Movement Disorders
Vol. 17, No. 3, 2002, pp. 598–624

Clinical/Scientific Notes

Camptocormia in Parkinson's Disease Mimicked by Focal Myositis of the Paraspinal Muscles

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Abstract: We report on a 63-year-old man with idiopathic Parkinson's disease who developed kyphosis and a severe forward flexion of the thoracolumbar spine. A typical feature was an increase during walking or standing and it completely disappeared in the supine position, mimicking the clinical phenomenon of camptocormia (bent spine). In addition to the abnormal posture, a weakness of the erector spinal muscles, local pain, reddening, and elevated temperature of the paraspinal muscles were evident. Creatine kinase was initially elevated, electromyography showed spontaneous activity and a myopathic pattern. Magnetic resonance imaging and bioptic examinations revealed a focal myositis of the paraspinal muscles. This case indicates that camptocormia can be mimicked by focal myositis of paraspinal muscles and must be included in the differential diagnosis, especially when additional symptoms as inflammatory signs or weakness are present. © 2002 Movement Disorder Society

Camptocormia (from the Greek *kamtos*, curved, and *kormos*, trunk) has been characterised by extreme flexion of the thoracolumbar spine with passive dropping of both arms and a variable degree of genuflexion. A typical feature is an increase during walking or sitting and a disappearance in supine position.[1] It was first mentioned by Brodil in 1837.[2]

Camptocormia in idiopathic Parkinson's disease (PD) has been described by Djaldetti and colleagues.[1] As possible pathogenetic factors, an extreme form of rigidity and a rare type of dystonia were discussed. In most of the reported patients, an underlying psychogenic conversion reaction has been assumed.[2,3] During World Wars I and II, camptocormia was just one of the conversion reactions in young soldiers who were unable to cope with battle stress.[4,5] The differential diagnosis includes spinal cord neoplasms, vertebral infections, intradural or extradural hematomas, occasionally a herniated disc, spinal stenosis,[2] and an adverse effect of valproic acid.[6] It may also be the result of a rare form of muscular dystrophy specifically affecting the paraspinal muscles.[7–9] Furthermore, a case of possible paraneoplastic aetiology in non-Hodgkins lymphoma has been described.[10]

We report on a patient with idiopathic PD and clinical features of camptocormia who suffered from a focal myositis of the paraspinal muscles.

Case Report

The 63-year-old man had suffered from idiopathic PD for 6 years when he was examined for the first time at the University Department of Neurology, Würzburg. The presenting symptoms of his disease were rigidity, bradykinesia, and a left-sided tremor (Unified PD Rating Scale [UPDRS] scores: I, 0; II, 9; III, 20; IV, 0). He was treated with levodopa and dopamine agonists with good success. Two months before admission following an enteral infection, he first noticed pain of the paraspinal muscles and developed a truncal flexion. At this time, creatine kinase (CK) was markedly elevated (about 900 U/L). Fever was not evident.

On clinical examination, apart from his parkinsonian symptoms the patient demonstrated a left lumbar and a right thoracic scoliosis. Muscular testing revealed a weakness of the spinal erector muscle. Left-sided thoracolumbar paraspinal muscles were painful, showing local skin reddening and elevated temperature. A forward flexion of approximately 40 degrees and a lateral shift were apparent on standing or walking and completely disappeared in the supine position (Fig. 1).

Laboratory findings were normal, notably no leukocytosis, eosinophilia, or increased erythrocyte sedimentation rate (ESR) could be found. CK was in the middle normal range (44 U/L), but declined to 14 U/L after the therapy with steroids. Serological examinations (among others, antibody testing for salmonella, yersinia, aspergillus, mucoracea, cryptococcus, campylobacter, echinococcus, toxoplasma, trichinella, cysticercus, legionella, borrelia, enterovirus, parainfluenza, HIV) excluded a specific infection.

Electromyography (EMG) of the thoracic spinal erector muscle (segment Th3) on the left side showed spontaneous activity (positive sharp waves and fibrillations) and a myopathic pattern (reduced amplitudes and duration of motor unit action potentials [MUAP], dense interference pattern at only mild voluntary muscle activation, polyphasic MUAPs). There were no pathological EMG findings in the contralateral spinal erector muscle, the biceps, and the interossei muscles of the right upper extremity.

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Received 10 May 2001; Revised 17 August 2001, 3 October 2001; Accepted 12 November 2001

Published online 12 February 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10110

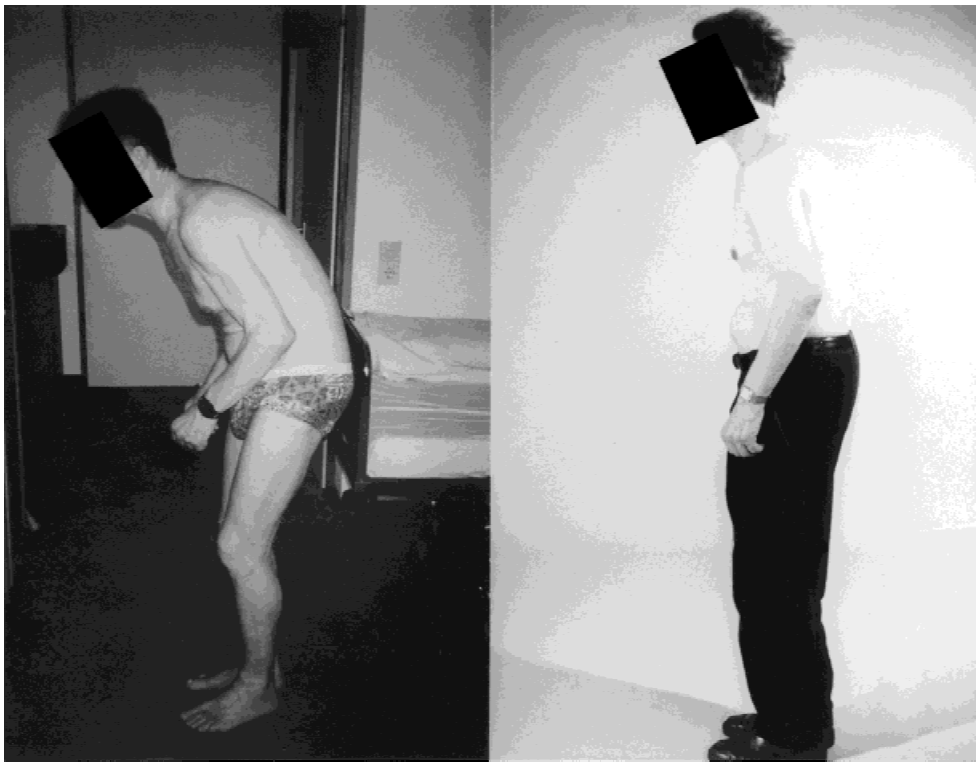

FIG. 1. Patient with PD and focal myositis of the paraspinal muscles before (**left**) and after treatment (**right**).

The T2-weighted sequence of magnetic resonance imaging (MRI) of the thoracolumbar spine showed an increase of volume and hyperintensity of the left-sided paraspinal muscles (quadratus lumborum, longissimus dorsi, and ileocostalis muscles) reflecting muscle edema. These findings were suggestive with a myositis of the paravertebral muscles (Fig. 2).

A muscle biopsy was taken from the left lumbar spinal erector muscle (segment L5). Histopathology showed marked perivascular infiltration of mononuclear cells, an increased variation of fibre size, several small angular fibres, an increased number of central nuclei, and mild to moderate focal proliferation of fibrous tissue. There were also a few necrotic fibres. Immunohistochemistry showed an increased number of endomysial macrophages, perivascular clustering of macrophages, and CD4- and CD8-positive T cells with a greater amount of CD8- than CD4-positive T cells within the infiltrates (Fig. 3).

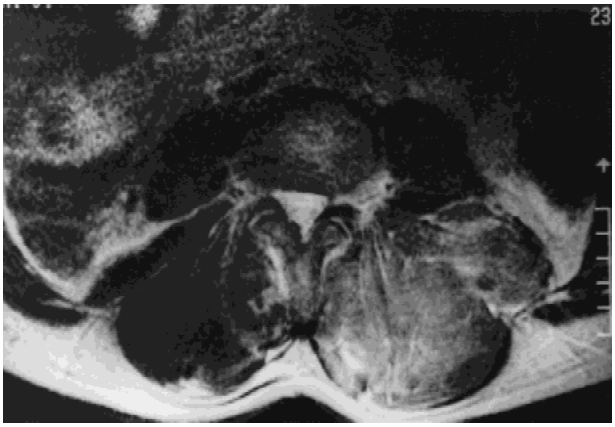

FIG. 2 Axial lumbal magnetic resonance imaging (MRI) scan, T2-weighted sequence. Increase of volume and hyperintensity of the left-sided paraspinal muscles (quadratus lumborum, longissimus dorsi, and ileocostalis muscles) indicating edema (right side of figure).

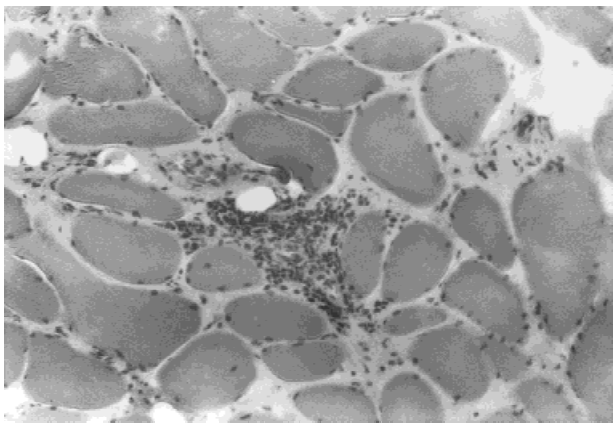

FIG. 3. Hematoxilin–eosin staining showing perivascular infiltration, an increased variation of muscle fibre size with some small (angular) and some hypertrophic fibres, some central nuclei, and moderate proliferation of endomysial fibrous tissue (×200).

After steroid treatment (methylprednisolon 250 mg intravenous for 3 days, 20 mg oral for the following months), a marked improvement of local inflammatory signs, pain, and muscle force was noticed. The control MRI scan 4 weeks after start of treatment showed a mild regression of edema. Under steroid treatment, anteflexion and scoliosis showed marked regression during rehabilitation. CK levels in the follow-up (every 2 weeks) were within the normal range (maximum, 23 U/L). The patient remained stable for several months and was then lost for follow-up.

Discussion

The patient described here developed kyphosis and severe truncal anteflexion 6 years after onset of idiopathic PD. Characteristic features of this abnormal posture were the increase while walking or standing and the absence in recumbant position. This phenomenon has been previously described as camptocormia (bent spine). In most cases, a psychogenic conversion reaction has been supposed.[2–5] In 1995, Laroche and colleagues[7] discussed camptocormia as a primary muscular disease. Studies on patients with camptocormia without extrapyramidal signs found low signal intensity of the paravertebral muscles on computed tomography (CT) and MRI. Muscle biopsies showed diffuse or lobulated fibrosis and atrophy of the type II fibres.[8,9] These results were consistent with myopathic changes in paraspinal muscles. The largest series reported 27 patients with camptocormia, among those 20 with a familial history of the disorder.[7] To our knowledge, camptocormia in PD has only been described by Djaldetti and associates[1]; the authors identified no linkage between the onset of levodopa therapy and the appearance of camptocormia. Electromyography excluded myopathic changes in the paraspinal muscles. Spinal CT and/or MRI showed lumbar spinal stenosis in 3 patients and spondylarthrotic degenerative changes in 5 patients. The pathogenesis of camptocormia remained obscure, and a rare type of dystonia or an extreme form of rigidity were discussed. Only recently, Askmark and coworkers[19] described the association between parkinsonism and an isolated neck extensor myopathy resulting in dropped head. Electromyography and muscle biopsy revealed myopathic changes.

The case presented here is the first report on camptocormia in PD due to focal myositis of the paraspinal muscles. Despite similar clinical features, our patient showed some marked differences to classical camptocormia. Examination showed a weakness of the spinal erector muscles, local pain, and inflammatory signs of the left-sided thoracolumbar paraspinal muscles. EMG showed spontaneous activity and a myopathic pattern. MRI scans and muscle biopsy of the paraspinal muscles lead to the diagnosis of a focal myositis. To our knowledge, no correlation between myositis and treatment with levodopa and/or dopamine agonist has been described so far. Although a primary inflammatory disease of paraspinal muscles can easily explain camptocormia in our patient, we cannot rule out that preexisting mild camptocormia from other reasons may have triggered focal myopathy.

Focal myositis is a very localised, benign, self-limited inflammation of skeletal muscles usually of unknown cause. First described by Heffner and colleagues in 1977,[11] only a small number of cases have been reported occurring in the upper and lower limb, neck, tongue, masticatory and temporal muscles, and the abdominal rectus muscle.[11–16] Focal paraspinal myositis causing forward flexion deformity may result from local infection, while to the best of our knowledge, an autoimmune origin has not yet been reported. In focal myositis, there is a high rate of spontaneous regression, but focal recurrence in other muscles or extension to polymyositis have been reported.[17,18] Usually, an anti-inflammatory treatment is needed.

In conclusion, focal myositis of the paraspinal muscles may mimic the clinical features of camptocormia. If additional symptoms such as muscle pain, weakness of the paraspinal muscles, CK elevation, and local inflammatory signs are present, further diagnostic measures are needed. EMG and MRI can easily show a myopathy and a possibly inflammatory cause. Because of the treatment options, this important differential diagnosis should not be missed.

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Reversible Parkinsonian Syndrome in Systemic and Brain Vasculitis

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Abstract: A young female patient with chronic renal failure due to a systemic vasculitis and a parkinsonian syndrome secondary to brain vasculitis, most likely systemic lupus erythematosus, is described. The patient had a dramatic response to a pulse of methylprednisolone, with remision of her parkinsonian symptoms.

