Clinical/Scientific Notes

Familial Cortical Tremor With Epilepsy and Cerebellar Pathological Findings

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Abstract: The clinical and neuropathological findings in a patient with familial cortical tremor with epilepsy (FCTE) are described. Clinically, the patient showed cortical myoclonus, tremor, and generalized seizures. Pathological investigation showed cerebellar degeneration and somal sprouting and loss of dendritic tree in Purkinje cells. Striking similarities were found in diseases caused by channelpathies such as spinocerebellar ataxia (SCA) subtype 6. © 2003 Movement Disorder Society

Key words: cortical tremor; myoclonus; epilepsy; neuropathology

Familial cortical tremor and epilepsy (FCTE),1,2 familial adult myoclonic epilepsy,3,4 benign adult familial myoclonic epilepsy,5 or autosomal dominant cortical myoclonus and epilepsy6 is a rare neurological syndrome characterized by (1) autosomal dominant inheritance, (2) essential-like tremor and distal myoclonus, (3) myoclonic and generalized seizures, (4) late onset, (5) moderate progressive course, (6) no pyramidal or cerebellar signs, and (7) good response to antiepileptic drugs. Electrophysiological studies reveal features of cortical reflex myoclonus, such as giant somatosensory evoked potentials, and enhanced long loop reflexes. Electroencephalograms may show polyspike-wave complexes.1–8 Eight Japanese and four European families have been described.1–7 Genetic studies revealed linkage to chromosome 8q23.3-q24.1 in five Japanese families and to chromosome 2p11.1-q12.2 in one Italian pedigree.3,5,6 Recently, we described a large Dutch FCTE pedigree (Fig. 1). Linkage analysis excluded linkage to both loci.2

Patients and Methods

Case Report

A Dutch woman died at the age of 68 years (Fig. 1; pedigree, II-11). She had suffered from progressive irregular trembling of the limbs provoked by movement from the age of 35, and myoclonic and tonic–clonic generalized seizures from the age of 38 years. Phenobarbital (daily 150 mg) and clonazepam (daily 40 mg) decreased the epileptic seizures, diminished the tremulous movements, and improved the ability to walk, but she deteriorated over time. At 68 years of age, she showed memory deficits (Mini-Mental State Examination score of 18/30), and mild rigidity was documented. Coordination tests were jerky. Tendon reflexes were moderately hyperactive, without pathological reflexes. She suffered from severe action tremor and myoclonus of the extremities and generalized epileptic seizures unresponsive to several antiepileptic drugs. A complete blood cell count and routine blood chemistry, antibodies to nuclear antigens, antineutrophil cytoplasmic antibodies, and vitamins showed normal results. Mutation analysis for spinocerebellar ataxia (SCA) subtypes 1, 2, 3, 6, and 7 and dentatorubropallidolysian atrophy were negative. A computed tomography (CT) scan of the brain showed atrophy, particularly of the cerebellum. She died 2 months later, and postmortem examination was performed with informed consent.

Dutch FCTE Family

The Dutch FCTE family has been described in detail.2 The pedigree showed autosomal dominant inheritance (Fig. 1). Of the 41 relatives, 13 were considered definitely affected, 3 were probably affected, 10 were unaffected, and in 15 the diagnosis could not be established. The disease was characterized by a kinesiogenetic tremor resembling essential tremor of the hands and legs, with superimposed fine distal myoclonus. The symptoms appeared between the ages of 12 to 45 years and were followed 1 to 33 years later by generalized epileptic attacks. The tremor was provoked by exercise and emotional stress. Antiepileptic drugs, especially clonazepam and valproic acid, were effective for tremor, myoclonus, and epilepsy. Tremor recordings showed a 10 to 16 Hz tremor, and C-reflexes and giant potentials could be found in affected individuals. SCA subtypes 1, 2, 3, 6, and 7 were excluded in the affected Case III:10. Magnetic resonance imaging of the brain was normal in 2 patients (II-3, 10), lactate and pyruvate levels were normal in Patient III:10, and no “ragged red fibers” were seen in a muscle biopsy in Patient III:3, thus making a progressive myoclonus epilepsy and MERFF unlikely. A genome screen in this family excluded linkage to chromosomes 22, 5q, 6q, and 21q (SCA 8, 10, 12, and 17, and Unverricht Lundberg, EPM1; unpublished data).

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Received 22 February 2003; Accepted 19 June 2003
DOI 10.1002/mds.10662
Tissue Preparation and Immunocytochemistry

Postmortem examination was carried out within 48 hours. Informed consent was obtained for the use of brain tissue. The brain was fixed in 10% buffered formalin solution for 3 weeks. After macroscopic evaluation, tissue blocks from the following regions were embedded in paraffin: neocortex (frontal, temporal, parietal, and occipital cortex), periventricular white matter, basal ganglia, amygdala, hippocampus, brainstem, and cerebellum (hemispheres, dentate nucleus, and vermis). Six-μm-thick sections were processed for conventional staining, including hematoxylin and eosin, Bielschowsky, Klüver-Barrera, and Nissl staining; and ubiquitin immunostaining. Several blocks of the cerebellar cortex were used for calbindin immunohistochemistry. Antibodies specific for calbindin, known to label Purkinje cells and their dendrites, were used (Sigma). Deparaffinized sections were incubated with 1% H2O2 and washed with phosphate buffered saline. Sections were then incubated with primary antibodies, and antibody binding was visualized using the avidin-biotin peroxidase complex method (Vector Elite) and 3,3-diaminobenzidine as a chromogen. Cerebellar tissue of 4 aged matched controls without neurological disorders and 2 ischemic brains were used to evaluate immunohistochemical stainings in normal and hypoxic conditions.

Results

General postmortem findings included severe atherosclerosis of the aorta, an acute purulent bronchitis, and pulmonary edema. The brain weighed 1,204 g, the pons and cerebellum weighed 160 g. Microscopically, the neocortex was normal (Table 1). No neuronal cell bodies were found in the white matter. The basal ganglia showed extensive mineralization in the globus pallidus, both in neurons and vessel walls, and foci of mineralization in the internal capsule. The claustrum showed fine vacuoles and higher cellularity (mainly astrocytes, microglial cells, and macrophages). Slight hippocampal sclerosis was found next to moderate neuronal cell loss and gliosis in the insular cortex. There were slight neurofibrillary changes in the entorhinal cortex and hippocampus (Braak stage I). The brainstem was

| TABLE 1. Neopatohological findings |
|-----------------------------------|
| Cerebellum                        |
| Cerebellar cortex                |
| Purkinje cell loss               |
| Bergmann gliosis                 |
| Atrophy of the molecular layer   |
| Patchy depletion of granule cells|
| Abnormal morphology of Purkinje cells |
| Stellate configuration with poorly developed dendritic tree |
| Short perisomatic dendrites      |
| Cerebellar white matter          |
| Dentate nucleus                  |
| Gliosis                          |
| Mild to moderate cell loss with gliosis |
| Neocortex                        |
| No significant histological abnormalities |
| Insular cortex                   |
| Moderate cell loss and gliosis   |
| Claustrum                        |
| Severe cell loss                 |
| Severe gliosis                   |
| Striatum                         |
| Normal Putamen and Caudatum      |
| Extensive mineralization of the Globus Pallidus |
| Thalamus                         |
| No significant histological abnormalities |
| Hippocampus                      |
| Slight hippocampal sclerosis (Wyler II) with loss of CA1 pyramidal cells and gliosis |
| Entorhinal cortex                |
| Mild neuronal degeneration and gliosis |
| Fusiform gyrus                   |
| Mild neuronal degeneration and gliosis |
| Brainstem                        |
| No significant histological abnormalities |

FIG. 2. A: Numerous radial dendritic sprouts of Purkinje cells (arrow; hematoxylin and eosin staining; ml, molecular layer; gl, granular layer). B: Empty basket cell (Bielschowsky silver staining). C: Absence of dendritic tree (small arrow) next to a normally arborized Purkinje cell (immunohistochemical staining for calbindin). D: Abnormal radial sprouting and absence of sprouting (calbindin staining). E: Detail of D. F: Heterotopic cell in the ml. G: Heterotopic cell in the ml (arrowhead) and three abnormally arborised Purkinje cells (arrows; calbindin staining). H: Purkinje cells with absence of arborisation. Inset: Abnormal arborisation. Scale bars = 200 μm in A,H, 125 μm in B, 280 μm in C,D, 100 μm in E,F, 320 μm in G. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com/jpages/08815-3185]
The clinical picture of FCTE includes myoclonus, epilepsy, and tremor. In literature this triad is considered to originate in the sensorimotor cortex.8,9 Gaze-evoked pathological state, cortical myoclonus, and epilepsy have been described previously and hypothesized to be a result of increased tonic facilitation of the motor cortex by a cortico-cerebello-thalamo-cortical loop.17 A similar association has been reported for cerebellar changes and epilepsy.18 An alternative is an important role of the claustrum in the formation of epileptiform activity as suggested by several reports.19 The claustrum showed marked morphological changes in our patient. The tremor might originate from the cerebellum. The FCTE tremor resembles essential tremor (ET), and functional magnetic resonance imaging and positron emission tomographic studies in ET patients have shown an important role of the cerebellum.20 Another imaginable explanation for the clinical triad in FCTE is a channelopathy with visible pathological changes in the cerebellum and functional changes of the cerebral cortex.

