Movement Disorders
Vol. 17, No. 5, 2002, pp. 1084–1100

Clinical/Scientific Notes

Depression Leading to Attempted Suicide After Bilateral Subthalamic Nucleus Stimulation for Parkinson's Disease

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Abstract: Subthalamic nucleus stimulation is emerging as an effective surgical therapy for Parkinson's disease. It is considered to be a safe procedure with little morbidity, the most common complications being intracranial haemorrhage and hardware failure. We report on three cases of depression, one of whom attempted suicide after bilateral subthalamic nucleus stimulation. © 2002 Movement Disorder Society

Key words: STN stimulation; Parkinson's disease; depression; suicide

Subthalamic nucleus (STN) stimulation is emerging as an important surgical therapy for Parkinson's disease.[1] However, not everything is known about this treatment because it has been in use for a relatively short period. Our results in 31 operated cases are encouraging but we encountered effects of STN stimulation we believe to be important. Three of our patients became depressed after a successful STN stimulation, and one of them attempted suicide, despite clinical improvement.

Cases 1 and 2

Case 1, a 55-year-old man suffering with Parkinson's disease for 6 years, and Case 2, a 58-year-old man suffering from Parkinson's disease for 11 years, underwent bilateral STN stimulation. Both these patients had history of preoperative depression, which was controlled by antidepressants. After STN stimulation, they had significant clinical improvement (Table 1). At 1-year follow-up, they complained of freezing and walking difficulty, which led us to alter their electrode combination (Table 2). Immediately after these alterations, they reported acute depression. They would break down into tears at slightest provocation. This response was "very unusual" and different from their preoperative depression. We were forced to revert back to the earlier electrode settings, within 2 days, and this improved their symptoms instantaneously.

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Received 2 October 2001; Revised 18 January 2002; Accepted 30 January 2002

Published online 1 May 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10198

Case 3

A 42-year-old dentist, suffering with Parkinson's disease for 9 years, underwent bilateral STN stimulation. Despite major difficulties in activities of daily living (ADL), he had no history of depression before surgery. He had frequent, unpredictable *off* periods that were marked by tremors, which were a functional handicap to his profession as a dentist. He had minimal drug-induced dyskinesias. Preoperatively his Unified Parkinson's Disease Scale (UPDRS) was 77 and 27 in *off* and *on* medication, respectively. He was on Sinemet CR (250 mg), selegiline (10 mg), and bromocriptine (2.5 mg/day).

Postoperatively, he had significant improvement in his Parkinson's disease symptomatology. He was totally free from *off* periods. His total UPDRS scores improved to 10, 30 and 18 at 1, 6, and 12 months follow-up in *off*-medication and on-stimulation state. The scores for UPDRS part I (items 2–4), which relates to the emotional state, were 0,0,0 and 0,4,4 before and after surgery, respectively. It is important to note that the UPDRS scores were worse at the peak of depression (6 months follow-up). However, UPDRS part I scores had major contribution in this. Postoperatively, he continued to take Sinemet CR (250 mg/day), while selegiline and bromocriptine were discontinued.

He first complained of depression soon after surgery. During this time he would sit and stare at visitors while keeping his hands folded across the chest. He stopped interacting with his family and could not initiate any activity. He developed anorexia and weight loss along with insomnia. He became insecure and could not stay alone, even in his room. He had repeated and frequent episodes of crying. In his own words, he described his state as, "This depression is unusual and uncontrollable for me. I cannot attribute this to any particular event but I cannot help being depressed. I also get an urge to end my life." The depression gradually worsened over 6 months, when he started having suicidal thoughts. He attempted suicide at this stage by taking an overdose of sleeping medication. At present, his depression is alleviated with fluoxetine, and he continues to do well 1 year after the surgery.

Discussion

Neuropsychological and behavioral changes after STN stimulation have been reported by others.[2–6] These changes have been in the frontal executive function in the form of lack of initiation, apathy, social withdrawal, lability, moodiness, and insensitivity. Depression is usually known to improve following STN stimulation.[4,7] In the series reported by Ardouin[4] the Beck's Depression Inventory score had remained unchanged in 75%, improved in 21% and worsened only in 4%, of the patients after STN or GPi stimulation. Occasionally worsening of depression or de novo depression has been reported following STN stimulation.[5,7–9] This has either been attributed to reduction/withdrawal of dopaminergic drugs[7,9] or due to stimulation of surrounding structures like Substantia nigra.[8] In our report of

