0.65	0.38	0.86	0.05
D3S3620	ET-2	0.61	0.61	0.57	0.52	0.39	0.22		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.24	0.25	0.27	0.29	0.26	0.17		
	ET-5	0.12	0.11	0.10	0.08	0.05	0.02		
	Combined	1.56	1.55	1.47	1.36	1.03	0.59	1.56	0.00
D3S3576	ET-2	0.51	0.51	0.50	0.47	0.36	0.22		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.02	0.02	0.01	0.01	0.01	0.00		
	ET-5	0.29	0.28	0.25	0.20	0.13	0.06		
	Combined	1.41	1.39	1.29	1.15	0.83	0.46	1.41	0.00
D3S3720	ET-2	0.43	0.44	0.45	0.44	0.35	0.21		
	ET-3	0.00	0.00	0.00	0.00	0.00	0.00		
	ET-4	0.75	0.74	0.69	0.62	0.45	0.25		
	ET-5	0.29	0.28	0.25	0.20	0.13	0.06		
	Combined	1.47	1.46	1.39	1.26	0.93	0.52	1.47	0.00
D3S1267	ET-2	−0.18	−0.17	−0.13	−0.10	−0.05	−0.02		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.37	0.37	0.37	0.36	0.29	0.18		
	ET-5	0.29	0.28	0.25	0.20	0.13	0.06		
	Combined	1.07	1.06	1.02	0.93	0.70	0.40	1.07	0.00
Haplotype	ET-2	1.12	1.09	0.99	0.85	0.58	0.31		
	ET-3	0.59	0.58	0.53	0.47	0.33	0.18		
	ET-4	0.46	0.46	0.44	0.41	0.32	0.19		
	ET-5	0.29	0.28	0.25	0.20	0.13	0.06		
	Combined	2.46	2.41	2.21	1.93	1.36	0.74	2.46	0.00

Discussion

We demonstrated genetic heterogeneity of familial ET in a small isolate in Northern Tajikistan. In one large family we definitely excluded both known loci on chromosomes 2p and 3q. These findings provide direct evidence for the existence of another, as yet unidentified, genetic locus associated with familial ET. Interestingly, this particular phenotype of familial ET is characterized by strikingly severe tremor and marked anticipation, which suggests the possible causative role of unstable trinucleotide repeat expansion in the pathogenesis of the disorder.

In a subset of families, we obtained reasonably high positive cumulative LOD scores with chromosome 3q markers, although not reaching the significant threshold of +3. Identification of a common haplotype in three of these families, apparently resulting from a founder effect, may serve as additional important evidence for linkage to chromosome 3. This common haplotype, not observed in the tested married-in individuals, covers a 2-cM region at 3q13 and favors the location of a mutant gene in the candidate region between markers D3S3620 and D3S3720, which is in good agreement with the position of the FET1 locus identified by Gulcher et al.[14]

As one may see on Figure 1, three clinically unaffected individuals from two families (III-6 in family *ET-4* and III-7 and III-8 in family *ET-5*) were found to carry haplotypes segregating with the disease. Because these individuals are the younger siblings in their nuclear families, the lack of evident tremor in these cases may be explained, most probably, by an age-dependent penetrance of the disease.[5]

The present population is an important source for clarifying molecular basis of familial ET. Extension of the pedigree *ET-1* could make it possible to perform a genome-wide search aimed at identifying a novel locus of familial ET. Taking into account a probable founder effect in the inbred population under study, further haplotype analysis in additional 3q-linked families would eventually allow narrowing of the candidate interval on chromosome 3q13, which is an essential requirement for cloning of a causative gene.

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Bilateral Striatal Necrosis Associated With *Mycoplasma pneumoniae* Infection in an Adolescent: Clinical and Neuroradiologic Follow Up

Bilateral striatal necrosis is usually the result of toxic or metabolic diseases, but infectious or post-infectious causes have also been recognized even though, in most cases, the etiology remains unknown.[1] Isolated reports describe an association with *Mycoplasma pneumoniae* infection.[2–5]

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We describe the case of a 17-year-old boy presenting with acute onset, a reversible akinetic-rigid syndrome, and magnetic resonance imaging (MRI) evidence of bilateral striatal necrosis associated with a *M. pneumoniae* infection.

Case Report

A previously healthy 17-year-old boy experienced a febrile illness with cough, abdominal pains, and vomiting lasting 3 days. During the next 4 days, he showed a progressive slowing of movements, sialorrhea, and dysarthria and was therefore referred to our hospital. On admission he was alert and afebrile, but chest auscultation revealed bilateral rhonchi. Neurologic examination revealed severe hypomimia, dysarthria, and bradykinesia with axial and limb rigidity. Eye movements were normal, and there were no pyramidal tract signs or involuntary movements.