The genetic background of FCTE has not been clarified yet. SCA 6 patients have a CAG repeat expansion encoding the voltage-dependent calcium channel subunit CACNA1A.13,14 Of interest, Rocker mice have a point mutation of the same calcium channel subunit.16 The similarities in abnormal morphology in combination with the paroxysmal clinical features suggest a channelopathy in FCTE.

In conclusion, FCTE is a distinct disease entity, which can be differentiated from other neurological disorders, not only clinically and electrophysiologically, but also based on unique pathological findings. However, pathological similarities are seen with diseases linked to the gene for the dependent calcium channel subunit CACNA1A, possibly pointing to a channelopathy.

Acknowledgments: Dr. Aronica is supported by the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, the Stichting AZUA-funds, the National Epilepsy Fund—“Power of the Small,” and Hersenstichting Nederland (NEF grant no. 02-10).

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Focal Dystonia as a Presenting Sign of Spinocerebellar Ataxia 17

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Abstract: We report on the clinical manifestation of spinocerebellar ataxia 17 (SCA17) in 3 members of a German family, in whom the pathological repeat expansion in the TATA-binding protein gene ranged from 53 to 55 repeats (normal: 29–42). The main clinical features were focal dystonia as presenting sign, followed by cerebellar ataxia, and, in the later course of one case, dementia and marked spasticity with signs of cerebellar and cerebral atrophy on brain computed tomography (CT) scan. In conclusion, SCA17 mutations should be considered in the differential diagnosis of focal dystonia. © 2004 Movement Disorder Society

Key words: SCA17; dystonia; ataxia; TBP gene

Spinocerebellar ataxia 17 (SCA17) is caused by a recently found unstable CAG trinucleotide expansion mutation coding for polyglutamine tracts in the TATA-binding protein (TBP).1 We reported recently two families with autosomal dominant inheritance of SCA17 and an abnormal CAG expansion in the TBP gene.2 Currently, only few other families have been described as affected,3,4 and little is known about the phenotypic spectrum that comprises cerebellar ataxia, extrapyramidal features, such as hypokinesia or dystonia, cognitive decline, and psychosis. We describe the detailed clinical symptoms of SCA17 in one of our SCA17 families of German origin (Fig. 1), with the first symptom being a focal dystonia in all affected individuals. Patients gave informed consent for videotaping and molecular analysis. To our knowledge, no video presentation of affected individuals has been published to date. We hope this description of SCA17 in 3 affected individuals will serve to alert neurologists to this entity and help facilitate recognition of patients with this movement disorder.

Case 1 (Index Patient, II:2)

The 48-year old mother of Case 2 (III:2) and Case 3 (III:3) was first seen in our neurology department in 1990 with a 3-year

A videotape accompanies this article.

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Received 10 February 2003; Revised 3 June 2003; Accepted 7 July 2003

DOI 10.1002/mds.10600
history of slowly progressive gait disturbance, dysarthria, and mild deterioration of intellectual function. According to her husband, symptoms had started with dystonic posturing of her left foot, followed by gait problems, and occasionally involuntary choreiform movements of her right hand. Shortly thereafter, her pronunciation became inarticulate, and she developed an increasing “excitability” and a loss of interest in social life.

Family history revealed that her elder sister (II:1) had an ataxic syndrome; this information was obtained from medical records as the patient was unavailable for examination. In addition, 2 of her 3 daughters (III:2 and III:3) were affected with a movement disorder, whereas her youngest (now 18-year-old) daughter was reported by her father to be unaffected.

On neurological examination in 1990, the index patient showed affective lability, reduction of drive, and impairment of short-term memory and concentration. Except for smooth pursuit eye movements interrupted by saccades and a cerebellar dysarthria, cranial nerve examination was normal. There was mild intention tremor of both upper limbs, along with mild dysmetria, and marked bradydysdiadochokinesia, more pronounced on the left-hand side. At this time, there were no pyramidal signs other than brisk tendon reflexes. Gait was somewhat unsteady, and involuntary choreiform movements of her right hand were seen intermittently. There were no sensory disturbances or autonomic dysfunctions.

Over the following 6 years, she developed a severe gait ataxia; by 1996 the patient was unable to walk unsupported and had become wheelchair-bound. There were little or no changes in her neurological status.

Between 1999 and 2000, a rapid progression of her disease was observed. On her last neurological examination in October 2000, the patient was awake and partial eye contact was possible. She was mute, did not follow any commands, and only occasionally cried out loud as if being afraid of pain. Cranial nerve examination revealed hypomimia with the mouth wide open, saccadic eye movements, and dysphagia. A marked spasticity of all four extremities with the beginning of contractures was found. Tendon reflexes were symmetrically hyperactive, and Babinski’s sign positive on the left. The patient was bedridden and could not sit up or remain in the sitting position unsupported. Oral ingestion of liquid or solid food had become impossible, and she was incontinent.

Between 1990 and 1996 medical treatment had been tried with 5-hydroxy-tryptophan and physostigmine and later stopped because of disease progression.

In 1990, cranial magnetic resonance imaging (MRI) revealed moderate cerebral atrophy. Motor, somatosensory, and visual evoked potentials were normal. In 1996, a brain CT scan (Fig. 2) revealed moderate cerebellar and cerebral atrophy. Another brain CT scan carried out in the 2000 showed the cerebral atrophy noted previously, which was most pronounced in the cerebellar region, but no further abnormalities. Examination of cerebrospinal fluid (CSF) and routine laboratory results for clinical chemistry including blood counts, copper, ceruloplasmin, and vitamins were normal. Molecular analysis revealed a repeat expansion in the TBP gene of 53 repeats in her case and 54 repeats in her elder sister (normal range: 29 – 42 repeats). No expansion of trinucleotide repeats was found in the SCA1, 2, 3, 6, 7, 8, 10 or genes.

Case 2 (III:2)

The 27-year-old daughter of Case 1 was first referred to our outpatient clinic in May 1999 when aged 23 years because of a 3-year history of “writing problems”. On writing, the patient showed dystonic features with involuntary flexion of the wrist and fingers of her right hand and coinversion of the left hand. In addition, there were severe dysfunction of fine finger movements, dysdiadochokinesia and dysmetria, more pronounced on the right-hand side. Neurological examination also revealed mild head ataxia and dysarthria but normal cranial nerve examination. Muscle tone was normal in all four extremities, reflexes were normal and pyramidal signs absent. In spring 2002, a moderate gait ataxia was noticed for the first time, but no other significant changes were observed on neurological examination. At the most recent follow-up visit, she reported severe gait problems and difficulty being understood and showed a wide-based ataxic gait and slurring dysarthria (not part of the video). There was no obvious intellectual deterioration; formal neuropsychological testing was not carried out.
Since September 2000, repeated local injections of botulinum toxin have been administered and have led to improvement of the focal dystonia of the hand.

An MRI scan of the head was normal. Routine laboratory investigations including serum analysis of copper, ceruloplasmin, thyroxine, and blood counts were normal. Molecular genetic testing for SCA1, 2, 3, 6, 7, 8 and DRPLA was negative but revealed a repeat expansion in the TBP gene of 55 repeats.

**Case 3 (III:3)**

In October 2001, the 23-year-old sister of Case 2 and daughter of Case 1 was admitted to our outpatient clinic with involuntary turning of her head to the right side. Additionally, she reported a feeling of instability when walking in the dark, symptoms that had started about 1 year previously. On neurological examination she had laterocollis to the left of 40°, torticollis to the right of 20°, and elevation of the left shoulder of 2 cm. The left sternocleidomastoid, trapezius, and levator scapulae muscles were hypertrophic. There were signs of mild gait disturbance with difficulty performing tandem gait. No further neurological deficit was found at that time. On her most recent neurological examination in July 2002, the beginning of bilateral impairment of fine motor function and bradydiadochokinesia was found. Intellectual function remained normal. Repeated injections with local botulinum toxin abated the dystonic symptoms. An MRI brain scan in 2002 indicated mild cerebellar atrophy but no changes in the brainstem or cerebral hemispheres. Laboratory results showed no abnormalities. Molecular genetic testing demonstrated a repeat expansion of 55 repeats in the TBP gene.

Two unaffected members of the family were available for clinical examination and molecular analysis. Both the mother (I.2) and the brother (II.4) of the index patient were neurologically normal and had no repeat expansions in the TBP gene. There was no history of ataxia in the father or the paternal ancestors of the index patient.