Angiitis or vasculitis of the central nervous system (CNS) is a rare form of vasculitis, of which we know relatively little. Most of the scientific knowledge is based on information provided by a small series of studies involving small numbers of patients.[1–3] CNS vasculitis can be either primary or secondary[1,2]; primary CNS vasculitis may respond to aggressive immunosuppressive therapy, but these are often fatal.[1–3] Secondary CNS vasculitis occurs in association with several forms of systemic vasculitic and nonvasculitic disorders (infections, neoplastic diseases, or toxics) with variable brain biopsy findings.[1–3]

Patients afflicted with systemic vasculitis may exhibit a wide spectrum of neurological and psychiatric symptoms. Movement disorders (MD) such as chorea, hemiballismus, and parkinsonism (PS) have been described in association with CNS vasculitis.[4–7] PS is a very rare clinical manifestation of CNS vasculitis and there are few reports of such an association.[4–9]

A review of systemic lupus erythematosus (SLE)-related neurological complications in adults showed that fewer than 5% of affected patients had some kind of MD, of which PS was very rare.[4–8] Walker and colleagues,[10] while studying Sjogren's syndrome, reported on 3 new cases of PS associated with Sjögren's syndrome (SS), and reviewed a total of 8 previously reported cases.[10]

We report on a patient with chronic renal failure, PS, and brain vasculitis most likely secondary to SLE. The patient had a dramatic improvement after pulse therapy with methylprednisolone with remission of the parkinsonian symptoms.

Case Report

A 33-year-old, African-American female was admitted to our service complaining of progressive slowing of body movements, dysarthria, rigidity, postural instability, tremors in the upper limbs, and auditory hallucinations that had begun roughly 1 year previously. The patient also had a psychiatric history (hallucinations and mood changes associated with behavior disorders) that had begun 3 years earlier. On that occasion, the patient was hospitalized for a few days for psychiatric treatment and was discharged with drugs (patient could not recall the names of the drugs, and her records were not available; however these were probably mood stabilizers or neuroleptic drugs), that she used for less than 3 weeks. Since then, she was free of any drug treatment (i.e., for at least for 2 and a half years). She complained of weight loss, anorexia, asthenia, arthralgiaes, and frequent vomiting. Physical examination was normal. Neurological examination showed a mask-face, discrete bilateral rest and kinetic tremor, severe bradykinesia, cogwheel rigidity (worse on the left side), parkinsonian gait, and postural disturbances. She also had dysarthria (slurred speech) and bilateral hyperreflexia and Babinski responses.

Laboratory testing disclosed anemia (2,800,000 erythrocytes/mm^3; hemoglobin, 8.6 g/dl; hematocrit, 26.6%), a leukocyte count of 2,400/mm^3, a platelet count of 44,000/mm^3; creatinine, 6.77; Cryoglobulins, 1:128 (precipitation test) and erythrocyte sedimentation rate (ESR), 95 mm. The patient had anti-histone antibodies of 1.5 U (borderline) and low levels of C3 (70 mg/dl; range, 94–149). She showed a persistent proteinuria of 1.1 g per day with mixed cellular casts in her urine. Cerebrospinal fluid (CSF) showed a protein of 96.9 mg/dl at hospital admittance with no cells. Lupus erythematosus (LE) cell preparation was negative.

Blood chemistry, thyroid function tests, Vitamin B12, folate, treponemal hemagglutination test, anti-Ro/SS-A, anti-La/SS-B, rheumatoid factor, lupus anticoagulant, antiphospholipid antibodies, and anti-neutrophilic cytoplasmatic antibodies (ANCA), and anti-DNA antibodies testing including n-DNA antibody testing were all normal/negative. Survey for heavy metals (Pb, Mn, Zn, Cr, Cu, Hg, Al) in blood and urine was negative. Ceruloplasmin was normal (24.6 mg/dl) and liver function was also normal. Corneal slit-lamp examination showed no abnormalities. Immunological tests for measles and mumps were also negative.

Brain magnetic resonance imaging (MRI) showed on T2/Flair weighted images (Fig. 1) a symmetric hyperintense signal in the basal ganglia, and multiple hyperintensities in the splenium of the corpus calosum. Single photon emission computed tomography (SPECT; Fig. 2) showed hypoperfusion of basal ganglia and frontal lobes, mainly on the right side, which correlated with the fact that her symptoms were more intense on the left side of her body.

Electroencephalogram showed a slow rhythm (6/8 Hz) with diffuse slow waves (2/4 Hz), but these changes disappeared during sleep. Nephrological investigation with the aid of an abdominal ultrasound revealed both kidneys to be atrophic, thus preventing a kidney biopsy from being performed.

Progressive symptomatic treatment with carbidopa/levodopa up to (slow titration) 25/250 mg four times/day, 6 hours, was then started and maintained for 14 days, but the patient showed no response to this initial approach. On the 14th day, she began having both visual and auditory hallucinations, frequent mood changes, and suicidal thoughts. Carbidopa–levodopa therapy was discontinued, but the psychiatric symptoms did not improve.

A new lumbar puncture performed on the 18th day showed

A videotape accompanies this article.

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Received 12 March 2001; Revised 3 August 2001; Accepted 4 August 2001

Published online 9 January 2001 in Wiley Interscience (www.interscience.wiley.com). DOI: 10.1002/mds.10029

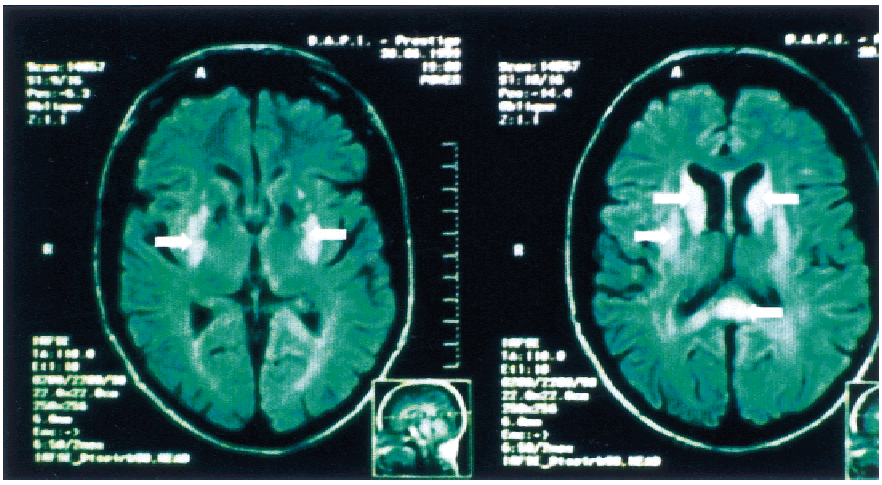

FIG. 1. Brain magnetic resonance imaging (MRI; T2/Flair-weighted images) show symmetric hypersignal (white arrows) in the basal ganglia, and multiple hyperintensities in the splenium of the corpus callosum.

an increase in the total protein level (148.0 mg/dl) with no cells. These results suggested that the vasculitic process was active and we decided to submit the patient to a pulse with methylprednisolone (1 g/day) for 5 days, after which she had an almost complete resolution of the parkinsonian symptoms and a complete recovery of the psychiatric symptoms. The videotape demonstrates the clinical features prior to (Video, Segment 1) and 2 days after the pulse with methylprednisolone (Video, Segment 2).

The patient was discharged from the hospital with azathioprine 150 mg daily and weekly sessions of hemodialysis. Now, almost 2 years after the treatment with corticosteroids, she has only mild dysarthria and discrete bradykinesia, without rigidity or tremor. She has remained *off* carbidopa–levodopa since this time.

Discussion

The patient had advanced chronic renal failure with completely atrophic kidneys, brain vasculitis, and a resulting parkinsonian syndrome. The imaging studies (brain MRI and SPECT) showed the involvement of the basal ganglia and white

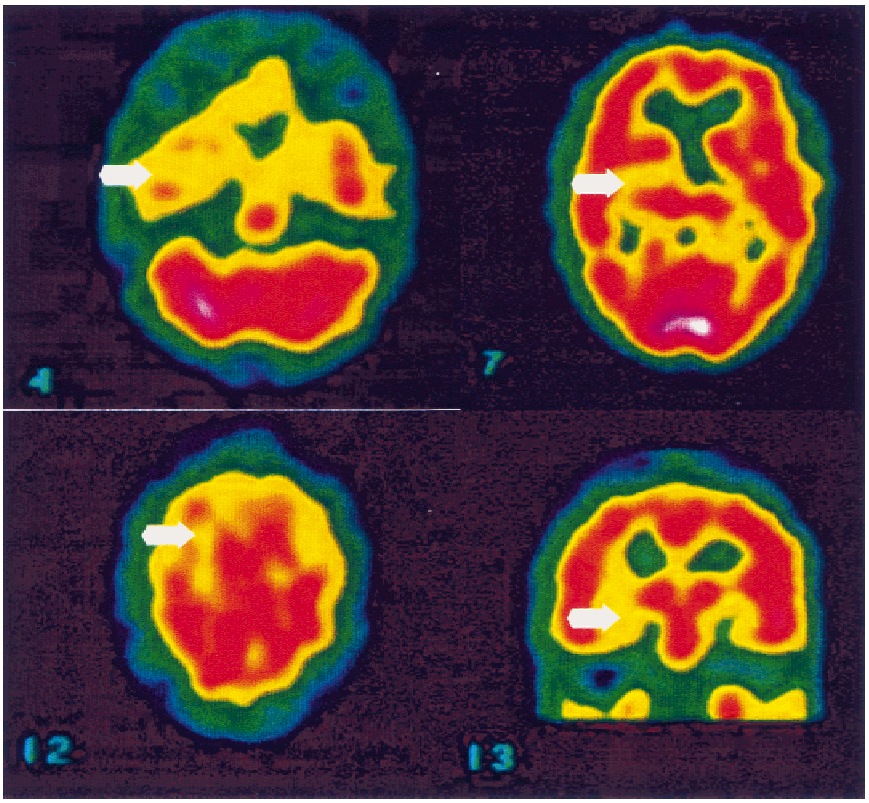

FIG. 2. Brain single photon emission computed tomography (SPECT; ^{99m}Tc-ECD SPECT cerebral scanning) in our patient showed hypoperfusion of basal ganglia and frontal lobes, mainly on the right side (white arrows).

matter areas, with no involvement of cortical areas. Brain MRI-1.5 Tesla angiography was normal; however, this exam has a low sensitivity for detecting changes in small vessels. The ^{99m}Tc-ECD SPECT showed hypoperfusion of the basal ganglia and frontal lobes, mainly on the right side. Brain computed tomography (CT) and MRI scans are useful, although often they show no abnormalities. Abnormal brain MRI scans mainly affecting subcortical and periventricular white matter regions can be found in 60–75% of cases of SS.[8,10–13] The patient did not improve with the antiparkinsonian drugs, and symptoms and CSF parameters worsened during hospitalization. The lack of response to levodopa supports the possibility that the parkinsonism originated from the demonstrated abnormalities in the basal ganglia rather than the substantia nigra. The treatment with a pulse of methylprednisolone led to a complete recovery of the parkinsonian and psychiatric symptoms, thus supporting the hypothesis that brain vasculitis caused the PS.

PS associated with connective tissue disorders or vasculitis is a rare occurrence, as most cases of PS associated with SLE or SS are case reports.[4–10,13,14] Most cases of parkinsonism associated with vasculitis, SS, or SLE described in the literature show no abnormalities in CT/MRI imaging of the brain, but in many cases the SPECT imaging of the brain was useful for showing abnormalities in basal ganglia blood flow.[10–13] Up to 75% of patients with SLE have neurological symptoms. The most common are: psychiatric disorders (psychosis, depression, bipolar affective disorders), strokes, dyskinesias (chorea), seizures, and polyneuropathy.

Patients with PS secondary to SLE or SS have variable responses to steroids and antiparkinsonian drugs.[4–10] Osawa and colleagues[4] reported on a patient with a past history of SLE (SLE in remission) who presented with transverse myelitis and parkinsonian symptoms. The former improved with a pulse of corticosteroids and the latter remitted with orally administered cyclophosphamide.

Young-onset Parkinsonism associated with connective tissue disorders is always a great diagnostic challenge even for the most experienced neurologist. Quite often, the diagnosis is made only by exclusion. Here, we excluded all other possible causes of young-onset and secondary parkinsonism (Wilson's disease, metabolic causes, heavy metal poisoning, infectious causes, and drug-induced parkinsonism). In this case, the most likely diagnosis, considering the patient's age, renal compromise, and neurological involvement as was SLE, she fulfilled at least four criteria from the American Rheumatism Association (ARA) for SLE.[15,16] However, she did not have positive LE cell preparations, antinuclear or anti-DNA antibodies. A negative n-DNA antibody testing does not exclude SLE, because they are positive in only 50–83% of patients with SLE. The presence of histone antibodies is characteristic of drug-induced SLE (DI-SLE). In this patient, the results were borderline, so we must consider that there are many drugs reported to cause DI-SLE, including psychiatric drugs, lithium, chlorpromazine, penicillin, piroxicam, and oral contraceptives. The presence of cryoglobulins (1:128 in precipitation test) is nonspecific and can occur in different forms of autoimmune connective tissue diseases. The low levels of C3 are also nonspecific.[17]

Unfortunately, we did not have access to the patient's records from her psychiatric admission, which occurred almost 3 years prior to her admission in our service, and the patient wasn't aware of the medication she was prescribed at that time.

Acknowledgments: This study was presented as a poster at The Sixth International Congress of Parkinson's Disease and Movement Disorders, in Barcelona, Spain, 11–15 June 2000.

Legends to the Videotape

Segment 1. Patient prior to pulse, after 2 weeks of progressive symptomatic treatment with carbidopa–levodopa up to (slow titration) 25/250 mg four times/day, 6 hours. She shows a severe bilateral parkinsonism, with severe bradykinesia, mask face, rigidity, slowness of the gait and postural disturbances. Hoehn and Yahr stage = 4.

Segment 2. Patient after 5 days of pulse with 1 g/day of methylprednisolone and without the use of carbidopa–levodopa (more than 7 days off carbidopa–levodopa). The patient has normal facial movements, an almost normal speed of her movements, with some bradykinesia on the left side. No rigidity is observed and the gait is almost normal. Hoehn and Yahr stage = 1.5.