Routine laboratory tests, including red and white blood cell counts, ESR, liver and renal function tests, glucose, serum electrolytes, PT, and PTT were all normal. Cerebrospinal fluid analysis revealed 11 lymphocytes and normal levels of glucose and protein.

A computed tomography (CT) scan on the first day showed diffuse hypodensity of the basal ganglia. The MRI, performed soon afterward, revealed swelling and prolonged T1 and T2 relaxation specifically in the striata bilaterally; there was no contrast enhancement after administration of gadolinium-DTPA e.v. (Fig. 1).

Chest x-ray was compatible with atypical interstitial pneumonia. The electroencephalogram showed normal background activity and generalized paroxysmal slow waves with a pseudoperiodic frequency.

Previous exposure to drugs or toxins was ruled out by the boy's parents. Metabolic diseases were excluded on the basis of normal levels of serum and cerebrospinal fluid lactate, and normal urinary organic and amino acid excretion. Serum ceruloplasmin and copper, and urinary copper excretion were also normal. Other investigations, such as funduscopic examination, visual, brain stem and somatosensory evoked potential studies, electromyography, and nerve conduction velocity studies all gave normal results.

Serologic tests for HIV, *Chlamydia pneumoniae*, and *Legionella pneumoniae* were all negative. The serum antimycoplasma antibody titer was 1:10240 (IgG and IgM). Treatment with erythromycin, rifampicin, and L-dopa combined with carbidopa was started. During the first week of treatment, oral dyskinesias and axial dystonic postures appeared; these disappeared after L-dopa dose reduction. L-Dopa was then gradually increased to 400 mg per day but withdrawn after 4 months.

The clinical course was characterized by initial spontaneous improvement of the patient's neurologic condition during the first 2 weeks, followed by a worsening of the symptoms with more severe bradykinesia and rigidity: the patient became almost unable to speak or swallow, and freezing phenomena were frequent and disabling. One month after the onset of symptoms, progressive improvement of the patient's neurologic condition was observed, which persisted after discontinuation of L-dopa treatment. After 4 months from the onset of symptoms, the neurologic examination showed only choreiform movements of the upper extremities and mild dystonic postures of the feet on walking, more evident on the right side; these neurologic signs had remained unchanged during the follow up at 20 months.

Follow-up MRI studies were performed 20 days, and 2, 3, 5, and 9 months (Fig. 2) after the onset of symptoms. The MRI performed at the 2-month follow up revealed a significant reduction of putamen and caudate nuclei size and an enlargement of lateral ventricles, mainly of the frontal horn. High intensity signal of these nuclei was still present, but the T2 relaxation time, as measured by T2 maps, had greatly decreased, from 240 msec to 140 msec. The MRI performed 3 months after onset demonstrated bilateral striatal atrophy with stabilized T2-weighted image hyperintensity, and these findings were confirmed on the last MRI 9 months after onset. At that time, a brain CT was also performed, which did not reveal calcification within the atrophic nuclei.

The patient underwent PET scanning with [^{18}F]fluorodeoxyglucose 19 months after the onset of symptoms. The qualitative analysis of the images demonstrated total absence of glucose metabolism in the putamen bilaterally and reduced metabolism

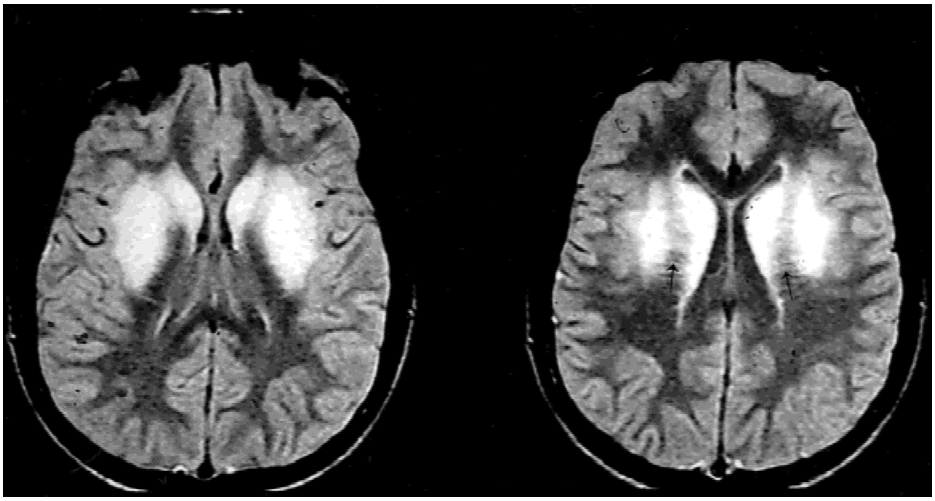

FIG. 1. Axial spin-echo images (TR: 2551, TE: 30) show marked swelling and abnormally increased signal intensity of the putamen and caudate nuclei bilaterally. The striatal cell bridges connecting the two nuclei (arrow) are also hyperintense.