**Discussion**

We present a family of German origin, in whom at least 4 members are affected by SCA17. Phenotypic features include focal dystonia and in the later course (Case 1) cerebellar ataxia, pyramidal and extrapyramidal signs, and progressive dementia, indicating the affecting of multiple neuronal systems. The CAG repeat expansions in the TBP gene in our cases range from 53 to 55 repeats, which clearly exceeds the normal range of 25 to 42 glutamine codons in this gene.\(^2,5\)

The diagnosis of a specific SCA is difficult based on phenotypic features alone. This is due to the variability of clinical symptoms within SCA subgroups on the one hand and the shared symptoms of dystarthisia, gait, and limb ataxia in all SCAs on the other hand. Furthermore, virtually all SCA types can look alike late in the course of the disease; however, some clinical features seem more common in certain SCA types than in others. Focal dystonia, for example, may be the first symptom of SCA2, SCA3, SCA6, SCA7 or DRPLA (dental-boral-pallidolysian atrophy).\(^1\) Focal dystonia has also been described in cases with unknown SCA genotype\(^7,12-14\) that have not as yet been tested for SCA17. As shown in our report, dystonia was the presenting feature of all 3 patients with SCA17, on whom detailed information was available. In fact, in 2 of our cases, focal dystonia had been the predominant symptom of the disease over several years.

A review of the scarce literature on SCA17 showed that Nakamura and colleagues\(^1\) found truncal dystonia in addition to the main clinical features of progressive cerebellar ataxia and dementia in 3 of 9 patients of Japanese origin. Ataxia and mental deterioration were described in a patient with 43 CAG repeats, which exceeds the normal range by one trinucleotide.\(^15\) Fujigasaki and coworkers\(^4\) did not observe dystonia in a Belgian family with at least 2 affected members but they described other extrapyramidal symptoms such as bradykinesia, rigidity, and choreoathetosis. The age at onset of the affected members in the Belgian family ranged from 34 to 55 years (46 repeat units), the youngest affected individual described by Nakamura and associates\(^3\) was 19 years (55 repeat units) and the oldest 48 years old (48 repeats). Koide and colleagues\(^3\) described a young Japanese girl with a sporadic CAG repeat expansion of the TBP gene (63 repeats). This girl developed ataxia and intellectual deterioration at the age of 6 years and later spasticity. These data suggest a negative correlation between age and onset and the number of repeat expansion in SCA17, as is known for other polyglutamine disorders, due to an instability of the mutation during transmission with an increase of repeat expansion, resulting in anticipation.\(^16\) Observations in our family would also be in accordance with anticipation: both daughters (each with 55 repeats) first showed signs of the disease almost 10 years earlier than their mother did (53 repeats), and, at least in the case of the elder daughter, there seemed to be a more rapid disease progression. All identified mutation carriers in our family were clinically affected; however, reduced penetrance in SCA17 has been recently described in a family with 3 unaffected and 4 affected mutation carriers.\(^17\)

To date, eight progressive autosomal dominant ataxias are known to be associated with CAG expansions. According to data published recently, SCA17 in Japan\(^18\) and in France\(^4\) seems less frequent than other known SCAs with trinucleotide repeats (SCA1, 2, 3, 6, 7, 12, and DRPLA). The underlying molecular mechanism of these diseases remains elusive. As mentioned above, in SCA17, the mutation somehow affects the TBP that is a general transcription initiation factor and the DNA-binding subunit of the RNA polymerase II transcription factor D (TFIID). The latter binds to the DNA at the TATA box and plays a role in the expression of many genes. Altered gene expression may be the reason for cell death as found in postmortem brain tissues of 2 patients with SCA17.\(^3,4\) Autopsy revealed marked atrophy of the cerebellum with loss of Purkinje cells. Mild atrophy was found in the basal ganglia and cortex, along with intranuclear inclusion bodies. Accordingly, we observed on neuroimaging cerebellar (and cerebral) degeneration in 2 of our 3 cases.

We report detailed clinical and genetic findings in one of the first described families with SCA17, and include a video presentation of 3 affected members. All developed focal dystonia as a first symptom, followed by cerebellar signs in all 3, and multiple system and cognitive involvement in the index patient with the longest disease duration. This report should serve to alert neurologists to this condition, on which very limited clinical information is available as yet. SCA17 mutations should be considered in the differential diagnosis of focal dystonia. In particular, patients with a combination of focal dystonia and a progressive cerebellar ataxia should be tested for SCA17. Analysis of a larger cohort of SCA17 patients from different ethnic groups will establish whether focal dystonia may be a characteristic phenotypic feature of this SCA subtype.
Acknowledgments: This work was supported by the Deutsche Dystonic Gesellschaft eV. We thank the family members for participation in this study.

Legends to the Video

Segment 1. This segment shows Case 2 with SCA17 in 2000 and 2002 at age 24 and 26 years, respectively. In addition to focal dystonia of the right hand, marked dysfunction of fine motor function, dysdiadochokinesia of both hands, and ataxic symptoms, including limb and gait ataxia, are seen with a slow progress over the 2 years.

Segment 2. Case 3 with SCA17 in 2001 (aged 23 years). The patient has laterocollis to the left, torticollis to the right, and elevation of the left shoulder.

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Cerebrospinal Fluid Analysis for Whipple’s Disease in Patients With Progressive Supranuclear Palsy

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Abstract: The clinical picture of neurological involvement in Whipple’s disease (WD) may resemble progressive supranuclear palsy (PSP). We looked for WD pathogen DNA in the cerebrospinal fluid of 9 patients with a clinical diagnosis of PSP. The analysis was negative for all samples, showing that WD is not commonly involved in the aetiopathogenesis of PSP.

Key words: PCR; PSP; Whipple’s disease

Progressive supranuclear palsy (PSP) is a sporadic neurodegenerative disorder of unknown aetiology, characterised by vertical supranuclear gaze palsy, postural instability, parkinsonism, pseudobulbar palsy, and frontolimbic dementia. Although the first case reports date from the 18th century, the syndrome was named PSP by Steele, Richardson and Olszewski only in 1964.

The differential diagnosis of PSP includes other conditions with shared clinical features, the so-called “pseudo-PSP” syndromes. Whipple’s disease (WD) is a systemic infectious relapsing illness whose pathogen, Tropheryma whippellii, is a gram-positive bacillus. Central nervous system (CNS) involvement in WD is not rare (5–40% of the cases), although difficult to diagnose. The most frequent CNS manifestations are behavioural and cognitive changes, ocular movement disturbance including supranuclear gaze palsy, myoclonus, hypothalamic upset, epilepsy, ataxia, meningitis, and focal cerebral signs. Eye movement abnormalities can be distinguished on clinical grounds from PSP in most of the cases, but they may occasionally resemble that of this condition. In WD, there is a selective slowing of vertical saccades (upward

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Received 6 March 2003; Revised 10 July 2003; Accepted 17 July 2003

DOI 10.1002/mds.10636
TABLE 1. Main clinical and CSF features of the patients included in the study

| Patient no. | Gender/age at onset (yr) | Disease duration (yr) | PSP diagnostic category | Clinical signs of malabsorption | CSF | PCR for T. whippelii | Biochemical values/cell count |
|-------------|--------------------------|-----------------------|-------------------------|-------------------------------|-----|---------------------|-----------------------------|
| 1           | F/62                     | 2                     | Possible                | No                            | Negative | Normal            |                             |
| 2           | F/50                     | 2                     | Probable                | No                            | Negative | Normal            |                             |
| 3           | M/72                     | 4                     | Possible                | No                            | Negative | Increased proteins (142 mg/dl) and cell count (42) |                             |
| 4           | F/71                     | 2                     | Probable                | No                            | Negative | Increased proteins (73 mg/dl) and glucose (88 mg/dl) |                             |
| 5           | F/60                     | 2                     | Probable                | No                            | Negative | Increased proteins (60 mg/dl); oligoclonal bands |                             |
| 6           | M/75                     | 1                     | Possible                | No                            | Negative | Increased proteins (57 mg/dl) |                             |
| 7           | M/51                     | 1                     | Possible                | No                            | Negative | Normal            |                             |
| 8           | M/74                     | 2                     | Probable                | No                            | Negative | Normal            |                             |
| 9           | F/69                     | 3                     | Possible                | No                            | Negative | Normal            |                             |

PSP, progressive supranuclear palsy; CSF, cerebrospinal fluid.

more affected than downward), smooth pursuit vestibulo-ocular reflexes are preserved and there are no square wave jerks on fixation. Moreover, pendular vergence oscillations of the eyes and concurrent contractions of the masticatory muscles, i.e., ocular-masticatory myokymia, represent a distinct movement disorder that has been recognised only in WD. Computed tomography and magnetic resonance imaging (MRI) of the brain in WD may show atrophy, white matter high-signal areas, ring-enhancing lesions, and hydrocephalus. Because CNS WD can masquerade as PSP, it has been included in the list of pseudo-PSP conditions. To improve accuracy in clinical identification of PSP, the most recent and widely used diagnostic criteria (National Institute of Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy, NINDS-SPSP) also consider WD as an exclusion criterion. Despite this, it is unclear how often WD presents as a clinically typical PSP syndrome. As WD is a treatable condition, a correct diagnosis of this disease would have important therapeutic implications for patient life prognosis, because antibiotics may lead to a partial or even complete resolution of neurological disturbances.