TABLE 1. *Clinical profile of the patients with post-STN stimulation depression*

Case no.	Age (yr)	Duration of disease	Preop UPDRS *off*	Postop UPDRS *off* (*on* stimulation)	L-dopa equivalent dose[10]		Antidepressants (mg)	
					Preop	Postop	Preop	Postop
1	55	6	72	19[a]	675	100	Dothiapine 50	Venlafaxine 75
2	58	11	108	38[a]	450	300	Chlordiazepoxide 5 & Amitryptyline 12.5	Nil
3	42	9	77	30[b]	250	250	Nil	Fluoxetine 20

[a]UPDRS score at 1 year follow-up.
[b]UPDRS score at 6 months follow-up.
STN, subthalamic nucleus; UPDRS; Unified Parkinson's Disease Rating Scale.

three cases we encountered depression despite successful STN stimulation with clinical improvement in Parkinsonism. In case one and two depression was noted following change of contact points after a successful stimulation, with corresponding clinical improvement, for one year. The changed contact points were just next ot the contact points that alleviated Parkinson' disease symptoms. The patients reported acute and severe depression without loss of anti Parkinson's disease effect of stimulation. The third patient was even more unique. He had parallel improvement in Parkinson's disease with progressive worsening of a de novo depression. He fulfilled most of the criteria for major depression i.e. insomnia, anorexia, weight loss, sadness, diminished interest, pessimistic and suicidal thoughts. These were clearly indicative of depression and not apathy.

One possible explanation for this is the global stimulation of the STN or stimulating the adjacent cells (e.g., substantia nigra, pars compacta) projecting to the frontal, anterior cingulate, and ventral striatal regions.[7,8] The other explanation is related to the differential stimulation of subdivisions of STN. STN is known to have motor and limbic components; however, the area of STN is so small that it is difficult to differentially stimulate its subregions. Hence, in some patients, there is a pure motor benefit without any behavioural changes and in some patients there are associated behavioural changes, depending on the placement of the electrode. The third explanation relates to abrupt withdrawal or reduction of the dopaminergic drugs, which occurs after a successful STN stimulation,[5,7] as a cause of depression. However, in our patient, there was no change in levodopa dose. Hence we feel that depression is due to STN stimulation or stimulation of surrounding structures. In conclusion, we would like to suggest that careful neuropsychiatric history and evaluation should form a part of preoperative protocol for STN stimulation. Following STN stimulation complains of depression or apathy should be considered seriously.

Acknowledgments: We thank Dr. S.M. Katrak for allowing us to use his clinical material.

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TABLE 2. *Stimulation parameters of the patients with post-STN stimulation depression*

Case no.	Before depression		At the time of depression		Postdepression	
	Channel 1	Channel 2	Channel 1	Channel 2	Channel 1	Channel 2
1	1(–), 60, 145, 2.4	0(–), 60, 130, 1.7	2(–), 60, 145, 2.1	0(–), 60, 145, 1.4	1(–), 60, 145, 2.4	0(–), 60, 145, 1.4
2	2(–), 90, 130, 3.1	2&3(–), 60, 130, 1.0	2(–), 90, 130, 2.6	2(–), 60, 130, 1.1	2(–), 90, 130, 2.6	2&3(–), 60, 130, 1.1
3	2(–), 60, 130, 1.6	2(–), 60, 130, 1.7	2(–), 60, 130, 1.6	2(–), 60, 130, 1.7	2(–), 60, 130, 2.0	2(–), 60, 130, 2.0

All patients had unipolar stimulation with case being +ve. Channel 1, left electrode; Channel 2, right electrode. There are four values presented per channel: the first value represents the electrode contact point and polarity; the second, the pulse width (μsec); the third, frequency (Hertz); the fourth, the voltage.

Posttraumatic Tremor Without Parkinsonism in a Patient with Complete Contralateral Loss of the Nigrostriatal Pathway

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Abstract: We present a patient with posttraumatic tremor who did not show any [^{123}I]FP-CIT uptake in the contralateral putamen and caudate. The absence of hypokinesia and rigidity is surprising in the presence of a striatal dopaminergic denervation that is even more severe than in Parkinson's disease. An explanation, therefore, could be that the lesion in the subthalamic nucleus in our patient prevented the onset of a Parkinson syndrome. © 2002 Movement Disorder Society