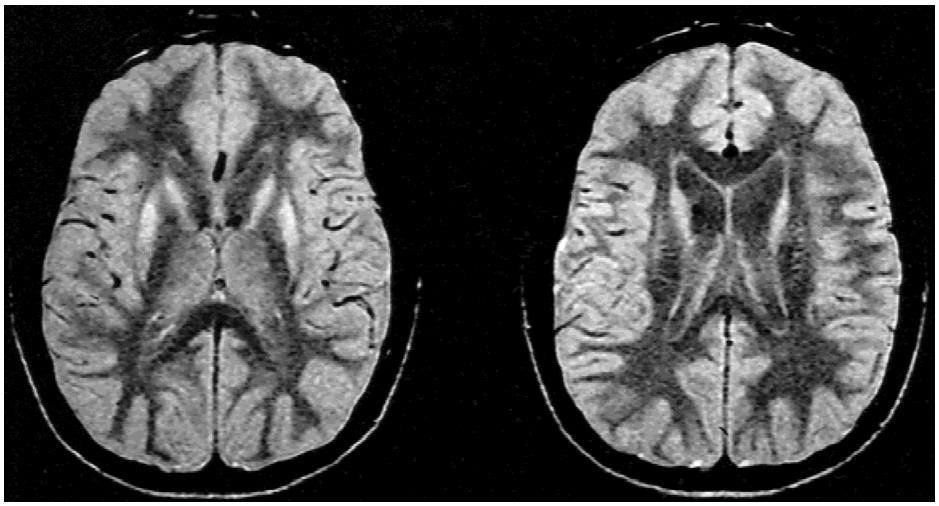

FIG. 2. Axial spin echo images (TR: 2551, TE: 30), performed 9 months later, show persisting high signal and atrophy with enlargement of lateral ventricles.

in the right frontal area, in the left cerebellar hemisphere, and in the temporo-parietal regions bilaterally (Fig. 3).

Discussion

Neurologic complications associated with *M. pneumoniae* infection are not rare and a wide range of disorders has been described.[6] The pathogenetic mechanism remains unclear; the most widely held theories suggest a possible neurotoxin-mediated injury, an immunologically mediated effect, or a direct invasion of the central nervous system.[7]

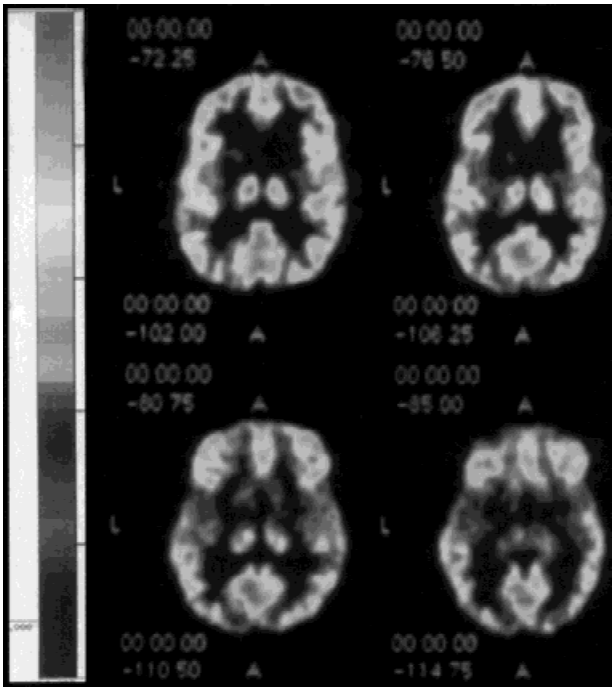

FIG. 3. PET images show total absence of glucose metabolism in the caudate and putamen nuclei bilaterally.