Patients and Methods

Polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF) of patients with suspected neurological WD now seems to be an essential and cost-effective screening tool for confirming CNS involvement in WD. Consequently, we looked for T. whippelii DNA in CSF and peripheral blood of 9 patients with a clinical diagnosis of PSP, based on NINDS-SPSP criteria (Table 1). The patients included 4 men and 5 women, with a mean age of 64.7 years (age range, 50–75 years) and mean disease duration of 2.2 years (disease duration range, 1–4 years). Previous MRI studies had already excluded focal brain lesions in all patients. None showed clinical (diarrhea, abdominal pain, weight loss, fever) or biological (anaemia, iron deficiency, hypoalbuminemia) signs of malabsorption.

After informed consent was obtained from the patients enrolled in the study, CSF samples (7 ml) were collected in the sitting position. PCR was carried out on both CSF and peripheral blood. Total DNA was extracted from CSF and peripheral blood by cell lysis with lysozyme and proteinase K. Nucleic acids were purified with QIAamp DNA-binding columns (Qiagen, Valencia, CA). DNA (5 μg) was mixed with the specific primers pW3FE and pW2RB, which correspond to the region spanning nucleotide 965 through 983 (PW3FE) and 1214 through 1231 (PW2RB) of the 16S rRNA gene of the T. whippelii. The PCR mixture (50 μl:0.2 mM of dNTP, 2 mM MgCl₂, and 25 pmol of each primer) was subjected to an initial 4-minute denaturation at 95°C. After this step, 40 amplification cycles were carried out (45 minutes at 95°C, 45 minutes at 60°C, and 1 minute at 72°C) in a Thermocycler 2400 (Perkin Elmer, Cyprus, CA). PCR products were detected by electrophoresis on a 2% agarose gel containing ethidium bromide.

Results

PCR for T. whippelii was negative for all samples, whereas 5 patients had slight abnormalities in their protein and cell CSF values, and 1 patient (Patient 7) had positive oligoclonal bands with no other clinical or laboratory signs of active inflammatory CNS disease.

Discussion

Based on this small series, we may assume that T. whippelii is not commonly involved in the aetiopathogenesis of PSP. The diagnostic value of CSF PCR in WD has been the subject of a detailed study by von Herbay and colleagues, showing that this test has a good sensitivity (80%) in cases with CNS involvement. Duodenal biopsy followed by PCR of bowel tissue is mandatory to confirm the diagnosis of WD, but was considered redundant in the present series due to the negative findings of CSF PCR and the lack of previous systemic and gut symptoms. Further studies on a larger series of subjects presenting with PSP syndrome are warranted to assess the prevalence of WD with CNS involvement diagnosed mistakenly as PSP. At present, however, PCR for T. whippelii should not be recommended routinely in the work-up of patients presenting with this devastating condition unless clinical and neuroimaging findings suggestive for WD are found.

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Abstract: Although tremor is highly prevalent in human beings, there are few reports of tremor occurring in other mammals. Such tremor can further our insight into the mechanisms and anatomical basis of human tremor disorders. We report on a southern sea otter with a slowly progressive 6.5 to 8.5 Hz action tremor of late life that shared several clinical characteristics with essential tremor. The main pathological finding was in the cerebellum, where there was extensive vacuolation of Purkinje cells. © 2004 Movement Disorder Society

Key words: tremor; essential tremor; animal; vacuolation; pathology; toxin

Action tremor is a highly prevalent condition in human beings, with the most common forms including enhanced physiological tremor and essential tremor (ET). There are experimental models for action tremor, including the harmaline and penitrem A models, in which these chemicals are administered to laboratory animals, resulting in acute, reversible action tremors. Also, action tremor has been observed in mutant strains of laboratory mice and inbred strains of domesticated mammals. With these exceptions, we know of few reports of action tremor occurring in other mammals. This is surprising given the very high prevalence of action tremors in humans. We report on a case of a late-life action tremor in a female southern sea otter.

Sea Otters

Sea otters (Enhydra lutris) are carnivorous marine mammals that are active both above and under water. They are one of three otter species worldwide. Sea otters are found off the central California coast (southern sea otters, E. lutris nereis) and off Washington, Canada, Alaska, and the Aleutian islands (northern sea otters, E. lutris kenyoni). They inhabit nearshore ecosystems and feed on benthic (i.e., bottom-dwelling) and midlevel invertebrates, including clams and mussels. They are an example of the transition of a terrestrial carnivore to an aquatic lifestyle. The weaning of sea otter pups begins at 4 months of age and females reach sexual maturity between 3 and 5 years. The average life span of wild female sea otters is 6 to 8 years and is higher for animals in captivity, during which time they attain weights of approximately 50 lb and lengths of 4 feet. Sea otters are among the few animals known to use tools on a regular basis while feeding. They also have the densest fur of any animal. Having been exploited for many years for commercial purposes, approximately 2,500 southern sea otters remain in the wild.

Case Report

Clinical

On February 22, 1984, “Goldie,” an orphaned female sea otter pup, was found at Asilomar State Beach, near Monterey, CA. Her age was estimated to be 5 weeks. There were no signs of trauma. She was transported to and raised in the Monterey Bay Aquarium in Monterey, CA. She died on June 27, 2002 at the aquarium at the age of 18.5 years. The cause of death was respiratory tract infection with sepsis. During most of her life at the aquarium, she shared living quarters with two other sea otters, a male and a female, neither whom developed tremor or other neurological signs. For the remaining 3 months of her life, she shared living quarters with one other female sea otter, who remains healthy.
While under observation at the aquarium, there was no history of trauma or toxin exposure. She was under the care of a veterinarian (M.J.M.) who conducted comprehensive medical checkups every 4 months. During these checkups, she was anesthetized, weighed, her teeth were examined, she had a full body examination, and routine blood tests were carried out including a complete blood count, a serum electrolyte panel, liver function tests, blood urea nitrogen and creatinine, and serum glucose, calcium and cholesterol. During her life, she was treated intermittently with short courses of antibiotics for dental problems or minor bite wounds, but had not been on any other medications. Later in life, she developed osteoarthritis of the lower limbs (coxo-femoral and crural joints), which was diagnosed radiographically.

Tremor was first noted by the veterinarian in the first few months of 1997, when she was 13 years of age. The tremor was a mild, rapid postural and kinetic (i.e., action) head tremor that occurred when she strained her neck to reach for food, when arching her neck to look around, or when stretching her neck to groom. It was not present when she lay with her head at rest. The history that her veterinarian gives is that the tremor worsened gradually over the ensuing 5 years, becoming less intermittent, of greater amplitude, and eventually involved her upper and lower limbs.

To document her tremor, her trainers videotaped her regularly, resulting in footage from twenty dates between March 1997 and May 2002. The videotapes include footage of her daily activities, including swimming, floating on her back, rolling in the water, walking on land, holding food between her forepaws, eating, and grooming. Review of this videotaped material confirmed that the head tremor became less intermittent over time and that the amplitude of the head tremor increased. One of the authors (S.L.P.) digitized and analyzed the VHS videotape recordings using iMovie and Final Cut Pro (Apple Computer) using a Macintosh computer. Frequencies of the head tremor were calculated from 8 randomly sampled 1.0-second epochs with video images proportioned to maintain inter-image physical consistency. Specific landmarks on the face or head provided reference points from which the analyses were obtained. This digitalization demonstrated that the average frequency of the head tremor in 1997 was 8.5 Hz. By 2002, this had decreased to 6.5 Hz. Her veterinarian reported observing tremor in the head and upper and lower limbs. Based on the videotape, a head tremor was identifiable in 1997, and an intermittent lower limb tremor by 1999. The tremor, which had postural and kinetic components (see Video), was very regular without any jerking or twisting movements or neck rotation. Her gait, swimming, rolling, floating, holding food between her forepaws, and grooming were all normal, with no signs of spasticity, clumsiness, loss of coordination, or ataxia.

She remained healthy in other respects and remained bright, alert, and responsive. She had consistently normal blood work, as noted above. In addition, her thyroid function tests (including T4) and serum cortisol, estradiol, and progesterone levels were normal, and her immunofluorescent antibody titers for the protozoan parasites *Toxoplasma gondii* and *Sarcocystis neurona* were negative (<1:80 serum dilution). Her blood lead concentration in 1997 (<0.06 ppm) was well below toxic levels (>35 ppm). In 1999, blood lead was undetectable. Her tremor was never treated with ethanol, β-receptor blocking agents, or other medications. Neuroimaging was not carried out. When she died, a complete necropsy was undertaken.