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Paradoxical Response to Apomorphine in a Case of Atypical Parkinsonism

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Abstract: We describe a patient with clinical signs of parkinsonism showing a paradoxical response to apomorphine injection. We discuss possible pathogenetic mechanisms with regard to the literature and suggest the diagnosis of a striatonigral degeneration at an early stage. © 2002 Movement Disorder Society

Apomorphine administration by subcutaneous injection is widely used as a predictive test of dopaminergic responsiveness in parkinsonian syndromes. About 90% of patients affected by idiopathic Parkinson's disease (PD) and 20% of patients affected by parkinsonisms (multiple system atrophy, progressive supranuclear palsy, etc.) show a positive response to apomorphine test. This finding usually predicts a good clinical response to prolonged levodopa (L-dopa) or dopamine agonist treatment. In the remaining patients, apomorphine test does not produce significant changes of extrapyramidal symptoms (negative response).[1]

We describe a patient with clinical signs of parkinsonism showing definite worsening of symptoms following apomorphine injection (paradoxical response).

Case Report

In March 1998, we observed a 51-year-old man presenting an extrapyramidal syndrome started 15 months previously, characterized by hypomimia, absence of left arm swing during walking, resting and postural tremor of left limbs, and mild (axial and left leg) to moderate (left arm) rigidity. Two therapeutic attempts with L-dopa (up to 600 mg/day for 1 month) had been discontinued due to worsening of symptoms. No cerebellar, autonomic, or cognitive dysfunctions were found.

Serum chemistry, plasma ceruloplasmine and urinary copper, tissue concentrations of manganese in blood, urine and scalp hair were normal. Molecular analisys for CAG expansion in IT15 gene excluded Huntington's disease. Brain magnetic resonance imaging (MRI), ^{99}TC-HMPAO single-photon emission computed tomography (SPECT), peripheral nerve conduction study, cardiovascular reflex tests, and anal sphincter electromyography (EMG) were normal.

An apomorphine test was performed after 3 days of treatment with domperidone, 20 mg three times daily to prevent side effects. L-dopa was discontinued 3 months before the test. Unified Parkinson's Disease Rating Scale (UPDRS)-Part III basal score was 19.[2] Twenty minutes after injection of apomorphine, 1.5 mg s.c., marked worsening of extrapyramidal symptoms was observed (UPDRS-Part III: 35). In particular, left limb tremor and bradykinesia increased and mild signs of parkinsonism appeared on the contralateral side. After 10 minutes, we injected 3 mg of apomorphine with similar results (UPDRS-Part III: 38). Worsening of symptoms lasted about 60 minutes, after which UPDRS score returned to basal values. Thereafter, the patient underwent a ^{18}FDG positron emission tomography (PET) study that showed an hypometabolism of the head of the right caudate nucleus. An ^{123}IBZM SPECT study disclosed a reduced binding in the left posterior striatum and in the head of the right caudate nucleus (Fig. 1).

In the following months, the patient developed a painful dystonic posture of the left hand, poorly responsive to botulinum toxin injection. After L-dopa therapy failure, other antiparkinsonian drugs (e.g., anticholinergics, selegiline, dopamine agonists) were tried unsuccessfully.

At present, the patient shows a bilateral asymmetrical parkinsonism with left-hand dystonia; all treatments were discontinued except for benzodiazepines to relieve tremor.

Discussion

Responsiveness to L-dopa and dopamine agonists is one of the cardinal diagnostic criteria for idiopathic PD. Therefore, a positive response to apomorphine strongly supports the diagnosis, while a negative result might suggest alternative hypothesis.

Worsening of parkinsonian symptoms following apomorphine administration (paradoxical response) has been described by Jenkins and Pearce in a single case.[3] However, in their report, the clinical deterioration seems to be related to the occurrence of a severe hypotensive state as a side effect of apomorphine injection; moreover, levodopa administration did not produce the same effect. Weiner and colleagues[4] described a patient affected by parkinsonism showing substantial worsening of rigidity and bradykinesia following both levodopa and lergotrile mesylate administration.

A transient worsening before improvement of parkinsonian symptoms following the acute administration of both levodopa and apomorphine has been reported by Merello and Lees[5] in 6 parkinsonian patients. The authors suggested that the biphasic response may be due to a differential presynaptic and postsynaptic temporal activation of dopamine receptors. In our case, both levodopa and apomorphine administration produced a paradoxical response that was not followed by a symptomatic improvement. This finding is not consistent with an IPD in spite of the suggestive clinical presentation.

A videotape accompanies this article.

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Received 14 July 2001; Revised 30 October 2001; Accepted 12 November 2001

Published online 12 February 2002 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.10113

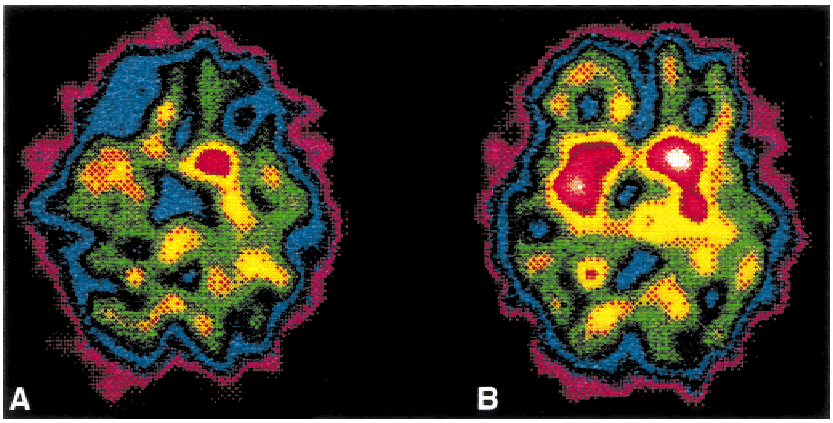

FIG. 1. ^{123}I-IBZM SPECT showing reduced binding in the head of the right caudate nucleus (**A**) and in the left posterior striatum (**B**).

^{18}FDG PET studies show a normal metabolism in patients with bilateral IPD,[6,7] whereas in unilaterally affected patients with early disease contralateral basal ganglia metabolism may be increased.[8] In contrast, a reduced glucose metabolism of basal ganglia, as observed in our case, has been reported in multiple system atrophy (MSA)[6,9,10] and other levodopa-unresponsive parkinsonisms.[11,12]

^{123}IBZM SPECT studies demonstrate normal striatal binding in IPD untreated patients,[13,14] and this finding predicts a good clinical response to levodopa and dopamine agonists.[14–16] On the contrary, a reduced striatal binding is typically observed in parkinsonisms.[14,17]

Both PET and SPECT findings in our case suggest the hypothesis of a striatonigral degeneration at an early stage. The occurrence of limb dystonia also supports this hypothesis, as it has been reported in 40% of patients with presumed striatonigral degeneration.[11] However, the paradoxical response to apomorphine and levodopa is difficult to explain. Consistent with preclinical and clinical studies,[5,18] the worsening of symptoms may be due to an autoreceptor activation at a presynaptic level, leading to a reduction of dopamine release. The loss of postsynaptic dopamine receptor in our case could account for the absence of a later clinical improvement.

Legends to the Videotape

Segment 1. Prior to apomorphine administration, the patient shows hemiparkinsonism with mild hypomimia, left arm resting and postural tremor, left arm bradykinesia, and reduced left arm swing during walking.

Segment 2. Twenty minutes after apomorphine injection, 1.5 mg s.c., the patient shows marked worsening of hypomimia, left arm tremor, and bradykinesia. Slowness of right hand movements and worsening of gait and postural reflexes are also evident.

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Spongiform Encephalopathy Mimicking Corticobasal Degeneration

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Abstract: The presentation of subacute spongiform encephalopathies (SSE) is varied. The following case of SSE presented clinically similar to corticobasal degeneration. The SSE diagnosis was suspected because of magnetic resonance imaging (MRI) findings and confirmed pathologically. © 2002 Movement Disorder Society

Subacute spongiform encephalopathies (SSEs) make up a group of neurodegenerative diseases. A considerable and persuasive body of evidence demonstrates that they are caused by the transmissible agent known as a prion.[1] The clinical presentation is varied and may begin with behavioral changes, and progress to other signs of cortical dysfunction. However, visual, cerebellar, pyramidal, and extrapyramidal signs are common at some point in the disease. Patients often develop myoclonic jerks and have a characteristic electroencephalogram (EEG) pattern.[1] Corticobasal degeneration (CBD) is a clinical syndrome characterized by asymmetric rigidity and apraxia, "alien limb" phenomena, hyperreflexia, cortical sensory loss, limb dystonia, postural instability, and focal reflex myoclonus.[2] We describe a patient with postmortem confirmed spongiform brain changes, who presented with the classic manifestations of CBD. He had little laboratory or clinical evidence of SSE except for findings on diffusion-weighted (DWI) magnetic resonace imaging (MRI).

Case Report

A 65-year-old, right-handed man was admitted to the hospital with an 8-month history of having difficulty tying his necktie into a Windsor knot, and trouble recalling recent names and events. He was fired from his engineering job for unclear reasons. This was followed by his left arm "not doing" what he wanted it to. Five months prior to admission, he was involved in four car accidents. He said that each accident was caused by the car leaping out of control as he was changing gears. Two months prior to admission, he saw a neurologist who documented no weakness, but did find left-hand cortical sensory deficits and increased left-sided deep tendon reflexes. He began locking himself out of the house, one time while wearing only his underwear. His family had noticed a soft whispery voice, stiffness in his trunk and limbs, problems getting out of a bed or chair, and frequent falls. They also noted that his left hand often searched or grasped objects apparently without his influence.

Neurological examination showed an alert and attentive man. Language was hypophonic and tangential. He followed commands after 10–20-second delays. Short-term memory was poor. He was markedly apraxic with the left hand and mildly with the right hand. Palmer grasp reflex was present bilaterally, most prominently on the left. Cranial nerve exam was remarkable only for saccadic intrusions on visual smooth pursuit. There were nearly constant athetoid movements of the fingers of the left hand, as well as frequent spontaneous groping and grasping movements of the left hand. Mirror movements were prominent in the left hand when performing tasks with the right. Distal myoclonic jerks of the left hand could be inconsistently elicited by tactile stimulus. There was a bilateral kinetic tremor of the hands, left worse than right. Stereoagnosia and extinction to double simultaneous stimulation were present in the left hand. Reflexes were brisk, on the left side more than on the right. Gait was narrow-based, with short steps and retropulsion.

Routine blood, urine, and cerebral spinal fluid (CSF) investigations for infectious, metabolic, toxic, or inflammatory causes were negative. CSF protein was 79 mg/dl (normal, 15–45), with no white blood cells and testing for CSF 14-3-3 protein was negative (<3 units). EEG showed diffuse background slowing; there were also frequent bursts of irregular sharp and slow waves predominantly bi-frontal-central, more over the right hemisphere. The EEG did not show the classic triphasic complexes of Creutzfeldt-Jacob disease (CJD). DWI showed restricted diffusion involving the right putamen, frontal, posterior temporal, parietal, and occipital gyri, as well as the left temporal-parietal gyri (Fig. 1).

The patient was transferred to a nursing home where his decline continued over the next few months. He required a wheelchair, became incontinent of urine and feces, developed hallucinations, and both arms became dystonic with groping movements. Seven months after transfer to the nursing home, tube feedings were stopped and the patient expired. Neuropathological evaluation showed marked frontal lobe spongiosis bilaterally, and moderate insular spongiosis. The left temporal lobe had extensive spongiosis and gliosis with neuronal loss; on

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Received 5 April 2001; Revised 16 August 2001; Accepted 1 October 2001

Published online 26 February 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds10166

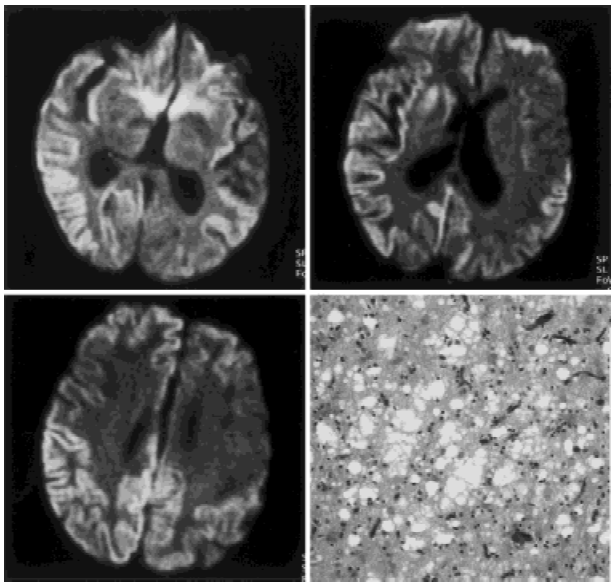

FIG. 1. Diffusion-weighted magentic resonace imaging demonstrating restricted diffusion in the right putamen, frontal, posterior temporal, parietal, and occipital gyri, as well as the left temporal-parietal gyri. Spongiform changes in the same brain seen at autopsy (hematoxilyn and eosin).

the right, the spongiosis was moderate. Severe spongiosis was present in the occipital lobes (left worse than right). The caudate had severe spongiosis bilaterally; putamen had moderate, and globus pallidus had minimal. The cerebellum had marked degeneration of the molecular layer and degeneration of the internal granular layer, with sparing of the Purkinje cell layer. A typical area of spongiosis is shown in Figure 1.

Discussion

We have described a patient who presented with the typical movement and cognitive signs and symptoms of CBD. The rapidity of disease progression was the only feature unusual for CBD. EEG was nondiagnostic, and CSF 14-3-3 was negative, making the diagnosis of spongiform encephalopathy less likely. CSF 14-3-3 protein immunodetection is 96–97% sensitive for spongiform encephalopathy.[8–10]

SSEs can present with varied cortical, or extrapyramidal signs or symptoms. There is increasing evidence that MRI and DWI in particular are useful in making this diagnosis. The characteristic appearance seems to be restricted diffusion in the cortical ribbon and basal ganglia structures correlating with clinical exam findings. The pathophysiological basis for restricted diffusion in cases of spongiform encephalopathy remains unknown. It has been proposed that it is due to either reduced diffusion secondary to vacuoles or deposition of b-pleated sheet conformation of prion protein.[4,5] In the present case, the presence of spongiform changes was more widespread pathologically than were the DWI changes. This may be due to the fact that autopsy was done 7 months after the MRI.