Four other cases, similar to our patient, with acute onset of extrapyramidal symptoms and MRI evidence of basal ganglia lesions, are reported in the literature.[2–5] In all these cases the presenting features were parkinsonism and/or dystonia, accompanied in three of them by seizures and impairment of consciousness. Despite the severity of the initial clinical presentation, all patients demonstrated progressive improvement with complete recovery or only minor residual neurologic deficit, mainly represented by dystonic or choreiform movements, over a period ranging from 1 month to 1 year. In all cases, MRI revealed selective involvement of the striata, except in the patient reported by Al Mateen et al.,[2] who had a clinical picture of encephalitis lethargica, and in which MRI also demonstrated involvement of the substantia nigra and pallidum. In one other patient, the lesions completely disappeared within 2 months.[4] The age and the severity of the symptoms at the onset did not seem to correlate with the radiologic outcome.

Our patient was 17 years of age, which suggests that this neurologic condition associated with *M. pneumoniae* infection is not restricted to children. We also observed that, unlike the reported cases, symptomatic therapy with L-dopa initially induced the severe side effects of oral dyskinesias and axial dystonic postures, and did not greatly influence the spontaneous course of the disease. The clinical course was characterized by three phases, as previously reported,[5] and the electroencephalography abnormalities reflected the following disease course. When the extrapyramidal symptoms worsened, diffuse slow waves were recorded. Notwithstanding the favorable clinical outcome, the radiologic findings in our patient indicate a severe dysfunction of the striatum and lends further support to the view that the radiologic data may not be useful in predicting the clinical course, which is self-limiting.

In conclusion, *M. pneumoniae* infection should be considered in all cases of acute onset of parkinsonism and dystonia

with radiologic evidence of bilateral striatal necrosis in children and young adults.

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Jaw-Opening Dystonia Presumably Caused by a Pontine Lesion

Jaw-opening dystonia (oromandibular dystonia with jaw opening) is a rare condition, and only a limited number of cases have been reported in the literature.[1–9] However, many patients may remain undiscovered or misdiagnosed, like the patient described in this report. The pathophysiology has remained enigmatic, but a peripheral cause has been suggested in some cases.[7,8] There are some inconsistencies regarding nomenclature as well. Gilbert[6] has suggested using the term Brueghel's syndrome[2] for jaw-opening dystonia without blepharospasm, whereas Meige's syndrome[10] should be used for blepharospasm with or without oromandibular dystonia (whether jaw-opening or, more often, jaw-closing). This article presents a patient with jaw-opening dystonia probably caused by a lesion in the pontine reticular formation.

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Case Report

A 71-year-old woman was referred because of involuntary jaw opening. There was no history of neurologic disease in the family, and no history of drug use or intoxication. Twenty-five years earlier, while cross-country skiing, her friends first noticed that she kept her mouth open all the time, despite a low air temperature. From then on she was unable to close her mouth except for a few seconds and with great effort. She managed to chew and talk only when she flexed her neck and supported her lower jaw with her hand. Despite this, she managed to continue working as a speech therapist until she retired at age 67. She had seen many doctors, and various diagnoses had been suggested, including hysteria, pareses of the masseters, and Huntington's chorea. Various symptomatic treatments, including clonazepam and levodopa, had been unsuccessful.

On examination, she had a rhythmic jaw-opening dystonia. The mouth was continuously wide open, but with a 4 to 5 Hz tremor of the jaw. There was conspicuous hypertrophy and rhythmic activity in the anterior belly of the digastric muscle on both sides but with a right-sided dominance. She also had mild involuntary movements in facial mimic muscles around the mouth. Neurologic examination was otherwise normal.

Standard blood tests were unremarkable. Electromyography (EMG) showed 5/sec rhythmic bursts in the anterior belly of the digastric muscle bilaterally but with higher amplitudes on the right side. Each burst lasted 0.12 to 0.14 seconds (Fig. 1). EMG from the masseter muscles showed poor recruitment, and the muscles appeared slightly atrophic. On attempted relaxation, small, irregular motor unit potentials were recorded. The orbicularis oris muscle showed normal recruitment. Rhythmic bursts were seen, but with lower amplitude and shorter duration than in the digastric muscle. Cerebral magnetic resonance imaging (MRI) was normal in T1W, T2W, and IVR images, whereas diffusion weighted images showed a lesion in the pontine reticular formation on the right side, presumably caused by a small, old infarction (Fig. 2).