**Pathological**

On gross examination, the brain seemed normal and there were no areas of softening or discoloration in the cerebellum, brainstem, or cerebrum. Hematoxylin and eosin (H & E)
stained sections from the cerebellum (2 oblique sections), neocortex (2), hippocampus (1), brain stem (2), and spinal cord (5) were examined microscopically. There was extensive cytoplasmic vacuolation of the Purkinje cells throughout all portions of both cerebellar sections (Fig. 1). Vacuoles were of varying sizes, with multiple (2–4) vacuoles in most cells, which along with the mild Bergmann gliosis, suggested a chronic process. One section including the neocortex and white matter showed a large, broad, curving area containing optically empty vacuoles especially involving the white matter. This area contained macrophages with foamy cytoplasm, reactive, mainly gemistocytic astrocytes, and spheroids suggestive of axonal swelling. Sections of the cerebellum and neocortex were stained further with periodic acid–schiff, Alcian blue, hematoxylin and eosin, counterstained with Luxol fast blue, and ubiquitin, which indicated that the vacuolar material was not glycogen (i.e., the vacuoles contained diastase-resistant PAS-positive material), not acid mucopolysaccharide (Alcian blue negative), not myelin-based (Luxol blue negative) and not ubiquinated protein (ubiquitin negative). A modified Bodian stain demonstrated only occasional empty baskets, indicating relative preservation of Purkinje cells. There were no detectable neurofilibrillary tangles or plaques. The hippocampus was normal, as was the caudate nucleus, putamen, globus pallidus and substantia nigra (pars compacta and pars reticulata). There were no Lewy bodies. The inferior olivary nuclei were normal, with no cell loss, gliosis or vacuolation. The spinal cord was unremarkable, with normal motor neurons and nerve roots.

Discussion

Action tremor is highly prevalent in human beings1-3 but has not been reported commonly in animals. Evaluation of action tremor when observed in animals is of potential importance for several reasons. The findings from these evaluations can be used to further our insight into mechanisms or the anatomical basis of human tremor disorders, which are poorly understood. Also, tremulous animals can be used, in some circumstances,14, 15 based on human tremor disorders, which are poorly understood, used to further our insight into mechanisms or the anatomical basis of these conditions are characterized by a broad range of neurological findings including upper motor neurons signs, ataxia, and tremor.

One consideration is that sections through the cerebellum were oriented in an oblique rather than a sagittal plane. Therefore, we were unable to examine cerebellum sections for cell loss in sagittal strips, which is a finding that has been described in the β-carboline model of tremor.49

In summary, we report on an animal with an action tremor of late life, which shared several clinical features with ET. As is thought to be the case in ET, the cerebellum was involved,
although the main pathological finding of extensive vacuolation of Purkinje cells has not been reported in ET.

Legend to the Video
Action tremor is illustrated.
1. A head tremor is visible while Goldie lies in the water on her back and forcibly pushes or head and neck forward.
2. It is not present while she floats on her back on land.
3. Tremor is not present while she lies, awake and reclining, on her back on land.
4. Head tremor occurs while she reaches for food and is also visible in between the chewing motions while she eats.
5. The head tremor occurs while she moves about a play tub (she is on the viewer’s left).
6. The head tremor is present while she is being fed.
7. Head tremor occurs while she walks, sniffing the ground in front of her.

Acknowledgments: This work was supported by the National Institutes of Health (ROI NS39422, ROI NS042859, P30 ES09089, and RR06645). We thank A.B. Johnson, M. Jeffries, L. Kovalek, and A. Giles for help in the preparation of the videotape and for providing clinical information.

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Hyperhomocysteinaemia in Treated Patients With Huntington’s Disease

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Abstract: Significantly increased plasma total homocysteine levels (t-Hcys) appeared in treated Huntington disease (HD) patients compared to controls and untreated HD subjects. Be-
cause the protein Huntingtin interacts with the homocysteine metabolism modulating enzyme cystathionine β-synthase, we hypothesize that homocysteine promotes neurodegeneration in HD. © 2004 Movement Disorder Society

Key words: homocysteine; Huntington’s disease; neurodegeneration

Increased plasma total homocysteine levels (t-Hcys) represent an independent single risk factor for atherosclerosis-related disorders and appear in neurodegenerative diseases, i.e., Parkinson’s disease (PD) and Alzheimer’s disease (AD), or correlate to brain atrophy.1–3 t-Hcys are associated with methylentetrahydrofolate reductase (MTHFR) enzyme activity. Homozygosity for a recessive mutation of the MTHFR gene reduces enzyme activity and consequently increases t-Hcys.4 Folic acid or vitamin B12 deficiency are additional causes for t-Hcys elevation in addition to onset of metabolic disorders, i.e., diabetes mellitus.2 O-methylation of levodopa supports t-Hcys increase and, thus, hypothetically accelerates neurodegeneration, since neurotoxic, excitotoxic (partially by means of N-methyl-d-aspartate [NMDA] agonistic), and mimicking property effects of homocysteine and its oxidation product homocystic acid were shown in various types of cultured human neuronal cell lines.1,5 Excitotoxicity also plays an important role in the pathophysiology of Huntington’s disease (HD). Striatal inclusion bodies occurring at elevated levels in postmortem brain tissue of HD patients showed fragments of the apoptotic cell death-inducing, mutated protein Huntington (mutHtt), which interacts with the homocystinuria-inducing enzyme cystathionine β-synthase.6,7 This interaction could also influence t-Hcys in HD patients. Therefore, we determined t-Hcys in HD patients and compared them to a healthy control group.

Subjects and Methods

We obtained blood samples drawn from 34 treated (defined as long-term intake of centrally acting compounds, e.g., anti-depressants, neuroleptics, benzodiazepines, tetrabenazine, anticholinergics) HD patients, 19 previously untreated HD subjects and 73 healthy controls (Table 1). Only Unified Huntington’s Disease Rating Scale (UHDRS) scores and HD duration significantly (P < 0.0001) differed between both HD groups. We excluded subjects with metabolic disturbances, i.e., diabetes mellitus, hypertension, nicotine abuse, hypothyroidism, reduced levels of vitamins, or increase of cholesterol and triglyceride.

Sample Collection

We took a blood specimen in the morning between 8 and 9 AM after 10 hours fasting from a peripheral vein, drop-wise in plastic vacuum ethanediaminetetraacetic acid tubes for t-Hcys determination. Samples were centrifuged 15 minutes, 300 × gav at 10°C without brake within 10 minutes. The resulting supernatant (plasma) was decanted and stored at −80°C. The time period between freezing and workup of the samples was no longer than 3 months. The t-Hcys were measured by an automated high performance liquid chromatography method with reverse phase separation and fluorescent detection, by NaBH4/mBrB reduction followed by monobromobimane derivatization. Additionally, we determined the MTHFR gene mutations.


**Statistical Analysis**

We used the analysis of covariance (ANCOVA) for comparison of homocysteine levels of all subjects. Covariates were age, sex, folic acid level, B6 and B12 levels, and the various MTHFR gene mutations. We used Tukey’s honest significance difference test for different numbers for the post hoc analysis and linear regression for correlation analysis.

**Results**

Homocysteine levels significantly differed between the three groups (ANCOVA $F_{(df 2, df 118)} = 8.67; P = 0.0003; \text{Table 1}$). The post hoc analysis showed significant differences between treated and previously untreated HD patients ($P = 0.0008$), between treated HD patients and controls ($P = 0.002$), but not between previously untreated HD patients and controls ($P = 0.91$). There was a significant effect of covariates ($F_{(df 5, df 118)} = 5.55; P = 0.0001$) due to folic acid ($\beta = 0.38; \text{coefficient} = -0.63; P = 0.02$). The remaining covariates had no significant impact (results not shown). The t-Hcys correlated to the UHDRS in previously untreated HD patients ($r = 0.52, t = 2.54, P = 0.02$) but not in treated HD patients ($r = 0.10, t = 0.55, P = 0.58$).