The characteristic neuroimaging finding of CBD is asymmetric cortical atrophy greatest contralateral to the side first affected.[2] More recently, DWI in 2 patients with clinically diagnosed CBD showed extensive hyperintensity in the frontoparietal white matter, more severe on the predominant side of cortical atrophy.[3]

There have been 2 cases previously reported of CJD presenting with the clinical features of CBD. The first of these had a course of progression similar to that of our patient,[6] and the second had features of CBD that developed over a 4-year period.[7] Only the second case was confirmed pathologically. DWI results were not reported for either patient. There have also been two other reports that discuss the alien hand sign in CJD; however, only 1 case was confirmed pathologically and DWI was not performed.[11,12]

This case highlights the importance of considering SSE in patients presenting clinically with CBD, even when the CSF 14-3-3 protein is negative, and suggests that DWI may be useful in distinguishing between the two diagnosis.

Acknowledgments: We thank Dawn Mechanic for assistance with preparation of the figure.

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Possible Sporadic Rapid-Onset Dystonia–Parkinsonism

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Abstract: Rapid-onset dystonia–parkinsonism is a hereditary disease characterized by a combination of dystonic and parkinsonian symptoms. Bulbar musculature is predominantly affected by dystonia. The onset is usually abrupt and the progression of the disease over years is minimal or absent. Homovanillic acid levels in cerebrospinal fluid can be diminished, suggesting that the pathogenesis of the disease is related to some dysfunction in dopaminergic neurotransmission. However, no abnormality has been found in positron emission tomography studies and levodopa does not improve symptoms. The genetic abnormality is not known, but evidence for linkage to markers on chromosome 19q13 has been reported. We describe the case of a woman with a clinical picture highly suggestive of rapid onset dystonia–parkinsonism (RDP) and no family history of the disease. © 2002 Movement Disorder Society

Rapid-onset dystonia–parkinsonism (RDP) is a rare movement disorder characterized by an acute onset over hours to days of combined dystonia and parkinsonism. Individuals are usually affected in their late teens to early thirties.[1–5] Many patients report the existence of a stressful event before the onset of symptoms. The progression of the disease over several years is minimal or absent. The only abnormality frequently found in complementary studies in affected and at risk subjects is a low cerebral spinal fluid homovanillic acid (CSF HVA) level.[6] However, this finding is not universal and some patients may have normal CSF HVA levels.[5,6] The existence of low CSF HVA levels suggests that the pathogenesis of the disease may be a deficit in the dopaminergic neurotransmission. However, positron emission tomography (PET) studies show normal numbers of dopamine reuptake sites,[7] suggesting that a defect in the presynaptic biogenic amine pathway rather than dysfunction or degeneration of striatal dopaminergic terminals. Furthermore, levodopa does not improve the symptoms[1–5] and therefore the role of the dopamine system remains to be elucidated. In a postmortem study, no pathological changes in the brain were found.[5] RDP is considered a hereditary condition with an automsomal dominant pattern. The genetic abnormality is not known but significant evidence for linkage to markers on chromosome 19q13 has recently been reported.[8] Three families have been previously described,[1–5] and no sporadic presentation of the disease is known.

We report on the case of a woman with a clinical picture highly suggestive of RDP and no family history of the disease.

Case Report

A 32-year-old woman was admitted to hospital in 1985 because of dystonia of the limbs, dysarthria, and dysphagia. The symptoms appeared suddenly without any apparent trigger. The first symptoms were speech and swallowing difficulties followed by dystonic spasms in both hands and feet over the course of the next 2 days. She was the third daughter of a nonconsanguineous marriage. A family history of a similar disease or isolated dystonia or parkinsonism was denied. The examination revealed the existence of dystonic movements affecting the arms and legs with dystonic postures of the fingers, orofacial dystonia with a sardonic smile, slow and slurred speech, drooling, mild bradykinesia of the lower limbs with slow finger tapping and a dystonic (tip-toe) gait with mild postural instability. An overflow phenomenon of the dystonic movements was evident. The remaining general and neurological examination was normal. Total scores in the Dystonia Movement Scale (DMS)[9] and in the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS III)[10] were 10 and 12, respectively. Brain computed tomography (CT) scan and magnetic resonance imaging (MRI) were normal.

All the causes of secondary dystonia[11] were ruled out by an extensive clinical, pharmacological, and laboratory work-up, including caeruloplasmin, 24-hour urinary copper levels, serum aminoacids, urine organic acids, liver, muscle, nerve and skin biopsies, a placebo test and a levodopa–carbidopa trial (750 mg/day for 6 months). HVA levels in CSF were 0.3 μm/L (normal range, 0.1–2.0 μm/L).

During the first year of evolution, the patient experienced several episodes of worsening of the symptomatology, particularly the lower face dystonia, with increasing difficulty eating and talking. These episodes occurred at times of stress and anxiety. Their duration was variable but usually the clinical situation returned to basal levels after less than 24 hours. No progression of symptomatology has been noted in these 15 years of evolution (see Video). Several pharmacological agents (levodopa–carbidopa 750 mg/day for 6 months), dopamine agonists (pergolide 3 mg/day for 6 months; amantadine 300 mg/day for 3 months), anticholinergics (trihexyphenydil 45 mg/day for 2 years; clonazepam 6 mg/for 3 years; pimozide 12 mg/day for 4 years; baclofen 90 mg/day for 1 year; tetrabenazine 150 mg/day for 2 years; carbamazepine1,200 mg/day for 3 months) have been tried without success. Currently the patient is receiving gabapentin (1,200 mg/day) and baclofen (90 mg/day). Over this long period of time, none of the family members has developed the disease (dystonia, parkinsonism, or a combination of dystonia and parkinsonism).

A videotape accompanies this article.

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Received 29 June 2000; Revised 14 March 2001; Accepted 23 May 2001

Published online 7 February 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10103

Discussion

Except for the lack of family antecedents, this woman fulfills the proposed clinical diagnostic criteria for RDP.[1–5] She had an acute onset and nonprogressive combination of dystonia and parkinsonism with prominent bulbar symptomatology. CSF HVA levels were in the normal range but this finding does not exclude the diagnostic possibility. Indeed, in the last family reported, only 1 of 3 affected individuals had low HVA levels.[5] Other causes of secondary dystonia were reasonably excluded. Other diseases in which a combination of dystonia and parkinsonism may occur were ruled out based on clinical grounds. For instance, dopa-responsive dystonia and juvenile parkinsonism were excluded because of the negative response to levodopa and the nonprogressive course of the process. Disorders related to defects of tetrahydrobiopterin metabolism, aromatic l-amino acid decarboxylase deficiency, and dopamine β-hydroxylase deficiency usually present a more complex clinical picture.[12] Therefore, the abrupt onset and the lack of progression might be considered the key elements to establish a clinical diagnosis of RDP with no other known "degenerative" disease evolving in a similar way. This can be supported by the existence of low CSF HVA levels and a positive family history.

As the phenotype of the disease may be heterogeneous, ranging from the classical presentation to mild limb dystonia and subtle parkinsonism of gradual onset, her family history has been a matter of careful investigation during the long follow-up period, always showing negative results. Therefore, we suggest that this case can be considered sporadic. As the genetic basis of RDP is not fully understood, other possible explanations, such as a new mutation to the same condition or an incomplete penetration of the genetic abnormality, could explain the apparently sporadic occurrence of the disease in this case. Note that truly sporadic phenocopies of RDP can exist. Low CSF levels of HVA have been reported in some at-risk people. We have considered the possibility of performing lumbar punctures on family members, but the lack of a genetic background makes this a difficult decision. As genetic studies are only just beginning, it could be better to wait until more information is available. PET studies with markers of both the pre- and postsynaptic slopes of the dopaminergic system are planned and will be performed in the near future.

Acknowledgments: We are extremely grateful to Dr. A. Brashear for her helpful comments on the manuscript.

Legends to Videotape

Segment 1. Seven years after onset of dystonia–parkinsonism. The clinical picture at onset was very similar. Note the dystonia affecting the face, arms, and legs and the mild bradykinesia.

Segment 2. Fifteen years after onset of dystonia–parkinsonism. Note that the clinical situation is similar to Segment 1 with no progression of the disease.

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Dystonia, Athetosis, and Epilepsia Partialis Continua in a Patient with Late-Onset Rasmussen's Encephalitis

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Abstract: Rasmussen's encephalitis is a rare autoimmune disorder characterized by intractable epilepsy and progressive hemispheric dysfunction. The disorder usually affects children, although cases have been reported with symptom onset in late adolescence or adulthood. Myoclonus is common in Rasmussen patients, usually occurring as part of epilepsia partialis continua (EPC); however, other hyperkinetic movements are

A videotape accompanies this article.

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Received 12 April 2001; revised 27 July 2001, 27 September 2001; accepted 12 November 2001

Published online 29 March 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10131

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rare. This report documents a 19-year-old woman with Rasmussen's encephalitis whose clinical presentation was dominated by foot dystonia, arm athetosis, and EPC. Intravenous immunoglobulin improved both hyperkinetic movements and EPC, but benefit was transient. The clinical significance and implications of these findings are discussed.

Case History

A 19-year-old woman was referred for evaluation of a 4-year history of left-sided involuntary movements. She was healthy until age 15 years when she experienced a generalized seizure. A head computed tomography (CT) was reportedly normal, however an electroencephalogram (EEG) showed right-sided epileptiform activity. She was treated with phenytoin with only partial success, and then switched to valproic acid, which completely controlled her seizures for 2 years.

One year prior to evaluation at our center, she developed involuntary writhing and posturing movements of the left index finger. Intermittent at first, movements slowly progressed to involve the entire hand. Six months later, her left ankle began to invert when she walked. This worsened over time to the point that she was unable to walk more than 100 feet. Four months prior to evaluation, she developed near-continuous twitching of the left face. Valproic acid was changed to topiramate, and despite a brief trial of trihexyphenidyl her gait did not improve.

Examination at our center showed an intelligent young woman with continuous involuntary movements of the left hemibody (see Video, Segment 1). Her speech, language, comprehension, and memory were normal. Cranial nerve examination was remarkable for epilepsia partialis continua (EPC) of the left face. There were no involuntary movements of the tongue or jaw. A mild left hemiparesis (MRC 4/5) was accompanied by left-sided decrease in pinprick and temperature sensation, and increased reflexes. Continuous, rhythmic athetotic movements of the left arm were present at rest. Attempts to move her hand triggered EPC of the left face. At rest and particularly when she arose to walk, her left foot inverted and assumed a dystonic posture. After walking only 30 feet, her left ankle was completely intorted, forcing her to walk on the lateral aspect of the foot.

Magnetic resonance imaging (MRI) of the brain (Fig. 1) showed atrophy and gross volume loss involving the inferolateral frontal lobe, right caudate nucleus, adjacent lentiform nucleus and subinsular region. An 18-fluoro-deoxy-glucose positron emission tomography (PET) scan showed hypometabolism in areas which were atrophic on MRI, no areas of hypermetabolism on the right, and normal metabolic activity in the left hemisphere.

The patient was admitted to the hospital with a provisional diagnosis of Rasmussen's encephalitis. Cerebrospinal fluid analysis was unrevealing. EEG showed moderate focal slowing in the right frontocentral region and occasional right frontocentral epileptiform sharp waves. A biopsy of the right frontal cortex showed gliosis, mild diffuse microglial activation, and a single microglial nodule, consistent with Rasmussen's syndrome. Immunohistochemical staining for herpes virus 1 and 2, cytomegalovirus, Epstein-Barr virus, and anti-gluR3 antibody were negative. She was treated simultaneously with intravenous immunoglobulin (IVIG), 400 mg/kg/day for 5 days, and intravenous ganciclovir, 500 mg/day for 14 days.

During treatment with IVIG, she experienced marked improvement in all left-sided hyperkinetic movements (see Video, Segment 2). EPC of the left face remitted, and she was able to walk independently with minimal inversion of the left ankle. However, involuntary movements of the left face returned after the IVIG treatment ended, and her left foot dystonia quickly worsened (see Video, Segment 3). The EEG was not repeated during IVIG treatment. Despite continuing to receive ganciclovir, there was no change in the EPC or hyperkinetic movements. Five cycles of plasmapheresis were performed using 5% albumin and saline to exchange one plasma volume per cycle, without clinical improvement. Given the dramatic response to IVIG, the patient was offered a treatment regimen of monthly IVIG with cyclophosphamide, to be followed by a right-sided hemispheric disconnection surgery if medical treatment was unsuccessful. She opted instead to undergo a complete right-sided hemidecorticectomy at another institution and was not evaluated again at our center.

Discussion

Rasmussen's encephalitis is a devastating illness characterized by intractable seizures and progressive hemispheric dysfunction.[1] The disorder typically begins in childhood with partial and secondarily generalized seizures, EPC, and focal unilateral hemispheric dysfunction.[1] Characteristic findings on neuroimaging include hemispheric atrophy, usually worse in temporo-insular areas, with corresponding areas of hypometabolism on single-photon emission computed tomography (SPECT) and PET imaging.[2,3] Typical neuropathology includes chronic inflammatory changes, neuronal loss, gliosis, microglial nodules, and perivascular lymphocytic cuffing.[4] Autoantibodies to the glutamate receptor GluR3 have been demonstrated in some patients with Rasmussen's encephalitis,[4] and others have been reported with cytomegalovirus infection of the brain.[5]

Rasmussen's encephalitis typically begins in childhood; however, a number of cases have now been reported with onset of symptoms in late adolescence or adulthood. While adult-onset Rasmussen's may mimic the early-onset form, symptoms and signs often progress more slowly than in the childhood form and there is a predilection for occipital lobe involvement in adults.[6] The pattern and time course of our patient's complaints, and the location of atrophy and hypometabolism on the scans suggest a profile more typical of childhood-onset Rasmussen's.

Treatment of Rasmussen's encephalitis remains empiric. Corticosteroids,[1] IVIG,[7] plasmapheresis,[8] selective IgA adsorption,[9] and ganciclovir[10] have been used in open-label therapeutic trials, with variable benefit in selected patients. In fact, transient improvement with IVIG or plasmapheresis is not uncommon.[1] Hemispherectomy is regarded as the most effective treatment to control seizures; however, due to the extreme nature of the procedure, it is usually reserved for children with intractable epilepsy and significant hemiparesis.[1] Our patient was treated with ganciclovir concurrently with IVIG in order not to miss an underlying cytomegalovirus encephalitis. Her dramatic response to IVIG and the lack of improvement when gancyclovir was administered alone, support an autoimmune etiology for her condition. It is more difficult to reconcile why plasmapheresis did not work, although similar cases have been reported.