Key words: posttraumatic tremor; Holmes tremor; Parkinson's disease

Incapacitating posttraumatic tremor often results from midbrain injury and prolonged coma.[1,2] It usually has features of a Holmes tremor. Holmes tremor is a rest and intention tremor with an additional postural component in many patients.[3–5] The frequency is usually less than 4.5 Hz.[3–5] Sometimes the tremor is accompanied by other cerebellar features such as ataxia.[3] Both the dopaminergic system and the cerebellothalamic system, must have lesions according to pathoanatomical and positron emission tomography (PET) data to produce a Holmes tremor.[3,6–9]

Case Report

A 19-year-old man sustained a severe head injury in an automobile accident in 1972 and remained comatose for 2 weeks. After recovery over several months he noticed a very slight occasional trembling of the left arm and leg. The tremor progressed slowly to the extent that he was not able to work as a cowherd anymore. He also developed pain in his neck, left shoulder, arm, and leg. The tremor and pain persisted when lying down and caused difficulties falling asleep. At age 41, he was seen for a second opinion in the University Medical Center of Nijmegen. On examination, he had a slightly irregular and jerky rest tremor of the left hand, and to a lesser extent also of the left leg. The hand tremor also had a prominent postural component with an occasional pill-rolling component. There was no rigidity or hypokinesia and his gait was normal. Coordination was intact, except for a slight dysmetria of the left hand, and there was no intention tremor. He had a left Babinski sign. Magnetic resonance imaging (MRI) of the brain showed a hemosiderin deposit, indicative of a previous small haemorrhage in the right subthalamic nucleus and anteromedial part of the substantia nigra (Figs. 1–3). Using [^{123}I]IBZM single photon emission computed tomography (SPECT), we found normal striatal binding bilaterally, indicating a normal density of postsynaptic striatal dopamine D_2 receptors. Imaging of the presynaptic dopaminergic system, however, with the dopamine transporter ligand [^{123}I]FP-CIT SPECT showed complete absence of binding in the right striatum (Fig. 4). The binding in the left caudate nucleus was normal, and in the left putamen, it was only slightly decreased, especially in the posterior part. No dopaminergic medication had been taken in the weeks before the SPECT studies. Electromyography showed alternating activity of the biceps and triceps muscles with a regular frequency of 4.5 Hz on tremor-registration. General cerebrospinal fluid parameters were unremarkable, except for a low normal homo-

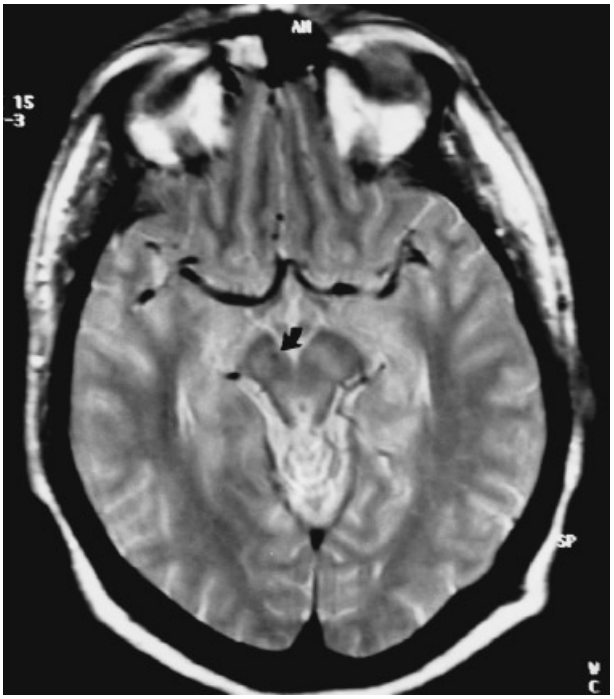

FIG. 1. Turbospin-echo T_2-weighted magnetic resonance image of the patient, showing hemosiderin deposit (black arrow), indicative of a previous small haemorrhage in the anteromedial part of the substantia nigra.

A videotape accompanies this article.