**Discussion**

We demonstrate an increase of t-Hcys in treated HD patients. The compounds administered to our HD patients for therapy are not metabolized by means of $O$-methylation, in contrast to, e.g., $\alpha$-dopa; therefore, we hypothesize that the t-Hcys increase could represent a biological metabolic marker for the ongoing neurodegenerative process in the treated HD patients. We assume that no relationship between UHDRS score and t-Hcys appeared due to the symptomatic benefit of drugs used in these more advanced HD patients. The positive correlation between UHDRS score and t-Hcys supports the hypothesis of the pathophysiological role of homocysteine in the neurodegenerative process in HD. Because hyperhomocysteinaemia is associated with atherosclerosis-related disorders, our results are also in line with epide-miological findings, which describe in particular cardiovascular disease and to a lesser extent cerebrovascular disorders in addition to pneumonia as leading causes of death in HD patients. An effective therapeutic approach for reduction of t-Hcys represents additional folic acid supplements, because folic acid and cobalamine catalyze and enhance metabolism of homocysteine to methionine. Methionine acts in combination with pyridoxal phosphate or S-methyl-$\alpha$-keto-butyric acid as a strong scavenger of oxidants, which in turn induce endothelial dysfunction. This homocysteine-induced endothelial dysfunction may further promote susceptibility to impaired mitochondrial energy metabolism as well as the known NMDA-mediated excitotoxicity. Thus, our results indirectly support the positive outcome of coenzyme Q10 and remacemide application in transgenic mouse models of HD.

In conclusion, we propose t-Hcys monitoring and folic acid supplementation for concomitant lowering of t-Hcys in HD patients. We also suggest a long-term trial of additional folic acid supplements in HD patients, because treatment this could hypothetically lower incidence of ischaemic heart and cerebrovascular disease and possibly decrease the neurodegenerative process in HD patients.

**Table 1. Clinical characteristics**

|                | Treated HD | HD*  | Controls |
|----------------|------------|------|----------|
| Number         | 34         | 19   | 73       |
| Age (yr)       | 47.59 ± 10.84 | 44 ± 12.14 | 55.16 ± 12.90 |
| Sex (M/F)      | 21/13      | 8/11 | 40/34    |
| $B_{12}$       | 454.26 ± 153.98 | 455.11 ± 154.03 | 421.47 ± 228.79 |
| Folic acid     | 6.64 ± 2.84 | 8.65 ± 3.54 | 6.51 ± 3.62 |
| MTHFR          | 17 (n), 11 (he), 6 (ho) | 9 (n), 7 (he), 3 (ho) | 35 (n), 27 (he), 11 (ho) |
| t-Hcys         | 17.74 ± 5.57 | 12.63 ± 3.80 | 13.31 ± 6.01 |
| Age of onset (yr) | 35.38 ± 10.06 | 41.05 ± 11.40 |
| Duration of disease (yr) | 4.94 ± 3.96 | 4.05 ± 3.27 |
| UHDRS          | 54.24 ± 20.13 | 22.63 ± 19.50 |
| CAG Hu         | 47.38 ± 4.62 | 45.18 ± 2.90 |
| CAG N repeats  | 18.43 ± 2.54 | 18.27 ± 2.12 |

Values are expressed as mean ± SD, unless otherwise indicated.

$n$, normal; $he$, heterozygote; $ho$, homozygote; HD, patients with Huntington’s disease; HD*, previously untreated HD patients; MTHFR, methylenetetrahydrofolate reductase gene mutation (number of subjects given for each allele); $B_{12}$, levels in pg/ml; folic acid, levels in ng/ml; t-Hcys, total homocysteine in plasma in μmol/L; UHDRS, score of Unified Huntington’s Disease Rating Scale; CAG Hu, CAG N repeats, number of trinucleotide repeats.

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**Movement Disorders**, Vol. 19, No. 2, 2004
Exercise-Induced Dystonia as a Preceding Symptom of Familial Parkinson’s Disease

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Abstract: Paroxysmal exercise-induced dystonia can occur with Parkinson’s disease (PD), and in rare cases, this can also be the presenting symptom. We report on 2 second cousins (no known consanguinity) who presented with paroxysmal exercise-induced dystonia who later developed clinical features of PD. Although autosomal recessive inheritance was suggested, and the dystonic features further suggest parkin as a possible cause, sequencing for parkin mutations was negative and this family may represent a genetic variant of PD. Further genotype–phenotype studies in this and similar families may give clues to pre-symptomatic symptoms in PD and may reflect a particular phenotype of interest for genetics studies in the future. © 2004 Movement Disorder Society

Key words: Parkinson’s disease; familial; exercise-induced dystonia; parkin

Dystonia is a well-known symptom of Parkinson’s disease (PD), and may even be the presenting symptom.1 However, there are few reported cases of intermittent, exercise-induced dystonia as a heralding or preparkinsonian manifestation.2–5 Purves-Stewart first reported intermittent “curling up” of the toe only upon walking as a symptoms of PD in 1890.2 Lees and colleagues reported “kinesigenic foot dystonia” in 3 patients with PD; one of those cases, a 42-year-old marathon runner, had this condition as the presenting symptom.3 Recently, Katzenschlager and associates (2002) reported a subject presenting with exercise-induced dystonia in whom a dopamine transporter SPECT scan provided early evidence of dopamine depletion, consistent with PD.4 We encountered 2 patients, second cousins without known consanguinity, whose presenting symptoms were exercise-induced dystonia. Both of them later developed clinical features of PD. The familial occurrence of this presentation has not been reported previously.

Materials and Methods

Clinical Evaluation.

Clinical evaluation including videotape recording, sampling, and genetic studies was performed following informed consent approved by an institutional review board. Subjects underwent a neurological history and videotaped physical examination, and donated blood samples which were subsequently tested for parkin mutations.6 The diagnosis of PD was based on UK Brain Bank criteria.7

Gene Screening.

DNA was isolated by standard phenol–chloroform extraction from venous blood. PCR amplification of the coding exons of parkin was performed using the primer pairs and conditions previously described.6 Five microliters of the resulting products were then electrophoresed on a 2% agarose gel containing ethidium bromide to confirm amplification. The remaining PCR products were then cleaned using a purification kit (Qiawick 96 PCR; Qiagen). Sequencing reactions were performed on the resulting eluant using the forward and reverse amplification primers and ABI BigDye terminator reaction kits (Applied Biosystems) per the manufacturer’s instructions. These reactions were then analyzed on an ABI3100. Sequence analysis was performed using Sequencher (GeneCodes Corporation). Sequences were compared to the publicly available sequence (GI:3063387).

A videotape accompanies this article.

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Received 10 February 2003; Revised 11 July 2003; Accepted 7 August 2003

DOI 10.1002/mds.10626
Results

Case Reports

Case 1 (Video, Segments 1 and 2).

This 59-year-old, Caucasian, left-handed man, an avid athlete, noted foot cramping when he was 53 years old. His left foot would involuntarily and painfully turn inwards after approximately 15 minutes of aerobic exercise such as bicycling or running. The foot would return to normal when he stopped the activity. His evaluation by an orthopedist included normal findings on the magnetic resonance scan of the foot; no orthopedic cause was found. A neurologist subsequently diagnosed him with “intermittent dystonia” and the patient was prescribed pramipexole (1.5 mg t.i.d.) and controlled release carbidopa–levodopa (Sinemet CR 50/200) once a day. On this regimen, he noted significant improvement of the exercise-induced cramps. He discontinued the medication because he noticed breakthrough symptoms a couple of months after starting the dopamine supplementation. This consisted of persistent left foot dystonia at rest without exercise. After he discontinued the medication the rest dystonia improved, but the exercise-induced dystonia returned. Eventually, he completely discontinued exercise due to exacerbation of symptoms.

Four years later, he noted new onset clumsiness of the left hand and worsening of his left foot dystonia. He restarted carbidopa–levodopa (Sinemet CR 50/200) once a day, which improved the foot dystonia but not the upper extremity symptoms.

On physical examination (off dopamine supplementation over 8 hours), he had mild masked facies and hypophonia. He had moderate left upper extremity cogwheel rigidity as well as mild rigidity of the right upper extremity (seen only with reinforcement). Rapid alternating movements were markedly slow on the left with breakdown of movement, and moderately slow on the right. He had no rest or action tremor. His gait showed decreased left arm swing and slightly flexed posture. After exercising on a stair-stepping machine for 5 minutes, his left foot turned outwards and became stiff. The foot returned to a normal posture as soon as he stopped exercising.

Case 2.

This 67-year-old, left-handed, Caucasian woman (the second cousin of Case 1; see Fig. 1) developed dystonia at age 58 years of age. She noted that her right toes would “crumple in” when walking quickly, especially on hard surfaces. When she stopped walking, the foot symptoms resolved in a few seconds. Symptoms progressed to include micrographia at age 59. The foot symptoms remained untreated and progressed. The symptoms of clumsiness and difficulty with coordination occurred over the next several years, and at age 62 a neurologist diagnosed her with idiopathic PD. She started carbidopa–levodopa (Sinemet 25/100 t.i.d.) and ropinirole (titrated up to 3 mg t.i.d.). She noted some improvement of her left hand symptoms but the foot dystonia persisted.

On examination (off dopamine supplementation and ropinirole over 8 hours), she had mild masked facies and mild hypophonia. She had mild to moderate cogwheel rigidity of the right upper extremity and, mild rigidity on the left upper extremity with reinforcement. Rapid alternating movements were slowed bilaterally, moderately on the right, and mildly on the left. Arm swing was decreased bilaterally. On pull testing, she had retropulsion but recovered unaided. She had difficulty walking due to an unrelated surgery, and no dystonia was observed. Genetic screening using direct sequencing has excluded a parkin mutation.