EPC is a common finding in patients with Rasmussen's encephalitis, often accompanied by ipsilateral hemiparesis. How-

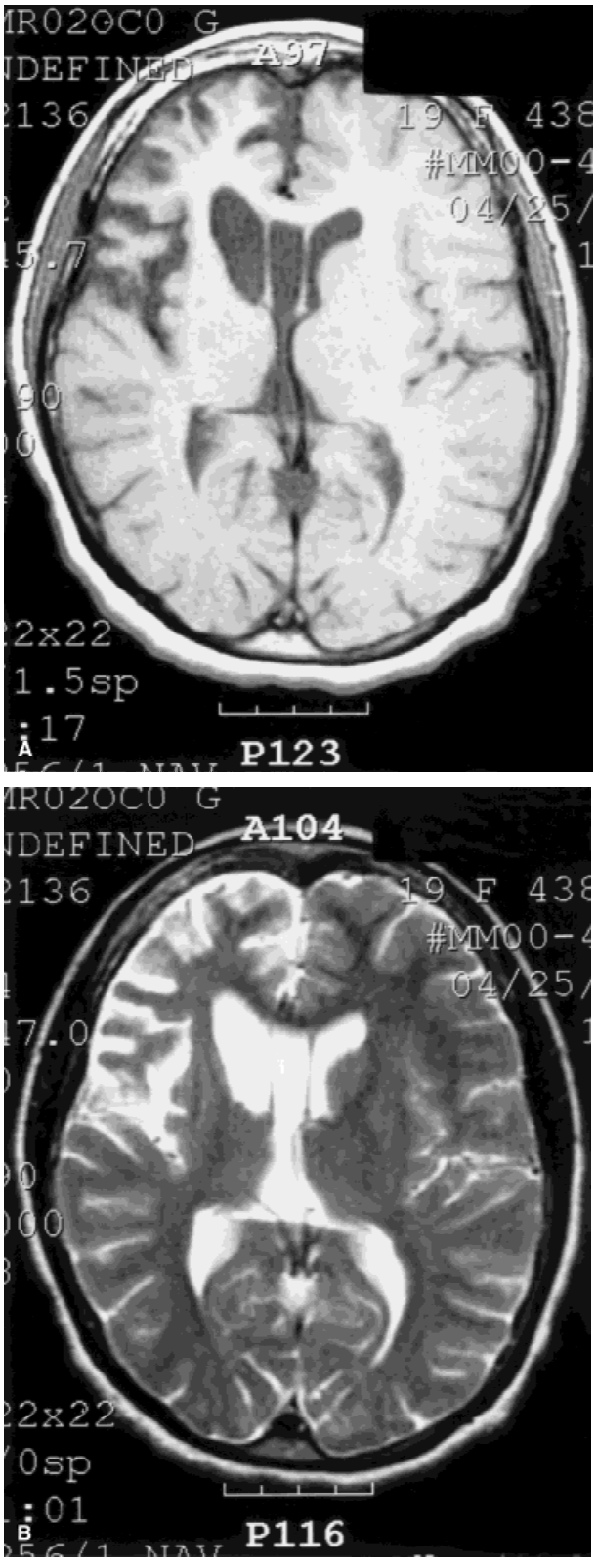

FIG. 1. Axial T1 (**A**) and T2 (**B,C**) magnetic resonanace imaging (MRI) images are shown. There is prominent atrophy of the inferior right lateral frontal lobe, with compensatory enlargement of the right lateral ventricle. There is also atrophy of the caudate, lentiform nuclei, and subinsular region. No contrast enhancement was seen when gadolinium was administered.

ever, athetosis and dystonia are distinctly uncommon. This may reflect the fact that the clinical picture of Rasmussen's is usually dominated by epilepsy and gross hemispheric dysfunction, and thus movement disorders may be overlooked or underreported. Mathews and colleagues[11] described a 10-year-old girl with Rasmussen's syndrome and episodes of chorea associated with EPC of the same limb. In a series of 21 patients with Rasmussen's encephalitis, 6 had prominent involvement of the basal ganglia and 2 of these patients presented with dystonia.[12] At our center, we have seen 1 similar patient with hemidystonia and Rasmussen's.[13] Neuroimaging studies in this patient were identical to ours with selective frontal cortical and caudate atrophy, suggesting the possibility of a shared neuroanatomic mechanism for the involuntary movements.

Our patient's arm movements were rhythmic with a frequency of approximately 1.5 Hz, suggesting the possibility that they were generated by the same epileptic mechanism responsible for her facial movements of EPC. EPC and involuntary movements abruptly improved with IVIG and then recurred when the IVIG was stopped. This suggests that a humoral autoimmune process was responsible for generating both EPC and involuntary movements, and that treatment with IVIG temporarily suppressed this process.

Given the profound cortical atrophy and hypometabolism in her right hemisphere, it is unlikely that her dystonic movements

were generated from a cortical hyperexcitable focus. Instead, it is possible that her leg dystonia may have arisen from epileptic activity elsewhere in the right hemisphere. Dystonic posturing of a limb contralateral to a seizure focus is common in medial temporal lobe epilepsy.[14–16] Kotagal and associates[17] proposed that it originated from spread of ictal activity from the amygdala and hippocampus to ventral striatum and pallidum. Coincident improvement in leg dystonia and EPC with IVIG would be consistent with this hypothesis.

Acknowledgments: I thank Drs. Robert Goodman and James Miller for their help in caring for this patient, and also thank the manuscript reviewers for their helpful comments.

Legends to the Videotape

Segment 1. Examination at the initial office visit reveals rhythmic choreoathetoid movements of the left arm and moderate dystonic posturing of the left leg at rest. Epilepsia partialis continua (EPC) is present in the left face, particularly when she performs motor tasks with the left arm or leg. Her gait is severely impaired by dystonic inversion of the left foot.

Segment 2. During treatment with intravenous immunoglobulin (IVIG), EPC, and athetosis of the left arm have abated. Dystonic posturing of the left leg is markedly improved as well.

Segment 3. Three days after completing treatment with IVIG, left foot dystonia and left arm movements have returned, although not to their pretreatment status.

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Myoclonic Dystonia as Unique Presentation of Isolated Vitamin E Deficiency in a Young Patient

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Abstract: We describe a young patient affected by vitamin E deficiency with mutation in the tocopherol tranfer protein alleles and the unique presentation as myoclonic dystonia, which was practically the only symptom for 6 years before ataxia became evident. Vitamin E supplementation markedly improved both symptoms. This unusual clinical phenotype must be considered, because isolated vitamin E deficiency is eminently treatable. © 2002 Movement Disorder Society

Isolated vitamin E deficiency is an autosomal recessive condition associated with a defect in the α-tocopherol transfer protein. It manifests clinically as progressive ataxia, hyporeflexia, and decreased proprioceptive sensation; dystonia is an infrequent accompanying symptom. The young patient we describe here is unique in that his clinical onset was characterized by the

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Received 20 April 2001; Revised 24 July 2001; Accepted 7 August 2001

Published online 29 January 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10026

development of myoclonic dystonia involving the head and trunk. These abnormal movements remained the isolated manifestation for 6 years, and only after the typical features of the disease had developed was the diagnosis made.

Case Report

The patient is a 15-year-old boy, the only child of healthy, nonconsanguineous parents. He was born at term after an uncomplicated pregnancy. Because of slight fetal distress, the delivery was Caesarean. There was nothing remarkable in the family history. The child's development was normal and he is attending school and making good progress. At age 8 years, small-amplitude head jerks began to occur during emotional stress, which apparently were reduced spontaneously after a few months. Two years later, torsion of the head on action or during emotional stress or concentration appeared. At age 11 years, these head jerks worsened; they began appearing more frequently during activities requiring concentration and were often associated with torsion of the trunk. Neurological examination at this time disclosed myoclonus combined with dystonic posturing of the head and slight dysarthria. Lower limb tendon reflexes could not be elicited.

Copper metabolism tests, microscopic *fundus* examination, cerebral magnetic resonance imaging (MRI), motor and sensory nerve velocity conduction studies were unrevealing. Cognitive function was normal (Wechsler Intelligence Scale for Children-revised [WISC-R] total score, 101; verbal score, 111; performance score, 90). Polygraphic electromyography supported the clinical diagnosis of myoclonic dystonia, as shown by electromyographic findings (Fig.1). Alcohol responsiveness was excluded.

Clonazepam was started, which significantly reduced the myoclonus but did not affect the dystonia. A year later, at age 12 years, gait unsteadiness appeared and was attributed to the therapy; no modification of this disturbance was obtained after the clonazepam was withdrawn.

We lost touch with the patient for a year and a half, and the next neurological check-up was performed at 13 years 10 months. This showed, in addition to dystonia and myoclonus, marked ataxia that worsened on eye closure. There was also dysmetria, vibratory and proprioceptive sensory loss in the lower limbs, and bilateral Babinski sign. Cerebral MRI, visual and auditory evoked potentials, and electroretinogram were unrevealing. However, somatosensory evoked potentials (SEPs) showed extinction of the cortical response. Sensory velocities were still normal, but there was a slight reduction in the amplitude of the sensory action potential.

Heart anomalies were excluded by electrocardiogram and echocardiography. Friedreich's ataxia was ruled out by DNA analysis. Vitamin E levels were deficient in blood (free, 0.20 mg/dl; normal, 0.60–1.20; total, 037 mg/dl; normal 0.80–1.60). Tests for cholestatic liver disease, fat malabsorption, and abetalipoproeinemia were negative. Isolated vitamin E deficiency was then diagnosed and confirmed by analysis of the gene coding for α-tocopherol transfer protein (α-TTP).

Alpha-tocopherol therapy was started at 2,400 mg daily. Vitamin E levels normalized a year later, with concomitant clinical improvement consisting of marked reduction in ataxia and dystonia. Slight myoclonus continued to manifest in stressful situations. One year and 9 months after therapy onset, SEPs were still severely abnormal.

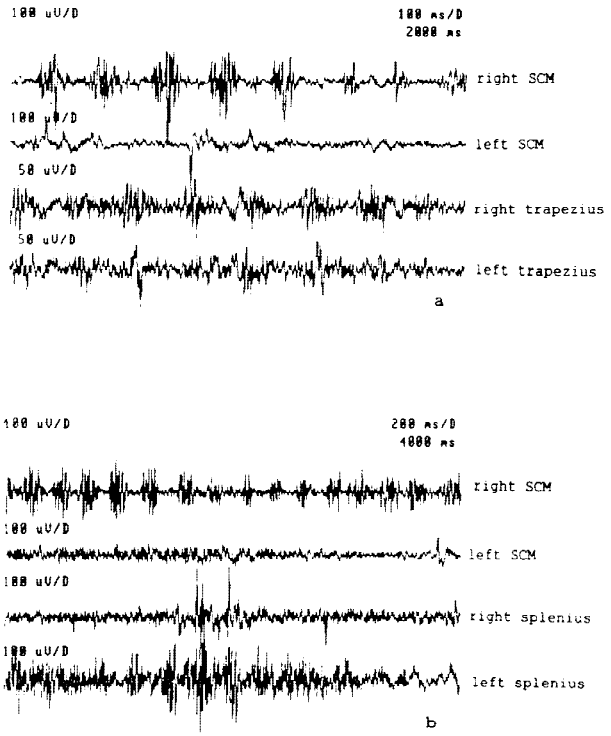

FIG. 1. Electromyographic recordings made while the patient was asked to maintain the head in the median position. **a** and **b** show an intermittent EMG activity with repetitive bursts on the right sternocleidomastoid muscle; more irregular bursts of clonic activity are present on the trapezius and splenius muscles bilaterally; SCM, sternocleidomastoid.

Molecular Analysis

Genomic DNA was extracted from peripheral blood leukocytes using standard procedures. The five exons of the α-TTP gene were amplified by polymerase chain reaction (PCR), as described.[1] The PCR products were sequenced on an automated sequencing system (373A; Applied Biosystems, Foster City, CA) using the Thermo Sequenase premix kit, v2.0 (Amersham Pharmacia Biotech, Piscataway, NJ). Both strands were sequenced. Analysis showed that the patient was compound heterozygous for two mutations in the α-TTP gene. The first was a TT doublet insertion at position 513 in exon 3 (513insTT); the second was a single base deletion in exon 5 (744delA). Both these mutations have been described previously in patients with isolated vitamin E deficiency.[2,3]

Discussion

Dystonia has been reported infrequently during the disease course of patients with isolated vitamin E deficiency, but to our knowledge has never before been described either as the presenting symptom or as a prominent feature of the condition. Myoclonus has never been observed. Because no other pertinent neurological signs or symptoms were present, the condi-

tion was initially misdiagnosed as primary myoclonic dystonia.[4] The lack of lower limb tendon reflexes, in the context of no neurophysiological indications of peripheral nervous system involvement, were puzzling and not helpful. It was only the appearance of ataxia, 6 years after the onset of the myoclonic dystonia, that pointed us to isolated vitamin E deficiency.

This unique clinical presentation shows that progressive ataxia is not the only phenotypic manifestation of isolated vitamin E deficiency, and suggests that this neurodegenerative disorder should be considered in the differential diagnosis of progressive disorders of movement, especially when combined with even minimal signs of posterior spinal cord involvement. The importance of considering isolated vitamin E deficiency rests in the fact that it is eminently treatable, particularly if vitamin E supplementation is instituted promptly.[5] Initiation of treatment in our patient resulted in a significant improvement in both the myoclonic dystonia and the ataxia.

There is convincing evidence that vitamin E's major role in the body is to scavenge free radicals, thereby preventing oxidative injury to tissues, not least membrane and myelin lipids in the nervous system.[6] However, the effects of α-tocopherol deficiency on brain function have been investigated mainly in animal models and only a few studies have been conducted on humans.[7] The main neuropathological features of vitamin E deficiency are degeneration of large-caliber myelinated sensory axons particularly in the posterior column, although the sensory roots and peripheral nerves are also affected. The two published neuropathological studies on humans with idiopathic vitamin E deficiency also revealed mild loss of cerebellar Purkinje cells.[7] These pathological findings are consistent with the spinocerebellar signs and symptoms typically observed in the condition.