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Received 23 February 2001; Revised 25 January 2002; Accepted 25 January 2002

Published online 10 April 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10203

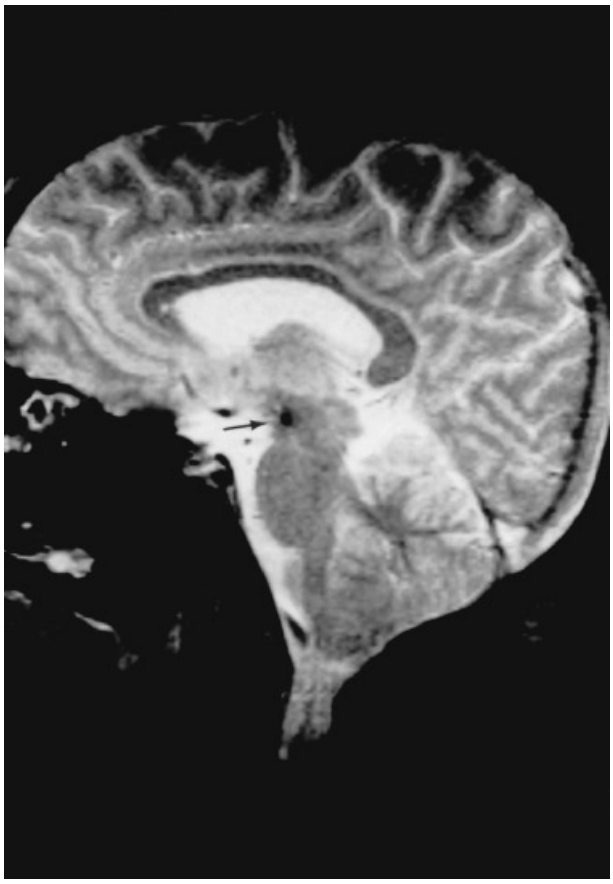

FIG. 2. Flash magnetic resonance image in the right parasagittal plane showing the lesion in the substantia nigra and the subthalamic nucleus (black arrow) in the exact plane as described in Figure 3.

vanillic acid concentration of 100 nmol/L (n: 100–400 nmol/L). Sinemet up to 750 mg per day did not influence the tremor. His tremor when drawing Archimedes' spiral improved slightly after a subcutaneous injection of apomorphine of 8 mg. A right-sided thalamotomy was performed, and the tremor and the pain in the left side of the body disappeared immediately after the procedure. He remained with a very slight upper motor neuron facial weakness and an increase of the dysmetria of the left arm.

Discussion

By using PET and [^{18}F]-dopa uptake techniques, Remy and colleagues[7] demonstrated significant dopaminergic denervation in patients with tremor caused by midbrain lesions, implicating damage to the substantia nigra, nigrostriatal pathway, or both. That levodopa sometimes provides therapeutic benefit substantiates the suggestion that the dopaminergic pathway is involved.[1,7,11] On the other hand, the postural and action components are probably related to the disruption of the cerebellar outflow pathway (e.g., the dentatothalamic and dentatorubral tracts) at the superior cerebellar peduncle and the rubro-olivary tract in the centrum tectum.[12,13]

This case with SPECT examination confirms the results of Remy and associates,[7] in that dopaminergic denervation in patients with midbrain tremor is even more marked than in severe

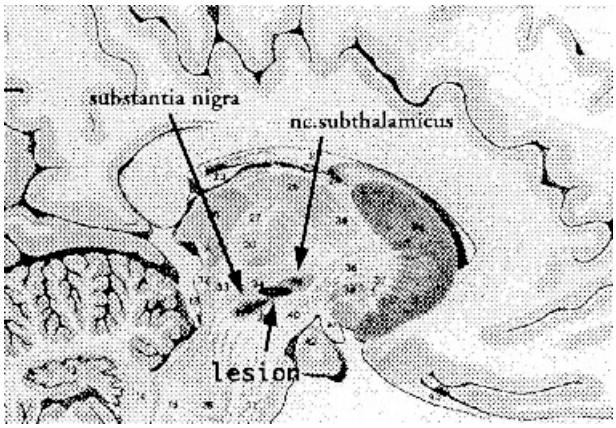

FIG. 3. Diagram of a parasagittal anatomical slice, showing the anatomical connection between subthalamic nucleus and the substantia nigra. The location of the lesion is indicated. Reproduced with permission from Nieuwenhuys et al.[10].