The condition was diagnosed as a rhythmic dystonia. Botulinum toxin treatment was started. Initially, only the right digastric muscle was injected. However, because the left digastric muscle also showed marked dystonia, bilateral injections are now given. She receives injections with botulinum toxin A (23 U Botox; Allergan, Westport, Ireland) on each side every 3 months. The patient has been treated for 2 years with good

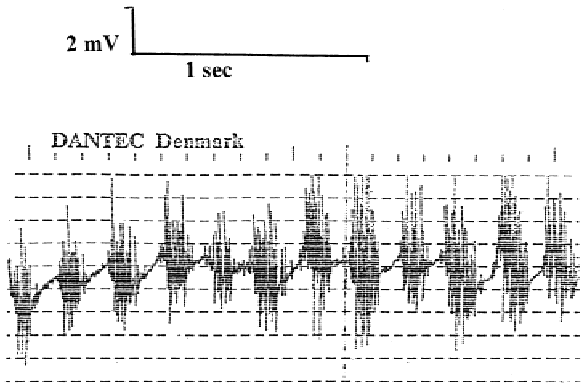

FIG. 1. EMG from the anterior belly of the right digastric muscle showing rhythmic dystonia.

symptomatic relief. She still has some degree of involuntary jaw opening and a slight tremor of the jaw, but she is able to keep her mouth closed for long periods of time without support. EMG from the anterior belly of the digastric muscle now shows small rhythmic muscle contractions of the same frequency, but with poor recruitment and low amplitude compared with before treatment.

Discussion

The EMG findings confirmed that bursts in the digastric muscles lasted for more than 100 msec. In accordance with the description by Rothwell,[11] the involuntary jaw opening and tremor in our patient is therefore classified as a rhythmic dystonia (or "myorhythmia").

Cerebral MRI in our patient showed a lesion, probably an old infarction, in the pontine reticular formation just outside the trigeminal motor nucleus. This nucleus innervates the anterior belly of the digastric muscle, which both clinically and electrophysiologically appeared to be the most active muscle. The jaw-opening dystonia in our patient started more than 25 years ago. Unfortunately, cerebral computed tomography was not available at that time, and the lesion was first detected on diffusion weighted cerebral MRI, as described here. However, because the patient has experienced no other episodes with symptoms from the brain stem, it seems reasonable to think her dystonia is caused by this lesion.

The rhythmic activity may be a "release" phenomenon caused by interruption of inhibitory inputs to trigeminal premotor or motoneurons. Neurons in the pontine reticular formation may suppress cortically evoked rhythmic activity in the digastric muscle.[12] Other reticular neurons may be part of the central oscillator network that may cause rhythmic 2 to 5 Hz activity in trigeminal motoneurons (see reference 12). Rhythmic firing has been demonstrated in interneurons in parts of the pontine reticular formation that project to the trigeminal motor nucleus.[13] A similar pathophysiology has been proposed for palatal[14] and bulbar[15] tremor (myoclonus). Rhythmic involvement of facial mimicatory muscles may be explained the same way. Neurons in the pontine reticular formation supply both the trigeminal and facial motor nuclei, possibly as part of the neural circuits that coordinate masticatory and facial muscles during oral motor behavior.[16,17] Tracer studies clearly show that inputs to the trigeminal and facial motor nuclei from premotor neurons in the pontine reticular formation are bilateral but with an ipsilateral preponderance (see references 16 and 17; Figs. 2 and 3 in both papers). This may explain why our patient showed a bilateral yet asymmetric dystonia after a unilateral lesion.

Our patient is the first reported case of presumed symptomatic jaw-opening dystonia of central origin. It is still unclear whether all such dystonias are caused by pontine dysfunction. Also, Gilbert[6] suggested a pontine localization for the pathogenesis because his patient had upbeating nystagmus. However, some cases of jaw-opening dystonia have been reported after dental procedures, suggestive of a peripheral origin.[7,8] On the other hand, focal dystonias are often considered a disease of the basal ganglia, and in some patients jaw opening is only part of a dystonic syndrome. Garcia-Albea et al.[3] failed to find a causative lesion in a patient with jaw-opening dystonia, blepharospasm, and torticollis, even after postmortem histologic examination, but brain stem lesions have been demonstrated in patients with other cranial dystonias.[18–20]