Pathological involvement of the nigrostriatal pathways has also been described in animal deficiency models[8] and vitamin E deficiency secondary to cystic fibrosis,[9] biliary atresia,[10] malabsorption due to abdominal irradiation,[11] and abetalipoprotein.[12] In these cases, the neuropathological features include nigral dopaminergic cell loss, axonal swelling in the globus pallidus and zona reticularis of the substantia nigra, reduced pigmentation of the substantia nigra, and lipofuscin-like pigment deposition in the glia of the globus pallidus, substantia nigra, and inferior putamen.

These findings are consistent with the prominent movement disorder, a myoclonic dystonia, which characterized the clinical presentation of our patient.

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Levetiracetam in the Treatment of Paroxysmal Kinesiogenic Choreoathetosis

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Abstract: Anticonvulsants are frequently used in the treatment of paroxysmal kinesiogenic choreoathetosis (PKC). Although they are often extremely effective in eliminating paroxysmal movements, short- and long-term side-effects may limit their use in young patients. Levetiracetam (Keppra), a novel antiepileptic drug approved for the treatment of partial seizures is well tolerated in patients with epilepsy. We report on the use of levetiracetam in the treatment of PKC. Levetiracetam was effective in eliminating paroxysmal events and should be considered as an alternative to standard antiepileptic medications in this disorder. © 2002 Movement Disorder Society

Paroxysmal kinesiogenic choreoathetosis (PKC) is a disorder characterized by intermittent, short-lived, choreoathetotic movements.[1] Mount and Reback[2] introduced the concept of choreoathetotic movements as a paroxysmal movement disorder. Kertesz[3] introduced the term PKC, a label that is useful and widely accepted, although it has been applied to patients in whom movements are not triggered by sudden movement or

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Received 23 July 2001; Revised 15 October 2001; Accepted 30 October 2001

Published online 14 February 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10118

startle.[4] PKC appears to be exquisitely sensitive to anticonvulsants[5] and Kato and Araki[6] were the first to describe the use of carbamazepine for this disorder, although phenytoin had been used before.[7]

Levetiracetam, the S-enantiomer of alpha-ethyl-2-oxo-1-pyrollidine acetamide, at doses of 1,000 to 3,000 mg/day, is approved for use as adjunctive therapy in adult patients with partial onset seizures.[8] Its mechanism of action is not known, but levetiracetam does not interact with known neurotransmitter receptors.[9] Levetiracetam antagonizes neuronal hypersynchronisation in a seizure-prone rat hippocampal model[10] and is also effective in some patients with cortical myoclonus.[11] It is rapidly absorbed after oral administration, has excellent bioavailability, linear kinetics, and minimal plasma protein binding.[12] It does not interact with commonly used drugs, including anticonvulsants.[8]

We report on a patient with PKC whose attacks were successfully treated with levetiracetam. This agent may be an acceptable alternative to standard anticonvulsants in the treatment of this condition.

Case Report

A 38-year-old woman was diagnosed with PKC at age 28 years. Her attacks began at age 12 years, coincident with the onset of puberty. When the patient stood up, the left side of her body including her arm, shoulder, and sometimes her leg would "turn in." Her tongue would curl so she could not speak, and there was occasionally involvement of the left side of her face. Abnormal movements lasted 10 to 15 seconds and were unaccompanied by loss of consciousness, balance, or incontinence. Attacks were intermittent, aggravated by stress, and typically occurred 30 to 60 times per day, but she had reported having had as many as 100 per day. She also described sensory symptoms preceding attacks, consisting of numbness or tingling in the affected body parts. Her past medical history was significant for a breast fibroma, an ovarian cyst, and mitral valve prolapse. Two siblings were similarly affected, although to a milder extent. Both parents, age 67 and 72 years, were unaffected.

At age 24, she was treated with carbamazepine (100 mg twice a day), which completely resolved her attacks. However, a weight gain of 8 pounds and sedation caused her to switch to lamotrigine (200 mg twice a day) at age 36 years. This drug also was effective in suppressing her attacks; however, she complained of a flattened affect and blunting of mood, so at age 38 she was switched to gabapentin (300 mg twice a day). Gabapentin was ineffective, and she had 30 to 60 attacks per day. She was reluctant to take a higher dose because of blurry vision and sedation. At age 38, levetiracetam was begun at 250 mg twice a day for the first week, and then increased to 500 mg twice a day for the second week. By the third week, she had reached a dose of 1,000 mg twice a day. At doses of 500 mg daily as well as 1000 mg daily, she continued to have 30 to 60 attacks per day. On increasing to 2,000 mg daily, attacks ceased. She continued to have premonitory symptoms of numbness several times per day. This remission lasted almost 2 weeks, after which she reduced the dosage to 500 mg twice a day after experiencing sedation and palpitations, subsequently related to isolated doses of citalopram (10 mg) that she had taken for dysphoria. Involuntary movements returned immediately and resumed at a severity of 30 to 60 every day. Because of her reluctance to resume levetiracetam, she was started on carbamazepine (100 mg a day) and levetiracetam was tapered off. Although she had no further attacks on this dose, she continued to feel premonitions of attacks, especially when driving, and the dose was increased to 100 mg twice a day with complete resolution of her symptoms.

Discussion

To our knowledge, this is the first reported case of the successful use of levetiracetam to treat PKC. Attacks of PKC ceased when the dose was raised to 2,000 mg daily. The reduction in dose was followed by a recurrence in the attacks, suggesting a dose threshold. Phenytoin and carbamazepine, both of which are effective treatments for this illness may be associated with side effects (gum hypertrophy with phenytoin; weight gain, agranulocytosis, and sedation with carbamazepine), which may limit their use in young patients. For patients with PKC who do not want to take these drugs or who cannot tolerate them, levetiracetam may be an acceptable alternative.

The dose of levetiracetam required to eliminate attacks was higher than comparable doses of phenytoin and carbamazepine that are effective for this disease. Although 1,000 mg per day is an effective anticonvulsant dose for levetiracetam, it did not eliminate her attacks. It is possible that the severity of her PKC required a higher dose of levetiracetam. Experience with levetiracetam in other patients with PKC will help to determine whether the drug can be effective at a lower dose.

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Painful Arm and Moving Fingers: Clinical Features of Four New Cases

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Abstract: The syndrome of painful arm and moving fingers associates pain in one arm or hand with involuntary movement of one or several fingers. In the 4 cases described, an association between a central and a peripheral nervous system lesion is demonstrated or suspected. Treatment of the condition is disappointing. © 2002 Movement Disorder Society

The association of a deep, aching and pulling pain in one or two limbs with spontaneous erratic and purposeless movements of the extremities is well known in the legs and called "painful legs and moving toes."[1] Many cases have been reported.[2,3] Both central and peripheral nervous system diseases have been associated with it, leading to different physiopathological mechanisms. Its equivalent in the upper limbs, painful arm and moving fingers (PAMF), has been more recently described and seems to be rarer.[4] We report on 4 new cases of PAMF with coexisting peripheral and central nervous system diseases in 3 cases.

Case Reports

Case 1.

A 68-year-old, right-handed Belgian man was admitted in July 1996 for pain in the distal medial part of the right hand and forearm for which he had seen many physicians and tried several drugs. Symptoms first appeared soon after the surgical treatment of coronary insufficiency, a double aortic coronary bypass in December 1986. It was confined to the right lateral part of the thorax and the internal part of the arm and was well tolerated. It then extended distally and became more disabling. In July 1992, distal nerve conduction studies were normal but proximal sites were not stimulated. Somatosensory evoked potentials of arms and legs were normal. Brain computerised tomography scan and magnetic resonance imaging showed many lacunes in the left and right hemispheres, compatible with cardiogenic emboli thought to be due to intermittent atrial fibrillation. Carbamazepine did not bring any relief, nor did the association of tilidine and naloxone. In 1994, a surgical transposition of the right ulnar nerve in the elbow was tried but did not modify the pain. The patient was then treated with amitryptiline and clonazepam with minor improvement. At admission, neurological examination revealed abnormal flexion–extension and mainly abduction–adduction movements of the fourth and, to a lesser extent, the fifth right fingers (see Videotape). Motor nerve conduction study of the right ulnar nerve disclosed a 66% conduction block between the axilla and the supraclavicular region, suggesting a lesion of the lower trunk of the brachial plexus. Magnetic resonance imaging showed a thickening of the right brachial plexus with a blurred aspect, which suggested an inflammatory or traumatic process. Diagnosis of painful arm and moving fingers was made. Pain disappeared transiently after treatment with calcitonin, and movement disorder was reduced by 50%. Oral baclofen was then added but only brought minor improvement.

Case 2

A 25-year-old, right-handed Belgian woman was seen in May 1997 for a severe aching and burning pain in the medial part of the right arm and in the lateral right part of the thorax. It started in 1993 while undergoing physical therapy and neck massage for a moderate low cervical pain. After one single cervical manipulation, a sudden intense pain was provoked in the right arm and shoulder that persisted except for short periods of partial relief. She underwent electrophysiological studies and cervical magnetic resonance imaging: all were normal. The history and the location of the pain suggested the diagnosis of a C8 traction radiculopathy. Several treatments were tried without or with unsatisfactory results: nonsteroidal anti-inflammatory drugs, benzodiazepines, clomipramine, and codeine derivatives. Neurological examination revealed mainly slow abduction–adduction movements of the fourth and fifth fingers of the right hand; a dystonic hyperflexed posture of that hand was also noted (see Videotape). Strength, reflexes, and sensation were all normal. Diagnosis of painful arm and moving fingers was made and the patient was treated with calcitonin, which only brought transient improvement.

Case 3.

A 49-year-old, right-handed Algerian man first consulted in November 1996 because he was walking with a limp which he attributed to a heavy left foot, evolving since 1994. He also reported anesthesia of the medial part of the fourth finger, the fifth finger, and the medial part of the left hand that occurred after a left forearm injury several years ago. On clinical examination, blood pressure was elevated at 180/125 mm Hg. Severe degenerative changes were present in his left knee, explaining the limping gait. He had a hypomimic face, an intermittent rest tremor with a frequency of 5 Hz of the left leg, hand and arm, the latter remaining immobile while he walked. Parkinson's disease was diagnosed. Prescription of levodopa 100 mg/benserazide 25 mg three times a day minimally improved the

A videotape accompanies this article.

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Received 8 March 2001; Revised 24 September 2001, 15 November 2001; Accepted 15 November 2001

Published online 26 February 2002 in Wiley InterScience (www.interscience.com). DOI 10.1002/mds.10116

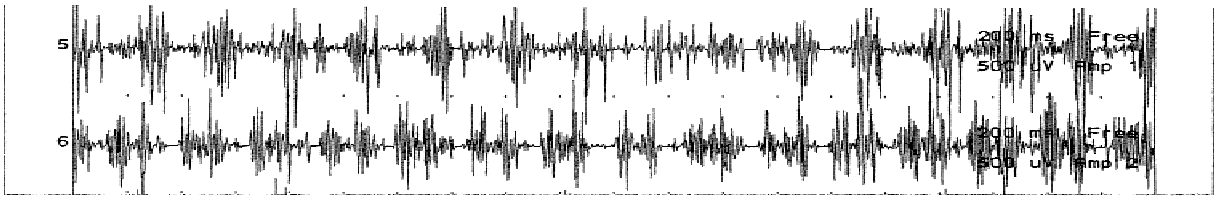

FIG. 1. Top: Surface electromyography (EMG) of left abductor digiti quinti (ADQ). Bottom: Surface EMG of left first dorsal interosseous. Alternated 50–200 msec bursts of 400–1,000 μV multiple motor unit potentials (MUPs).

tremor. The treatment was further increased up to six times a day with a controlled-release form, but in September 1997, he complained of left arm and wrist pain, as if it were compressed by an armband. Intermittent nonrhythmic writhing flexion–extension involuntary movements of the third, fourth and fifth fingers were noticed (see Videotape). The diagnosis of PAMF was made, secondary to a chronic traumatic ulnar nerve lesion and triggered by recent onset of predominantly left-sided Parkinson's disease. The movements were not abolished nor enhanced by distraction such as mental calculation, and were not dependent on the timing of drug intake. In February 1998, pergolide 0.25 mg twice a day and amantadine 100 mg twice a day were progressively added to the treatment for Parkinson's disease, leading to a further diminution of rest tremor and also of the painful movement. The abnormal movements of the left hand and fingers were noted on several occasions between 1998 and December 2000.

Case 4.

A 66-year-old, right-handed Belgian woman consulted in July 1999 for a constant left burning hand pain, predominantly over the palmar side, and affected mainly the fourth and fifth finger. It appeared in November 1997, 4 months after a subcortical stroke in the right posterior cerebral artery territory, which initially only provoked a left superior quadrantanopia. Treatment with carbamazepine and capsaicine was not tolerated because of side effects. Neurological examination revealed abduction–adduction of the third, fourth, and, to a lesser extent, fifth left finger (see Videotape). When she kept her arms stretched, a flexion–extension component was also present. The clinical diagnosis was PAMF due to the concomitant existence of a chronic nonsymptomatic ulnar nerve lesion at the elbow and an acute right hemisphere stroke. Electrophysiological studies disclosed a slowing of both ulnar motor nerve conduction velocities at the elbows. Electromyocardiogram (EMG) showed spontaneous 50–200 msec alternated bursts of multiple motor unit potentials in the left first dorsal interosseous and adductor digiti quinti muscles (Fig. 1), those bursts being concomitant between the latter and the left fourth dorsal interosseous (Fig. 2). Cervicodorsal magnetic resonance imaging study only revealed signs of osteoarthritis, without spinal or radicular compression. Oral baclofen was initiated but not tolerated whereas cannabis smoking was associated with reproducible pain relief.