Parkinson's disease patients. The dopaminergic denervation in our case and in those of Remy and coworkers[7] was very severe or complete in both caudate and putamen, whereas in Parkinson's disease caudate function is relatively spared.[14,15] The absence of increased D_2 receptor binding in this patient with a profound loss of FP-CIT activity on the right side can be ex-

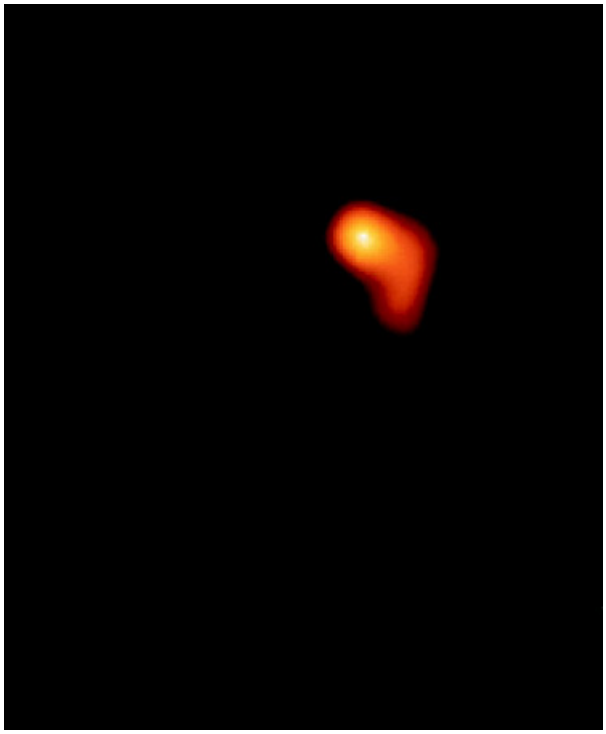

FIG. 4. Transversal [^{123}I]FP-CIT single photon emission computed tomography image showing only visualization of dopamine transporters in the left striatum. The binding in the left caudate nucleus is normal and in the left putamen slightly decreased in the posterior part only. This finding indicates that the nigrostriatal pathway is lost at the right side of the body.

plained by the use of anti-Parkinson medication before he was sent to our hospital.

As indicated by MRI, the topographical distribution of the lesion showed predominant involvement of the anteromedial portions of the substantia nigra and the subthalamic nucleus. Following current models, in which dopaminergic neurons in the anteromedial portions of the substantia nigra project primarily to the caudate nuclei, while the putamen is mainly innervated by the lateral portions,[16–18] highest reductions of [^{123}I]FP-CIT binding were expected to be found in the caudate and less so in the putamen. However, the [^{123}I]FP-CIT uptake in both right putamen and caudate was absent in our patient. This decrease in uptake could not be explained by anatomical or functional damage to the striatum itself, because a striatal lesion could be excluded by MRI scan and a normal [^{123}I]IBZM SPECT. Thus this reduction probably reflects severe striatal dopaminergic denervation of both the medial and lateral segments of the nigrostriatal pathway ipsilateral to the upper peduncle lesion, in the absence of an anatomical lesion in the lateral part of the substantia nigra. The MRI lesion probably represents only a fraction of the actual brain damage.

In the presence of such a damaged nigrostriatal pathway, the absence of rigidity and hypokinesia is surprising.[18,19] According to the current basal ganglia models, a lesion in the subthalamic nucleus can compensate for substantia nigra lesions and dramatically decrease rigidity, hypokinesia, and tremor, mainly in the contralateral limbs.[20–22] Therefore, an explanation could be that the lesion in the subthalamic nucleus in our patient prevented the onset of a Parkinson syndrome. The only case of Remy and colleagues[7] in which the subthalamic region was lesioned besides the upper peduncle showed hypertonia without hypokinesia caused by a corticospinal tract lesion, which also gave a slight hemiparesis. This case supports preliminary results of subthalamotomy in Parkinson's disease.[21,22]

In conclusion, this case provides some support for lesioning the subthalamic nucleus as a therapy for Parkinson's disease. Furthermore, it shows that SPECT can be used to distinguish the dopaminergic denervation in patients with posttraumatic tremor from the denervation of Parkinson's disease patients.

Legend to the Videotape

A 47-year-old patient with a posttraumatic tremor in the left hand and leg. The tremor is slightly irregular and jerky in rest and during posture. Occasionally it is alternated with pill-rolling. There is no rigidity or hypokinesia. His gait is normal. Coordination is intact, except for a slight dysmetria of the left hand. The tremor does not meet all criteria for a Holmes tremor because of its absence on intention.