Discussion

These 2 patients were second cousins with no known consanguinity. We suspect a genetic cause of PD, most likely autosomal recessive. Although PD itself is rather common, paroxysmal dystonia is more rare, making these 2 cases in the same family less likely to be a coincidence. In addition to the inheritance pattern, these cases resemble the parkin phenotype carrying parkin mutations, which often have fixed dystonia at onset. Exercise-induced dystonia can even be the presenting symptoms in parkin mutation. However, the ages of symptom onset are older in the patients reported here than the classic cases with parkin mutations. Although we did not identify any coding mutations within the parkin gene on the proband, we cannot exclude the possibility of heterozygous whole exon deletion or insertion mutations within parkin in the case examined here. Gene dosage analysis is necessary to address this possibility.

The first patient began to experience left foot dystonia at rest shortly (a couple of months) after initiating dopamine therapy. This timing may possibly represent dyskinesias from levodopa therapy, especially. However, there was no correlation between the timing of his medication and his left foot dystonia at rest, and this explanation is unlikely. There is also a clinical similarity to the “augmentation” phenomenon observed in restless legs syndrome. In augmentation, patients begin to experience
daytime symptoms (when they were symptom-free before starting the medication) after initiating levodopa treatment and enjoying clinical response of the nighttime restless leg symptoms.10

The differential diagnosis of paroxysmal exercise-induced dystonia includes the entities of the paroxysmal dyskinesias. This category contains paroxysmal exercise-induced dyskinesias (PED), which may be familial or sporadic.11 Other unusual causes of paroxysmal exercise-induced dystonia, such as lumbar canal stenosis or tetany-like presentation of hypoparathyroidism, are reported.12,13

Heyes and coworkers reported that, in rats, the striatal dopamine levels as well as dopamine metabolite levels were significantly increased with strenuous exercise.14 These authors estimated that the turnover of striatal dopamine increased by at least 85% at exhaustion. Such increases are more prominent in the later phase of exercise. Another experiment showed increased striatal tyrosine hydroxylase activity, dopamine, and 3,4-dihydroxyphenylacetic acid (DOPAC, a dopamine metabolite) concentration only after 15 minutes of exercise.15 In humans, dopamine transporter (11C-labelled 2-β-carbomethoxy-3β-(4-fluorophenyl) tropane or 11C-CFT) PET demonstrated that dopamine metabolism may be regulated in response to gait.16 Based on these observations, there are two possible physiological explanations for this phenomenon. In the presymptomatic stage of PD, patients with little reserve of dopamine may not be able to meet the increased metabolic demand from exercise, leading to reversible dystonia. Alternatively, the increased release of dopamine during exercise may overstimulate the dopamine receptors, which became hypersensitive or upregulated due to subclinical dopamine deficiency.

Symptoms of foot cramps only during prolonged exercise may not be taken seriously by either patients or physicians but, nonetheless, may be the earliest signs of PD. In our first patient signs of PD developed 4 years after the paroxysmal dystonia. Thus, such symptoms deserve a thorough evaluation as well as possible predictors of future PD.

Acknowledgments: We thank Devee Schoenberg for helping with manuscript preparation. This work was supported by the National Institutes of Health (43533 to L.J.P.).

Legends to the Video

Segment 1. After being on the stair-stepping machine for 5 minutes, patient’s left foot is turning outwards.

Segment 2. Left foot dystonia is demonstrated by walking immediately after the exercise. In addition, his gait shows parkinsonian features, such as hypomimia, decreased arm swing (bilateral but more on the left), and flexed posture.

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Clinical and Genetic Features of Myoclonus–Dystonia in 3 Cases: A Video Presentation

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Abstract: Many cases of myoclonus–dystonia (M-D) are caused by mutations in the e-sarcoglycan (SGCE) gene. We describe 3 children with a similar clinical picture of autosomal dominant M-D and an SGCE mutation in only one of them, suggesting that M-D is genetically heterogeneous. © 2004 Movement Disorder Society

Key words: myoclonus–dystonia; SGCE gene; genetic heterogeneity

Myoclonus–dystonia (M-D) is characterized by onset of myoclonus usually in the first or second decade of life and additional dystonic features in more than half of those affected.1,2 Table 1 summarizes the recently revised diagnostic criteria.2

Currently, only a few families with linkage to or mutations in the SGCE gene have been described clinically.3–10 Of interest, several members of an otherwise typical M-D family with an SGCE mutation were reported recently to suffer from epilepsy and to show epileptic electroencephalograph (EEG) changes,15 illustrating the necessity to re-evaluate the above-mentioned diagnostic criteria in larger, genetically defined patient cohorts.

We report the detailed clinical phenotype of 3 unrelated children suffering from inherited M-D, 2 of whom were initially considered sporadic and given an unclear diagnosis. An SGCE mutation was found in only one of them. To our knowledge, this is the first video presentation of genetically defined M-D patients that may serve to alert neurologists and neuro-pediatricians to this probably underdiagnosed movement disorder.

Case Reports

Case 1

A 4-year-old girl was first seen in our outpatient clinic in 2000 with a 2-year history of clumsiness and action-induced involuntary jerky movements. At the age of 2 years, her mother first noticed difficulties in lifting a cup, eating with a spoon, or drawing an image, which gradually worsened over 1 year and then remained stationary. Both arms were equally affected, but there was no leg involvement, and the patient could walk, run, and even dance normally. Involuntary movements worsened with stress or febrile conditions.

She was the second daughter of unrelated, healthy parents. Pregnancy, delivery, and early developmental milestones were normal, as was past medical history, and family history was negative for neurological or other hereditary diseases.

On neurological examination in 2000, the patient showed marked action-induced myoclonus of the upper extremities and the head. Drawing an image evoked writer’s cramp and some truncal dystonia, along with myoclonic jerks of both arms and overflow to the neck. Myoclonus and dystonia were absent at rest, and cranial muscles and the lower extremities were completely spared. The remainder of the neurological examination was entirely normal, and a diagnosis of M-D was established on clinical grounds. A levodopa trial to rule out the unlikely diagnosis of dopa-responsive dystonia did not have any effect on the patient’s M-D, and the parents did not agree to try any other medications. At follow-up in 2001, the condition was unchanged; in early 2003 the patient, now 6 years of age, and her mother reported a mild improvement of symptoms. Parts of the neurological examination are presented in Segments 1, 2 (August 2001), and 3 (January 2003) of the videotape. Neurological examination of both parents was unrevealing.

Routine laboratory testing for clinical chemistry, including blood counts, copper, ceruloplasmin, and vitamins, EEG, and magnetic resonance imaging (MRI) were normal. Molecular genetic analysis revealed a 1-bp insertion in exon 5 of the SGCE gene (625insG) in the patient and in her unaffected father. Genetic but not clinical details have been presented elsewhere.16

Case 2

A 5-year-old boy presented with a 3-year history of gait problems and action-induced involuntary jerky movements of both arms and the neck. After an initially normal motor devel-
TABLE 1. Diagnostic criteria for M-D

Cardinal clinical diagnostic criteria
- Onset of myoclonus usually in the first or second decade of life; dystonic features are observed in more than half of those affected in addition to myoclonus and may rarely be the only manifestation of the disorder.
- Males and females about equally affected
- A relatively benign course, often variable but compatible with an active life of normal span in most cases
- Autosomal dominant mode of inheritance with variable severity and incomplete penetrance, which is dependent on the parental origin of the disease allele; affected individuals usually inherit the disease from their father.
- Absence of seizures, dementia, gross ataxia, and other neurological deficits
- Normal EEG, normal SSEP, normal results of neuroimaging studies (CT or MRI)

Optional criteria
- Response of symptoms (particularly of the myoclonus and to a lesser degree of the dystonia) to alcohol
- Various personality disorders and psychiatric disturbances
- Genetic testing
  - SGCE mutations confirm the diagnosis of M-D

M-D, myoclonus–dystonia; EEG, electroencephalogram; SSEP, somatosensory evoked potential; CT, computed tomography; MRI, magnetic resonance imaging.

opment, his parents first observed difficulties in walking with stumbling and falling at age 2 years. One year later, he developed action-induced jerky movements of both arms that severely interfered with fine motor skills and many activities of daily living, such as eating and drinking. The movement disorder worsened with stress; gait, however, gradually improved over the years. Different diagnoses included “cerebral palsy” and a “psychogenic movement disorder” due to the mother’s “nervousness.” The patient was the product of an uneventful pregnancy and delivery; early developmental milestones and past medical history were normal. In particular, he had never had epileptic seizures.