Discussion

Painful limb and moving extremities (PLME) is defined as the association of pain in at least one limb and slow involuntary, writhing and wriggling movement of flexion–extension and/or abduction–adduction of at least one finger or toe. Pain more often precedes the movement disorder, sometimes by several years as in our first, second, and probably third and fourth cases.[1,4] Only 3 cases of PLME have been described in the superior limb, including one involving both hand and foot.[4–6] It develops in the setting of peripheral nerve system lesions in the majority of cases: polyneuropathy, peripheral nerve compression or trauma, plexopathy, and radiculopathy.[1–3] In some instances, it accompanies buccofacial dyskinesias or hemifacial spasms.[7] Limb pain is often reported as intense, of constant or throbbing type, of crushing or burning quality and it affects quality of life.[1] Movement disorder of the extremities often appears later, and is difficult to imitate. Each finger or toe moves independently from the other in a more or less rhythmical slow clawing–fanning pattern, which is intermittent or continuous during the day and disappears at night.[2] An effort to inhibit the movements may suppress them, but only for a short time. In some patients, the amplitude of movement seems to correlate with intensity of the pain.[1,5] Its relationship to other movement disorders is unclear, which reflects the fact that physiopathology of the syndrome remains speculative.

It is well known that peripheral nerve lesions disturb the normal relationship between the afferent information and the

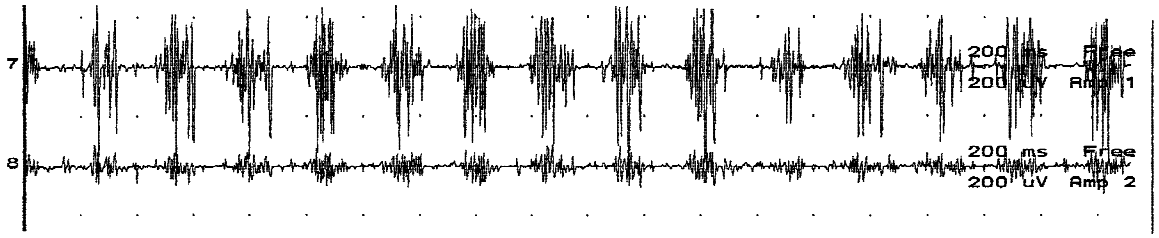

FIG. 2. Top: Surface EMG of left ADQ. Bottom: Surface EMG of left fourth dorsal interosseous. Concomitant 100–150 msec bursts of 200–1,200 μV multiple MUPs.

motor system.[9] In PLME injuries involving more specifically A delta and C fibres are to be considered. They might lead to structural changes in the somatosensory pathways as has been shown in previous studies.[9,10] Peripheral nerve lesions of the painful moving hand were present in three of our cases and probable in Case 2. Furthermore, three of our four patients had coexistence of peripheral nerve and central nervous system disorders. Whether the level of dysfunction that produces alteration of the motor behaviour is the spinal interneuron or other supraspinal centres is not known, but the coexistence of peripheral and central nervous system disorders may be particularly prone to induce abnormal sensory motor integration. Such physiopathological mechanisms are suggested to cause complex regional pain syndromes, Dejerine-Roussy syndrome, pseudo-athetotic movements, focal dystonias or spinal myoclonus, but it is their combination that might render PLME original. Treatment of this condition is difficult.

Legends to the Videotape

Segment 1. Case 1: Dystonic posture and nonrhythmic abduction–adduction movements, predominantly of the fourth right finger.

Segment 2. Case 2: Spontaneous right-hand posture and intermittent nonrhythmic abduction–adduction movements predominantly of fingers four and five.

Segment 3. Case 3: Predominantly flexion–extension movements of left fingers four and five. Intermittently, they may be rhythmic.

Segment 4. Case 4: Fast intermittent adduction–abduction movements of left fingers three, four, and five.

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Hallervorden-Spatz Syndrome Resembling a Typical Tourette Syndrome

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Abstract: A young man presenting with a Tourette syndrome-like disorder that was the main clinical manifestation of Hallervorden-Spatz syndrome is described. It is recommended that, even in the case of slow progression, HSS should be considered in the differential diagnosis of TS-like disorders.

Both motor/vocal tics and obsessive–compulsive behavior resembling a Tourette syndrome (TS) may occur in Huntington's syndrome, idiopathic dystonia, and neuroacanthocytosis.[1] We describe the case of a young man presenting with a TS-like disorder that was the main clinical manifestation of Hallervorden-Spatz syndrome (HSS). Hallervorden-Spatz disease (HSD) is a rare autosomal–recessive disorder of unknown cause, pathologically characterized by neuroaxonal swelling, spheroids, neuronal loss, iron accumulation, and gliosis in the globus pallidus and substantia nigra.[2–4] It begins in the first or second decade of life with dominant extrapyramidal signs (dystonia, rigidity, and choreoathetosis) and progressive intellectual impairment.[5] However, adult-onset sporadic cases, referred to as HSS, have been described in about 20% of patients in a large series.[5] Brain magnetic resonance imaging (MRI) shows a very distinctive picture characterized by symmetrical hypointense lesions in T2-weighted images in the globus pallidus with a small central hyperintense area, due to iron accumulation and gliosis, respectively. This sign is known as "eye of the tiger."[6,7]

Case Report

The patient was a 22-year-old man, the second son of nonconsanguineous parents. He was born at term after a normal pregnancy by uncomplicated delivery. He had no delays in developmental milestones, but as a child he presented with hyperactivity, poor school performance, difficulties in concentration, and a disturbed relationship with other children. When he was 10 years old, he began to stutter. At the age of 17 years he developed unsteady gait with frequent falls. Motor tics, repetitive movements, compulsive behavior, and vocalizations appeared when he was aged 18 years, together with increased

A videotape accompanies this article.

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Received 9 November 2000; Revised 12 April 2001; Accepted 25 May 2001

Published online 16 January 2001 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10105

hyperactivity and impulsiveness. A slowly progressive cognitive impairment was diagnosed. No seizures were described. His motor tics included repetitive touching of objects or body parts and "juggling" objects, and his vocal tics consisted of throat clearing and palilalia. The disorder was characterized by the overwhelming desire to carry out the motor actions and vocalizations, but the patient was able to voluntarily control them for a few seconds. There was no family history of neurological syndromes.

The neurological examination showed clumsy and unsteady gait with difficulties in positional changes and a tendency to fall when arising from a chair, dysarthria with palilalia and stuttering, mild limb rigidity, very brisk reflexes, impairment of finger tapping, and dysdiadochokinesia. There was no clinical impairment of visual acuity. Fundoscopic examination excluded the presence of retinite pigmentosa. His general physical examination was normal except for deformed teeth.

Laboratory tests, including serum copper and ceruloplasmin, were normal. A molecular test for Huntington's syndrome was negative. The presence of acanthocytes was excluded on repeated fresh blood films by light microscopy. High-resolution lipid electrophoresis excluded the presence of hypoprebetalipoproteinaemia. Brain computed tomography (CT) was normal. Brain MRI, performed at 0.5 Tesla, revealed the eye-of-the-tiger sign (Fig. 1). On the Wechsler Adult Intelligence Scale, he achieved a score of 87 for verbal IQ, 72 for performance IQ, and 79 for total IQ. A diagnosis of HSS was made based on age of onset, sporadic occurrence, progressive course, presence of extrapyramidal dysfunction, mild mental deterioration, and typical MRI findings.

Discussion

To establish a diagnosis of Hallervorden-Spatz disorder, the so-called "obligatory features" and at least two of the corroborative symptoms should be present.[8] The obligatory features are: (1) onset during the first two decades of life; (2) a progressive course; and (3) evidence of extrapyramidal dysfunction. The corroborative symptoms include: (1) pyramidal tract signs; (2) progressive mental deterioration; (3) hypointensity in the basal ganglia on MRI; (4) occurrence of seizures; (5) ophthalmological symptoms in the form of retinitis pigmentosa or optic atrophy; (6) positive family history; and (7) abnormal cytosomes in circulating lymphocytes and sea-blue histiocytes in bone marrow.

HSD typically presents as a relentlessly progressive disorder of the extrapyramidal type. Clinical onset is generally after early childhood, with dystonia mainly causing unsteady gait or dystonic posture of the foot.[9] In most cases, a rapid generalization of the dystonia occurs and causes increasing speech and feeding difficulties.[5] In the patient, the syndrome onset and progression were atypical. The onset was characterized by behavioral disturbances, followed after several years by the appearance of motor and vocal tics suggestive of TS. In a large series of pathologically proven cases of HSS, foot dystonia and gait difficulty were the presenting symptoms in most cases (37 of 42), while behavioral disturbances were observed at onset in 4 patients and no patient presented motor and/or vocal tics.[5] Nevertheless, in our case, the diagnostic criteria were fulfilled.

Several clinical features differentiate the case of TS-like HSS reported by Nardocci and colleagues.[10] Their patient presented at age 11 years with hyperactivity, social maladaptation, and motor/vocal tics, and developed gait dystonia at age 16 years and generalized dystonia 1 year later. The case was described without videotape.[10] Our patient had a relatively mild course: behavioral disturbances began during early childhood, motor and vocal tics developed at age 18 years, and generalized dystonia did not occur. The mean duration of HSS is 11 years, but longer survivals (up to 33 years) have been reported.[5] We suggest that, even in the case of slow progression, HSS should be considered in the differential diagnosis of TS-like disorders.

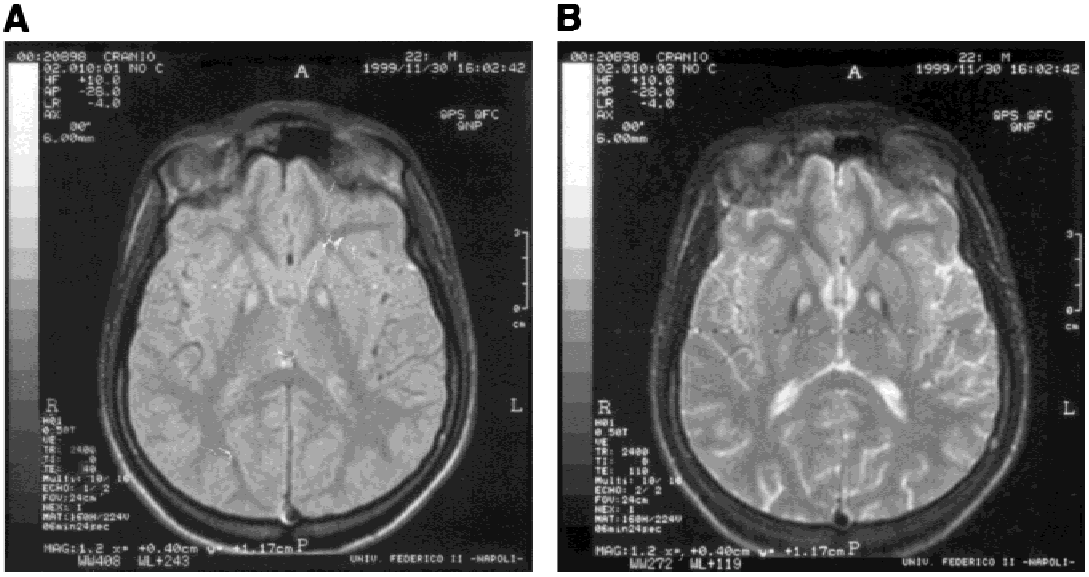

FIG. 1. Magnetic resonance imaging at 0.5 Tesla. Proton density (**A**) and T2-weighted (**B**) images showing pallidal hyperintensity and surrounding rim of hypointensity ("eye-of-the-tiger" sign).

Legend to the Videotape

Relevant clinical findings of the patient. Motor and vocal tics are present with repetitive touching of body parts, "juggling" objects, palilalia, and throat clearing. Impairment of finger tapping and dysdiadochokinesia are also shown.

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Tardive Tremor Due to Metoclopramide

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Abstract: Tardive tremor is a very uncommon neuroleptic-induced tardive syndrome which was initially described in 5 patients by Stacy and Jankovic (Stacy and Jankovic, Mov Disord 1992;7:53–57). Since then, there have been only 3 additional case reports attesting to the apparent rarity of this condition, although it is unknown whether other unreported cases have been observed. We describe a patient with persistent tardive tremor that was associated with tardive dyskinesia, who closely resembles previously reported cases. © 2002 Movement Disorder Society

Case Report

A 68-year-old woman was treated with metoclopramide, 40 mg per day for 5 years, without appearance of involuntary movements, before undergoing partial colectomy for diverticulitis. Metoclopramide was discontinued postoperatively, shortly after which she developed "heaving" involuntary movements of the trunk and abdomen. Within several weeks, she also developed bilateral upper extremity resting and postural tremor, which increased in severity over the next several months. Six months after onset of dyskinesia and tremor, she was placed on haloperidol (6–8 mg/day) for the first time followed by prompt disappearance of abdominal dyskinesia but only mild improvement in tremor. Repeated attempts to reduce haloperidol over the next several years resulted in exacerbation of abdominal dyskinesia. On one occasion, discontinuation of haloperidol for several weeks was followed by marked exacerbation of both truncal dyskinesia and tremor. Haloperidol was resumed, and dyskinesia and tremor both improved. However, tremor later exacerbated and gradually returned to near baseline severity. Mild truncal dyskinesia occasionally reappeared unaccompanied by changes in medication.

Examination was performed 4 years after discontinuation of metoclopramide, at which time she was taking haloperidol (5 mg/day), reserpine (0.2 mg/day), and mirtazapine (7.5 mg/day; see Video, Segment 1). She was depressed, had reduced facial expression, and had severe, disabling, large-amplitude (4 Hz) resting and postural tremor in both upper extremities, involving right more than left side. There was also tremor of the jaw, perioral muscles, and tongue. Upper extremity tremor transiently suppressed with finger-nose-finger testing and other repetitive voluntary movements. There was no bradykinesia or rigidity. Dyskinesia was absent. Re-examination 6 months later, while on haloperidol (7 mg/day), reserpine (0.2 mg/day), mirtazapine (7.5 mg/day), and trihexyphenidyl (3 mg/day; see Video, Segment 2), showed similar tremor, this time associated with continuous abdominal dyskinesia. Facial expression continued to be reduced without bradykinesia or rigidity.

Reserpine (0.2 mg/day) produced moderate improvement in dyskinesia without effect on tremor. Tetrabenazine (25 mg/day) and primidone (150 mg/day) were not tolerated because of sedation. Benztropine (1 mg/day), trihexyphenidyl (6 mg/day), diphenhydramine (100 mg/day), metoprolol (100 mg/day), mirtazapine (15 mg/day), clonazepam (0.75 mg/day), carbidopa/levodopa (12.5/50 mg daily), and bromocriptine (2.5 mg/day) had no consistent effect on dyskinesia or tremor. She continues to be maintained on haloperidol (8–10 mg/day) and reserpine (0.2 mg/day) with complete suppression of dyskinesia but persistence of tremor.