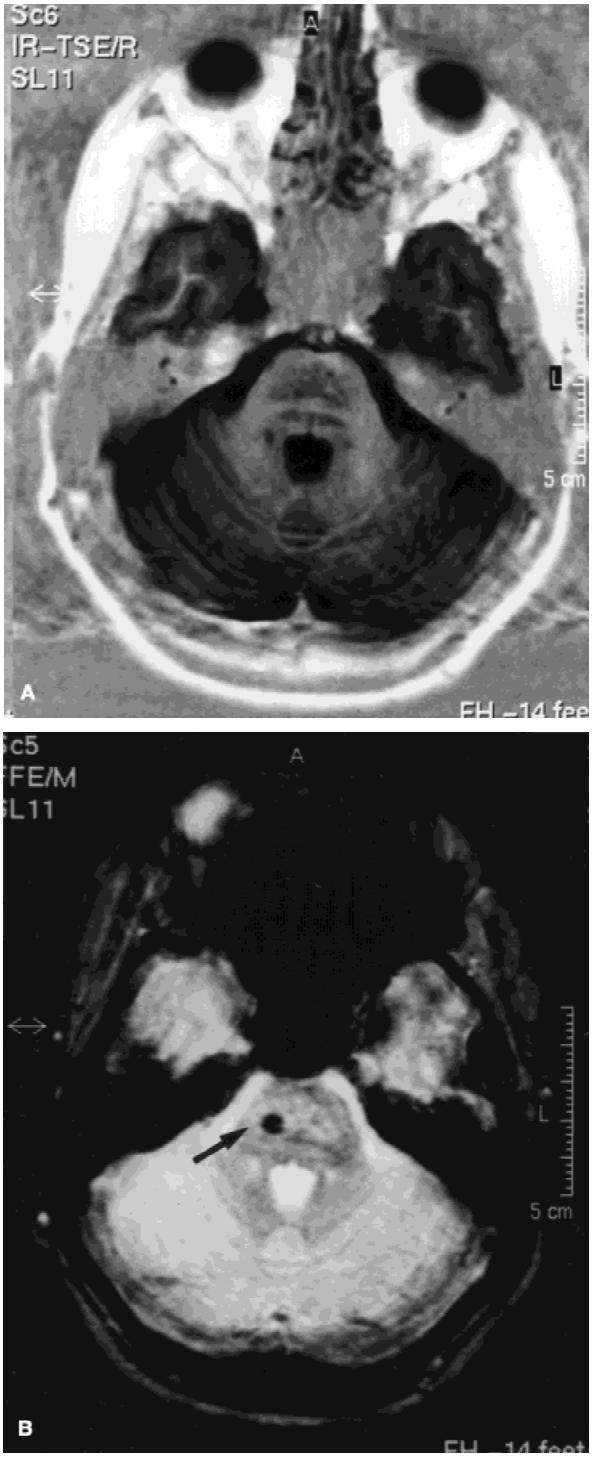

FIG. 2. (**A**) Axial IVR (inversion recovery) MRI through pons shows no pathology. (**B**) Axial DWI (diffusion weighted) MRI through the same region reveals a lesion in the reticular formation on the right side (arrow).

As suggested by others,[6,7] botulinum toxin should be the "drug-of-choice" for jaw-opening dystonia.

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Eyelid Dystonia in Machado-Joseph Disease

Machado-Joseph disease (MJD), or spino-cerebellar ataxia type 3 (SCA-3), is an autosomal-dominant, multisystem degeneration caused by an unstable expansion of CAG repeat located on chromosome 14q32.1.[1] Although originally described among subjects of Azorean descent, MJD/SCA-3 now has been reported in patients of diverse ethnic background. Core clinical features include cerebellar ataxia, external ophthalmoparesis, cerebellar ataxia, extrapyramidal and pyramidal signs, and peripheral neuropathy.[2] Parkinsonism, characterized by bradykinesia and rigidity, and dystonia, usually involving the limbs or neck, are the movement disorders most commonly described.[3] There are rare descriptions of facial dystonia but, to our knowledge, there is no report of blepharospasm and apraxia of eyelid opening in MJD.[2,4] We describe two unrelated patients testing positive for the MJD gene who presented with dystonia of the eyelids and who were successfully treated with botulinum toxin injections.

Case Reports

Patient No. 1

At age 28, this 37-year-old man developed speech, swallowing, and gait difficulties. These symptoms progressed slowly and relentlessly. Six years after the onset of the disease, the patient noticed difficulty opening his eyes, which worsened on speaking but could be overcome by touching the lateral corner of the left eyebrow. There is no mention of cognitive decline or sphincter disturbance. A member of the patient's family has a gait impairment but no other relative has presented abnormalities of the eyelids. When first seen at the Federal University of Minas Gerais Movement Disorders Clinic at age 33, the most important findings on neurologic examination were apraxia of eyelid opening combined with blepharospasm and lower facial dystonia (see videotape segment 1); supranuclear ophthalmo-

A videotape accompanies this article.
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paresis; mixed dysarthria with pseudobulbar and cerebellar components; spastic tetraparesis with bilateral upturned toes; generalized bradykinesia; and severe gait cerebellar ataxia which made walking possible only with assistance. Computed tomography of the brain showed mild atrophy of the brain stem and cerebellum. Search for the gene of MDJ/SCA-3, by previously described methodology,[5] showed that the patient was heterozygous. Electromyography (EMG) of the pretarsal portion of the left *orbicularis oculii* demonstrated that at rest there was no abnormal activity of the muscle but attempts to voluntarily open the eyes triggered muscle contractions. For the past 4 years the patient has been treated with injections of botulinum toxin type A (Botox®; Allergan, Irvine, CA, USA) at dosages of 5 U, 10 U, and 7.5 U injected into each eyebrow, upper eyelid (pretarsal portion), and lower eyelid. With this treatment the patient remains capable of opening his eyes for an average of 16 weeks and has not developed any significant complication (see videotape segment 2).