The parents were unrelated, and family history was initially reported to be negative by the mother (the father was not present at the initial visit). Upon more detailed history taking, the 32-year-old father described involuntary jerky movements that had started in early childhood. The movement disorder gradually improved over the years and was compatible with an active professional and social life. Symptoms responded to alcohol; no medication had been tried. No other family members were affected with M-D or a similar condition.

On neurological examination of Case 2 at 5 years of age (January 2003), he had action-induced myoclonus and dystonia of the upper extremities, the trunk, and neck, but could walk, run, and play football normally. Intermit- tently, however, dystonia was also observed in the legs. Overall, dystonia was more pronounced on the left hand side (see Video, Segment 4). Symptoms were absent at rest, and cranial muscles were unaffected. The patient had no other neurological signs, and a diagnosis of M-D was made. In 2001, levodopa (150 mg/d) was given for a few months without any effect. Parts of the neurological examination are shown in Segment 4 of the videotape. Neurological examination of the father, who did not agree to be videotaped, revealed mild, clinically typical M-D with predominant myoclonus and little dystonia, both confined to the upper body half with cranial muscles spared.

Routine laboratory testing of the index patient was normal, as was brain MRI. EEG at the age of 5 years revealed a left temporoparietal spike-wave focus, compatible with a Rolandic focus. At one point, generalized discharge was observed. The background activity was appropriate for the boy’s age; no focal slowing occurred, and many former EEGs had been normal. Sequencing of the coding region and of exon/intron boundaries of the SGCE gene revealed a known polymorphism in intron 3 (IVS3-43A>C) but no mutations. Furthermore, we excluded the GAG and the recently described 18-bp deletion in the DYT1 gene, as well as the known mutation in exon 3 of the DRD2 receptor gene.

Case 3

This 12-year-old boy presented with a 3-year history of shakiness in both arms. He had noticed this first when carrying objects. His handwriting became slower and scribbly, followed by a mild head tilt to the left. Neither he nor his parents were aware of other symptoms. Treatment has as yet not been considered necessary by his parents or himself.

The 33-year-old father had developed tremulousness of both arms at the age of 9 years. Like his son, he recalled that he had first noticed shaking of both arms when carrying trays or lifting a cup and saucer. His handwriting became slow and clumsy. Until the age of 18 years, these symptoms did not change noticeably. Over a period of several months his head and neck then gradually started to turn to the left and tilt to the right. Involuntary head movements soon became very brisk and jerky, particularly when trying to turn his head to the left. Abnormal head movements completely ceased when he was drinking six to eight pints of beer. In his late twenties, he also developed hand and arm jerks, particularly when turning his arms. In addition, the paternal grandmother and one of the two paternal aunts were reported to have involuntary twisting head movements but not severe head jerks. They declined to be examined.

Laboratory testing, EEG, and neuroimaging of Case 3 were normal; no SGCE mutations were found by genetic testing. On neurological examination, Case 3 had mild left laterocollis and mild action-induced pro- and supination myoclonus of both arms, particularly when holding a glass in his hands, but no myoclonic jerks affecting the neck/head. His writing was slow and irregular, but there was no abnormal posturing and no myoclonic jerks. Neurological examination was otherwise normal.

His father had mild left torticollis and right laterocollis when sitting upright in a chair with his hand holding his chin. When releasing his head and trying to hold it still, irregular jerky head movements with changing direction immediately started. Any voluntary head movement induced violent “lightning jerks” superimposed on somewhat slower variable “background” jerks. When holding out his arms he also had a mild postural up and down tremor of both arms and position specific myoclonic jerks on pro- and supination movements but there was no dystonic posture. Both Case 3 and his father are shown in Segment 5 of the videotape.

Discussion

Here we describe 3 children with clinically similar M-D and a proven SGCE mutation in 1 of them. Despite the typical clinical presentation, the diagnosis of M-D was established in
all 3 patients and the fathers of Cases 2 and 3 only with considerable delay and after referral to a specialized movement disorders clinic. M-D is a rare condition of unknown prevalence but likely often mis- or underdiagnosed. As illustrated by all 3 of our children, disease manifestation may be mild and, particularly in the early stages of the condition, only obvious upon careful neurological examination.

Although onset of symptoms usually occurs in the first or second decade of life (average age of onset 9 years; range, 0.5–38 years), symptoms started rather early in 2 of our cases, i.e., at age 2 years. All 3 patients presented with the typical action-induced myoclonus and to a lesser degree dystonia, confined to (Cases 1 and 3) or most pronounced in (Case 2) the upper body half. In contrast to other early onset dystonias with frequent symptom onset in the legs and subsequent generalization, prominent involvement of the upper extremities and relative sparing of the lower extremities is a well-described feature of M-D, even in cases with a very early onset such as ours. Of interest, the leg dystonia was only intermittently present in Case 2.

Case 3 met all of the M-D diagnostic criteria listed in Table 1. Case 2, however, showed focal EEG changes in the left hemisphere with rare generalization. Of interest, the dystonia was most pronounced on the ipsilateral side, rendering a connection between the EEG changes and the movement disorder highly unlikely.

Cases 1 and 2 initially appeared sporadic and, thus, did not conform to the fourth diagnostic criterion for M-D (Table 1). However, detailed history taking and clinical examination revealed mild but clinically definite M-D also in the father of Case 2, suggesting autosomal dominant inheritance and underlining the necessity to personally examine even reportedly unaffected family members. Likewise, M-D in Case 1 turned out to be familial, as molecular analysis revealed an SGCE mutation in her father. The latter was shown to express only his normal SGCE allele, which explains his being unaffected. In this case, autosomal dominant inheritance of the mutation/condition could only be detected by mutational analysis of the SGCE gene but not by history taking or clinical examination of the father.

Surprisingly, an SGCE mutation was only found in 1 of the 3 cases, although the clinical picture was remarkably similar. Sequencing of the entire coding region and exon/intron boundaries is considered the gold standard of mutational analysis. However, it is possible that we may have missed mutations in parts of the gene that were not tested (introns or promoter regions) or exon rearrangements that are not detectable with conventional methods. Alternatively, Cases 2 and 3 may carry a mutation in the unidentified M-D gene on chromosome 18 or in yet another M-D gene.

Our case reports stress the importance of careful genetic counseling. Counseling issues in M-D include variable expressivity and reduced penetrance, genetic heterogeneity, and probably also nongenetic phenocopies. Finally, it should also be kept in mind that lack of a proven SGCE mutation does not exclude a genetic disorder per se, as illustrated by our Cases 2 and 3 with dominantly inherited M-D. The clinical and mutational spectrum of M-D should be re-evaluated using a larger patient sample of genetically defined cases.

Acknowledgments: We thank the patients and family members who participated in this study. This work was supported by a research grant from the Fritz Thyssen Foundation (C.K., N.K.) and the Volkswagen Stiftung (A.M.).

Legends to the Video

Segment 1. Case 1. August 2001 (at 5 years of age). Action-induced myoclonus of both arms and hands and of the neck when placing small pins or wooden building blocks in wells or when filing beads on a string. Mild cervical dystonia is occasionally present.

Segment 2. Case 1. August 2001 (at 5 years of age). The patient can walk and run normally. Hopping on one leg is normal for the patient’s age. Dystonic posturing of both arms with superimposed myoclonic jerks. On the finger-to-nose test, action-induced myoclonus occurs bilaterally but no intention tremor is present. Attempting to drink water from a cup is almost impossible due to myoclonic jerks, predominantly of the neck and both arms. Drawing an image provokes writer’s cramp, torticollis, and myoclonus of the upper body half. The patient can only perform these tasks by using both hands.

Segment 3. Case 1. January 2003, 17 months later (at 6 years of age). Walking and running remain normal. Ability to hop on one leg improved (according to the patient’s otherwise normal motor development). Action myoclonus on finger-to-nose test slightly decreased; drinking from a cup and writing is still only possible with both hands but is associated with less myoclonus and dystonic posturing.

Segment 4. Case 2. January 2003 (at 5 years of age). Occasional myoclonic jerks of the arms and head when performing fine motor tasks. Dystonia (only intermittently present) of the left leg on walking and running. Gait abnormalities disappear when walking backward. Drawing an image elicits (predominantly truncal) dystonia and myoclonic jerks of the upper body half. The patient is unable to lift a cup without spilling the contents and has to bend forward to drink. Occasional myoclonic jerks are visible.

Segment 5. Case 3 and his father. July 2002 (son at 9 years of age, father at 33 years of age). Gait is normal in both father and son. The father has mild left torticollis and right laterocollis with irregular jerky head movements with changing direction. Holding the arms outstretched and counting backward provokes “lightning jerks” of both arms with slower variable involuntary head movements continuing. During pro- and supination movements of his arms, he develops position-specific myoclonic jerks. Case 3 has mild left laterocollis and mild dystonic posturing of both hands. Pro- and supination movements are slightly irregular. When holding a glass in either hand, there are mild action-induced pro- and supination myoclonic jerks.

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