Discussion

This patient developed tardive tremor after chronic treatment with metoclopramide, a gastric promotility drug with dopamine receptor blocking properties well known to cause tardive dys-

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A videotape accompanies this article.

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Received 28 February 2001; Revised 15 June 2001; Accepted 6 July 2001

Published online 15 April 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10227

TABLE 1. *Case reports of tardive tremor*

Authors	Exposure (yr)	Neuroleptic drug	Drug status	Location of tremor	Predominant tremor type	Duration (yr)	Associated dyskinesias
Tarsy and Indorf	5	Metoclopramide	*On*	Arms, head, face	Postural, resting	6	Truncal
Stacy and Jankovic[1]	2	Perphenazine	*Off*	Arms, head, lips	Postural, resting	7	Truncal, arms, blepharospasm
	4	Chlorpromazine	*Off*	Arm, legs	Postural, resting	12	Cranial, cervical, truncal
	20	Prochlorperazine	*Off*	Arm, legs	Postural, resting	?	Oromandibular, truncal, legs
	6	Multiple	*On*	Arm	Postural, resting	?	Cranial, truncal, extremities
	10	Metoclopramide	*Off*	Arms, legs	Postural, resting	?	Cranial, truncal, toes
Storey and Lloyd[3]	?	Multiple	*On*	Arms, head, legs	Postural, kinetic, resting	27	Oral
Delecluse et al.[4]	15	Multiple	*Off*	Head, arms, foot	Postural, resting	?	Buccal

kinesia and tardive dystonia.[5] Neuroleptic-induced tremor occurs under two circumstances. First, it may occur while taking neuroleptic drugs, when it is usually associated with bradykinesia and rigidity, which can coexist with tardive dyskinesia.[6] In this situation, tremor subsides when the neuroleptic drug is discontinued. Second, tremor may appear in the form of rabbit syndrome, a low-frequency tremor limited to the perioral region, which occurs at variable intervals after initiation of neuroleptic treatment, is often associated with parkinsonism, and subsides with neuroleptic discontinuation or treatment with anticholinergic drugs.[7]

By contrast with parkinsonian tremor, which may coexist with tardive dyskinesia in patients still taking neuroleptic drugs,[8] tardive tremor appears after prolonged use of neuroleptic drugs but persists long after their discontinuation. Pharmacological features that distinguish tardive tremor from parkinsonian tremor are exacerbation rather than improvement after discontinuation of neuroleptics and suppression rather than exacerbation when treated with a dopamine depleting or dopamine receptor blocking agent. In the patient reported here, tremor appeared for the first time together with abdominal dyskinesia shortly after withdrawal of metoclopramide after 5 years of treatment with this medication. It was present for 6 months before the introduction of haloperidol and has persisted unchanged without other significant signs of parkinsonism for 6 years after discontinuation of metoclopramide. Haloperidol suppressed the abdominal dyskinesia and mildly improved the tremor.

In this case, tremor is not likely to be a direct parkinsonian effect due to continued haloperidol treatment, because tremor preceded haloperidol exposure by 6 months, partially improved in response to haloperidol on two separate occasions, and exacerbated with discontinuation of haloperidol. This pattern of medication response is consistent with a tardive syndrome rather than parkinsonian tremor.[9]

The large-amplitude postural and resting tremor in our patient is similar in appearance to seven previously reported cases[1,3,4] of tardive tremor involving the upper extremities (Table 1). In all 8 patients, upper extremity tremor was 3 to 6 Hz and more severe during postural maneuvers than at rest. Tremor was severe and disabling in all cases. There was coexisting tardive dyskinesia in all 8 patients, 6 of whom displayed truncal or abdominal dyskinesia. There is also one additional report of an isolated but atypical appearing, low-frequency, resting jaw tremor together with a very low-amplitude postural hand tremor.[2]

Tetrabenazine was markedly effective for tardive tremor in seven previously reported patients but was not tolerated in our patient because of sedation. Tremor did not respond to low-dose reserpine but did partially respond to haloperidol. One previous patient who was unable to tolerate tetrabenazine because of depression responded to clozapine.[4]

In conclusion, tardive tremor appears to be a rare but well documented complication of chronic neuroleptic treatment. In our patient as well as previously reported cases,[1,3,4] tremor appeared after prolonged neuroleptic treatment, was associated with tardive dyskinesia, and was accompanied by little or no parkinsonism. Tardive tremor is large in amplitude, predominantly postural rather than resting, and seriously interferes with activities of daily living. It does not respond to beta blockers or primidone and resembles tardive dyskinesia rather than parkinsonian tremor because it increases after withdrawal of neuroleptic drugs and is usually improved by tetrabenazine.

Legends to the Videotape

Segment 1. Patient *off* metoclopramide for 4 years. She exhibits resting and postural tremor involving right more than left arm together with tremor of tongue, jaw, and perioral muscles. She is taking haloperidol (5 mg/day), reserpine (0.2 mg/day), metoprolol (100 mg/day), and mirtazapine (7.5 mg/day).

Segment 2. Patient 5 months later still *off* metoclopramide. She exhibits truncal dyskinesia, persistent resting and postural tremor in arms, and less tongue and jaw tremor. She is now taking haloperidol (7 mg/day), trihexyphenidyl (3 mg/day), reserpine (0.2 mg/day), and mirtazapine (7.5 mg/day).

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Treatment of Pseudobulbar Laughter After Gamma Knife Thalamotomy

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Abstract: We describe a case of pathological laughter after gamma knife thalamotomy which resolved after treatment with sertraline. It is important to identify this potentially treatable complication of surgical therapy. © 2002 Movement Disorder Society

Pathological laughter or crying, manic states, and depression have all been described as a result of injury to a variety of structures including the globus pallidus, thalamus, internal capsule, pons, and subcortical white matter.[1–8] We describe a case of pathological laughter after gamma knife thalamotomy that resolved after treatment with sertraline.

Case Report

A 46-year-old man presented with a 7-year history of tremor predominant idiopathic Parkinson's disease. Tremor was severe in both upper extremities. Adequate titrations of oral medications including carbidopa–levodopa, parlodel, trihexyphenidyl, selegiline, benztropine, mysoline, and pramipexole were not effective in controlling tremor.

The patient was considered a candidate for microelectrode guided pallidotomy but elected to go to an outside institution for gamma knife thalamotomy. After right gamma knife thalamotomy targeting the ventral intermedius nucleus (VIM) there was no improvement in his tremor. Over the ensuing weeks however, he developed numbness of his upper lip, left arm and hand. The numbness in his lip resolved over the following year, however the numbness in his hand persisted.

Uncontrollable fits of laughter occurred approximately 6 months postoperatively. He reported fits of laughter even though he found no humor in the circumstances leading to the outbursts. In fact, these would often occur during bible studies in his home. He did not have any symptoms of depression or elated mood. Tremor and other symptoms of Parkinson's disease did not improve during the follow-up period. Magnetic resonance imaging (MRI) showed an area of increased T2 signal intensity approximately 10 mm × 15 mm within the right posterior thalamus in the region of the pulvinar and right posterior limb of the internal capsule (Fig. 1). Treatment with sertraline (50 mg/day) led to resolution of the symptoms within 48 hours. There were no other medication changes made during the follow-up period. This remission has been sustained over the period of an 8-month follow-up.

Discussion

Emotional incontinence and pseudobulbar affect can be associated with lesions of the basal ganglia, thalamus, pons, and subcortical white matter.[4–8] Lesions of the thalamus have been implicated in pseudobulbar affect. A study of post-stroke depression and emotional incontinence[24] showed the prevalence of emotional incontinence associated with unilateral thalamic lesions to be as high as 16%. Although conventional wisdom has held that lesions have to be bilateral to cause pseudobulbar affect, unilateral lesions in other locations other than the frontal lobes are common.[24]

Black proposed that pseudobulbar laughter might exist on one or more of three anatomical levels.[17] These included a cortical level, a bulbar or effector level, and a synkinetic or integrative level located in the region of the hypothalamus. Disruption of one or more of these levels may lead to uncontrollable laughter as seen in pseudobulbar palsy, gelastic epilepsy, or in psychiatric illness. In support of this proposal, lesions causing pathological laughter have been reported to occur after lesions of all three levels.[5–8,17–20] Additional cases of pathological laughter have been reported after IV administration of sodium valproate,[18] inhalation of insecticide.[19] and after infarction of the basis pontis, thalamocapsular region (as in our case), or subcortical white matter.[5–8]

Sackeim and colleagues[25] reviewed the reports of 119 patients who had pseudobulbar affect from unilateral lesions and found that although left-side lesions were associated with crying, right-side lesions are associated with laughter. Although the mechanism of this dichotomy is unknown, both lesion[26] and physiological studies[27] suggest that whereas the left hemisphere's frontal lobes appear to mediate emotions with a positive valence the right hemisphere mediates emotions with a negative valence. In addition to its projection to the parietal lobes the pulvinar projects to the frontal lobes[28] and perhaps the inappropriate laugher observed in this patient is related to dysfunction in this pulvinar–frontal network.

Pseudobulbar affect historically has been shown in the literature to potentially resolve quickly with treatment. Administration of a tricyclic antidepressant or a serotonin reuptake inhibitor may lead to resolution of symptoms as quickly as the first 24 hr.[20–23] The response is not affected by the site of injury.[23] It is unknown why pseudobulbar affect responds quicker than the 4 to 6 week response time seen in clinical depression, but the mechanism may be due to activity in cortical areas receiving input from this region of thalamus. One potential explanation of the rapid response to treatment would be alteration of cortical areas involved in cognitive processing. This alteration may result in changing of the cognitive context causing a resultant elevation of the threshold required to evoke pseudobulbar laughter.[29] Alternatively, drugs may act on induction sites or serotonin receptors that are found in paralimbic as well as diffuse brain regions.[30]

In addition to the treatment of pseudobulbar laughter this case illustrates the importance of accurate lesion placement for Parkinson's surgery. It is the first reported case of thalamotomy that has resulted in pseudobulbar laughter. It would seem unlikely, however, that other cases have not occurred. A careful

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Received 29 July 2001; Revised 18 October 2001; Accepted 2 November 2001

Published online 20 March 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10174

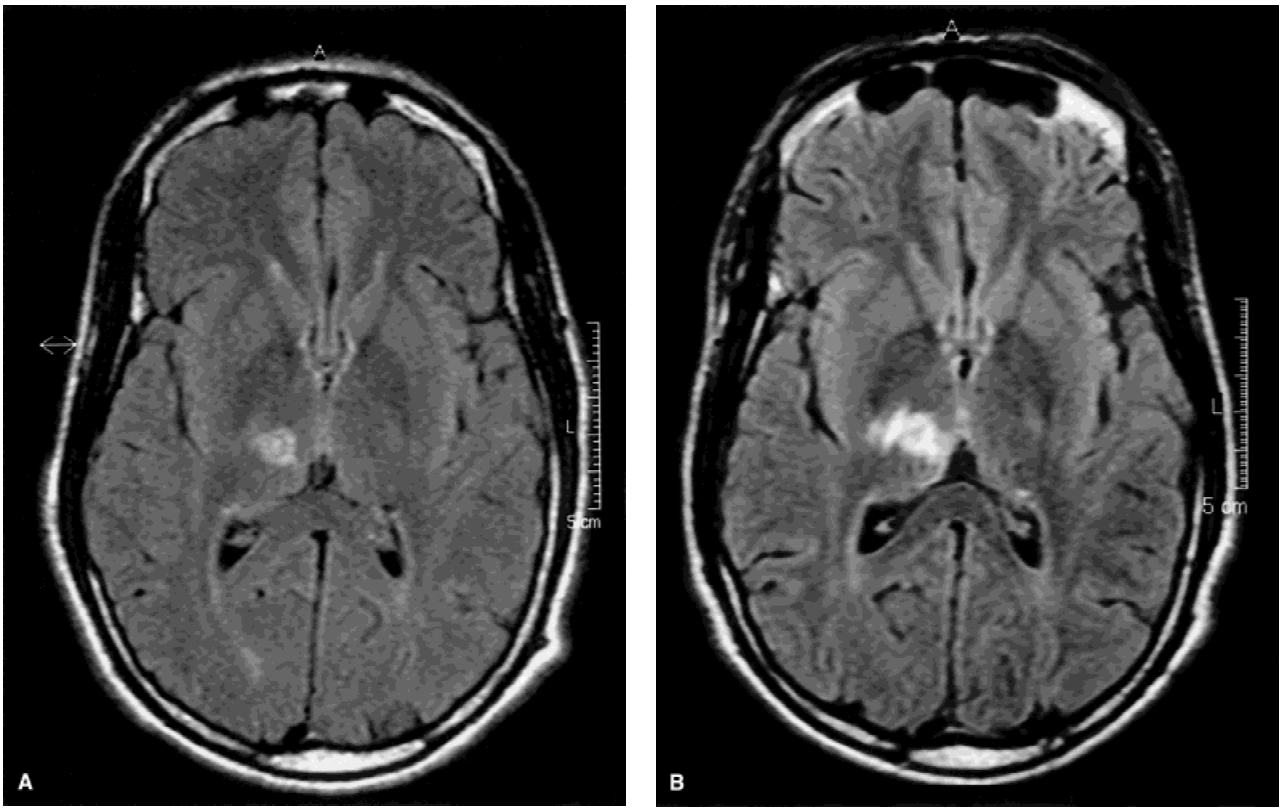

Figure 1. Approximately 3 months after right GK thalamotomy. (**A**) Axial flair magnetic resonance image (MR) shows an approximately 10 mm hyperintense target lesion of the right thalamus. (**B**) After the first MR scan (2.5 years) an axial flair image demonstrates interval enlargement of the T-2-hyperintense lesion. The interval enlargement over this extended period of time is strongly suggestive of radiation change/necrosis.

history for affective changes in patients who have undergone thalamotomy should be performed. Additionally, it should be noted that in cases involving radiosurgery, delayed effects from the surgery are not uncommon.[31] Pseudobulbar symptoms can be easily missed despite the profound impact on the patient's quality of life. It is even more imperative to identify this potential complication of surgical therapy because it can be treated quickly and effectively with a low dose of a serotonin reuptake inhibitor.

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