Patient No. 2

This 23-year-old woman was healthy until age 19, when gait impairment and facial involuntary movements appeared. Neurologic examination revealed spastic paraparesis with bilateral Babinski signs as well as dysarthria and fasciculations in the tongue. One year later, she developed vertigo and, in addition to the previous findings, the examination showed nystagmus, blepharospasm, and lower facial dystonia, dystonic posturing of the feet, and unsteadiness on standing with lateropulsion to the left (see videotape segment 3). Mental status and the sensory examination were normal. Her grandfather, father, and one brother died with a similar slowly progressive neurologic disorder but there was no family history of cranial dystonia. The EMG showed positive waves in the left anterior tibial muscle. Spinal fluid analysis, cranial computed tomography, and magnetic resonance imaging scans were normal. The genetic study showed that the patient was heterozygous for the MJD/SCA-3 gene. Treatment with 50 U Botox improved the blepharospasm and did not cause undesired side effects.

Discussion

We have described two patients, belonging to unrelated families, with molecularly proven MJD/SCA-3 who developed blepharospasm and, in one, apraxia of eyelid opening (AEO). The latter has been defined as an inability to initiate lid opening related to inhibition of levator palpebrae (LP) activity but in the absence of concomitant dystonic activity of orbicularis oculi (OO).[6,7] Although we have not done EMG recording of the LP, the inability to open the eyelid with lack of clinical and electrophysiological evidence of OO activity strongly supports the fact that our patient no. 1 has AEO. Attempts to initiate lid opening triggered dystonic contractions in the OO, keeping with the observation that AEO is commonly associated with blepharospasm.[6–9]

Limb dystonia, which has been described in association with SCA-3, and retraction of the eyelids causing bulging eyes has been regarded as a clinical hallmark of MJD in patients of Portuguese background.[2–5] However, apart from a few vague descriptions of facial dystonia,[2,4] we have not found any report of blepharospasm or apraxia of eyelid opening associated with this condition in an electronic search of English and French literature since 1966. Furthermore, our patients improved with botulinum toxin injections without the development of any serious side effects. This is in contrast with the experience of Tuite and Lang[10] who described a patient with MJD and cervical dystonia who, after treatment with this medication, developed long-lasting dysphagia. It is possible that the use of low dosages in our patients explains their good response to botulinum toxin. The increased risk of complications after blocking neuromuscular transmission in patients with MJD may be related to the existence of peripheral neuropathy in this condition.[2,3]

The mechanism underlying the blepharospasm and apraxia of eyelid opening in MJD/SCA-3 remains to be determined. However, because both conditions have been described in association with upper brain stem and/or basal ganglia lesions,[8,9,11] it is tempting to speculate that neuronal loss in the nuclei of the midbrain, as well as in the pallidum, described in MJD[2,3] accounts for their occurrence. Regardless of the lesion responsible for these movement disorders, our and others' observations of improvement of AEO with botulinum toxin injections into the pretarsal portion of OO supports the hypothesis that it is a dystonic phenomenon.[8,9,12,13] However, the finding of electric silence of OO during the episodes of inability to open the eyelids seen in our patient no. 1 and by others[6,7] argues against such theory. Further studies are warranted to define the mechanisms underlying AEO.

Legends to the Videotape

Segment 1: Patient no. 1 before injection of botulinum toxin. An inability to open the eyes, characteristic of apraxia of the eyelid opening, is seen with superimposed blepharospasm.

Segment 2: Patient no. 1 4 weeks after injections of botulinum toxin. He is now capable of opening the eyes and the blepharospasm is no longer seen.

Segment 3: Patient no. 2 before treatment with botulinum toxin, showing blepharospasm and lower facial dystonia.

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Choreic Movements Induced by Cibenzoline: An Ic Class Antiarrhythmic Effect?

Cibenzoline (CBZ) is a class I antiarrhythmic drug (AAD) with probable Ic class properties. Its usual neurologic side effects are headache, dizziness, visual disturbances, tremor, and a myasthenia-like syndrome.[1] We report a case of transient choreic movements associated with persistent orofacial dystonia, possibly induced by CBZ, and discuss their physiopathologic mechanism.

Case Report

A 77-year-old woman with a medical history marked by an atrioventricular block, which was treated by a pacemaker, presented with cardiac arrhythmia resulting from auricular fibrillation. CBZ at a dosage of 260 mg per day was introduced in May 1996 without any concomitant medication. One week later, without prior neuroleptic or toxic exposure, orofacial abnormal involuntary movements (AIM) involving the cheeks, tongue, chin, and the lips and mimicking chewing appeared. It progressively worsened in the following weeks. She then developed choreic AIM of the four limbs. Four months later AIM were suspected to be related to CBZ, which was replaced by 200 mg flecainide per day. After 2 weeks, the AIM spontaneously worsened with anguish and restlessness. Flecainide was stopped. One month later, the AIM disappeared. A few weeks later 100 mg sulpiride per day was introduced because of numerous somatic complaints. Sulpiride was stopped 5 days later when AIM reappeared and confusion developed. There was then orofacial dystonia with severe persistent movements of the tongue, generalized choreic syndrome with distal predominance, and hypotonia of the four limbs. She was then admitted to our unit. The Mini-Mental Status (MMS) score was 27/30 with slight attention and working memory deficit. On computed tomography scan of the brain there were slight hyperdensities of both pallidum suggesting mild calcifications. Magnetic resonance imaging was not performed because of the pacemaker. The electroencephalogram was normal. The routine biologic tests, TSH, FT3, FT4, antinuclear antibodies, anti-DNA native anti-Sm, anti-histones, anti-SSA, anti-SSB, and antiphospholipid antibodies were negative. There was no family history of chorea and the molecular biology excluded Huntington's disease. Eleven months later, choreic movements had completely disappeared and only mild orofacial dystonia persisted.

Discussion

In this patient there was no justification for the usual causes of acquired chorea such as lupus, antiphospholipid syndrome, recurrence of Sydenham's chorea, metabolic diseases, or toxic etiologies. There was also no grounds for a hereditary neurodegenerative disease because the family history was negative, molecular biology was excluded for Huntington's disease, and, mainly, chorea was transient. On the contrary, the responsibility of CBZ could be evoked because of a possible relationship between the presence of chorea and CBZ therapy. Moreover, the rebound effect observed with flecainide, a Ic AAD which can be responsible for dystonia,[2] suggests a link between AIM and Ic AAD. Chorea and dystonia are considered to be related to basal ganglia dysfunction. More precisely, chorea involves dysfunction of the indirect pathway from the caudate and putamen to the internal globus pallidus and dystonia is generated by dysfunction of the direct pathway.[3,4] In fact, the AIM observed with flecainide[4] were similar to those observed with neuroleptic drugs and could be related to its benzamide-like structure which is responsible for antidopaminergic properties.[5] However, this explanation cannot be retained for CBZ in which the structure is different. Therefore, it could be hypothesized that AIM could be related to the pharmacologic properties of these two AAD. CBZ decreases the two different components of K: a sensitive, rapidly activating component with a strong inward-going rectification property (IKr) and an insensitive, slowly activating component with little rectification (IKs), whereas flecainide decreases only the IKr component.[6] The inhibition of IKr prolongs the duration of action potentials and refractory periods.

On the contrary, mexiletine, another class I AAD, does not affect IKr or IKs.[6] Because chorea and dystonia had been observed with flecainide or CBZ (our case) but never with mexiletine, it can be hypothesized that they are related to inhibition of K channels (perhaps Ikr current). The neuroleptic-like effect of flecainide and CBZ could be related to the functional relationship between dopaminergic receptors and Na and/or K currents. In fact, it has been demonstrated that in acutely

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isolated rat neostriatal neurons, activation of D_1 and D_2 class receptors modulate the K and NA currents.[7] According to Missale,[8] although the influence of D_1-like receptors on the activity of K channels has not been well documented, the role of D_2-like receptors in modulating K currents seems to be better justified. The increase of outward K currents provoked by D_2-like receptor activation in rat striatal neurons is one way of signal transduction of dopamine receptors.[8] By decreasing the K current, CBZ and flecaine could modify the signal transduction of the D_2-like receptors leading to an imbalance in the dopaminergic transmission. It is noteworthy that AIM in our case reappeared when sulpiride was introduced. On the other hand, propafenone, another Ic AAD without a benzamide structure, had been reported to induce movement disorders such as myoclonus and gait apraxia, which are usually considered to be related to more diffuse subcortical or cortical dysfunction.[9,10]

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