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Levodopa-Induced Dyskinesia in an Autopsy-Proven Case of Progressive Supranuclear Palsy

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Abstract: It is common for patients with idiopathic Parkinson's disease to develop levodopa-induced dyskinesia. This report provides what we believe is the first videotape presentation of levodopa-induced dyskinesia in a patient with progressive supranuclear palsy. To our knowledge, there is only one previous report of an autopsy-proven case of this kind. © 2002 Movement Disorder Society

Key words: Parkinson's disease; levodopa-induced dyskinesia; progressive supranuclear palsy

Levodopa-induced dyskinesia (LID) is common in patients with idiopathic Parkinson's disease (PD). Among Parkinson plus syndromes, striatonigral degeneration is frequently associated with LID. However, it is so rare in cortical–basal ganglionic degeneration (CBD) that a case by Frucht and colleagues[1] is the only demonstration of LID that we know of in an autopsy-proven case. Progressive supranuclear palsy (PSP) is also very rarely associated with LID. To our knowledge, only two published studies describe LID in PSP.[2,3] Kompoliti and associates describe the only known autopsy-proven PSP patient with LID.[3] Herein, we report on a second autopsy-proven PSP case with LID.

Case Report

A 61-year-old woman was admitted to the hospital because she had frequent falls and gait impairment. Since the age of 58 years, her movements had slowed, her gait had become unsteady, and she had frequently fallen. Six months before referral, levodopa–carbidopa (levodopa 125 mg three times a day) had been initiated with minimal improvement. Four months later, dyskinetic movements appeared in the left leg for about 1 to 2 hours after each dose of levodopa. There was no history of other medical diseases or any other medications, and no family history of neurological illnesses.

On neurological examination the patient was alert and oriented with a staring look, her speech was slow and thick, the mental-status examination was normal, and pupils were equal and reactive. The visual fields were full. Saccades were very slow but full in horizontal directions. Her upward gaze was completely absent; the downward gaze was impaired to 20 degrees, and vestibulo-ocular reflex was maintained. Her facial expression was impassive with virtually no blinking, the tongue and uvula were midline, and the gag reflex was normal. Motor power was intact and sensory examination was normal. Deep-tendon reflexes were brisk, plantar responses were flexor, frontal lobe release signs were absent, and there was bilateral bradykinesia with prominent axial rigidity. No rest or postural tremor was observed. The patient could stand with the assistance of 1 person, and with the assistance of 2 she could take several steps.

The results of hematological tests were unremarkable. Blood chemical and enzyme levels were normal. Magnetic resonance imaging was normal. After discontinuation of levodopa–carbidopa, bradykinesia and gait disturbance worsened slightly. Dyskinesia in the left leg disappeared. Levodopa–benserazide was started, and doses of levodopa were gradually increased to 300 mg per day, leading to slight improvement of bradykinesia, rigidity, and gait disturbance. However, dyskinesia of the left leg emerged again, which began 1 hour after taking levodopa and lasted for approximately 1 hour. The dyskinesia consisted of semirhythmic flexion–extension of the left knee and internal rotation and adduction of the hip joint (see Video). Reduction of levodopa provided relief from dyskinesia, but bradykinesia and gait disturbances worsened. The patient was discharged on 300 mg of levodopa per day.

After discharge the tendency to fall increased, and over the next year her gait deteriorated further until she became unable to walk even with assistance. Levodopa did not benefit her, but it was continued at the request of the patient and her family. LID disappeared with the loss of levodopa benefit. The patient died of aspiration pneumonia at the age of 65.

The pathological findings included neurofibrillary tangles (NFTs), neuropil threads, neuronal loss, and gliosis. Neuronal loss and gliosis were present in the substantia nigra, red nucleus, pontine nuclei, striatum, and pallidum. Neuronal loss and gliosis was most severe in the substantia nigra and red nucleus. Dense NFTs and neuropil threads were found mainly in the substantia nigra, pontine nuclei, inferior olive, and nuclei of medulla oblongata (Fig. 1). There was also a lesser degree of NFT pathology in the dentate nucleus, locus ceruleus; frontal, parietal, and temporal cortices; parahippocampus; and cingulated gyrus. The smallest numbers of NFTs were seen in the caudate nucleus, putamen, globus pallidus, superior colliculi, and hippocampus. The majority of the NFTs had a rounded shape, and some NFTs were flame-shaped. Deposition of senile plaques or granulovacuolar degeneration of hippocampal neurons were not observed. There were no Lewy bodies or glial cytoplasmic inclusions. Asymmetric and circumscribed lobar atrophy, ballooned neurons, or astrocytic plaques, suggesting CBD, were not found. Increased corpora amylacea were seen in the periventricular area and beneath the pia mater. There was moderate atherosclerosis in both internal carotid, middle cerebral, and posterior cerebral arteries.

A videotape accompanies this article.

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Received 4 August 2001; Revised 6 November 2001, 19 February 2002, 8 March 2002; Accepted 11 March 2002

Published online 7 May 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10246

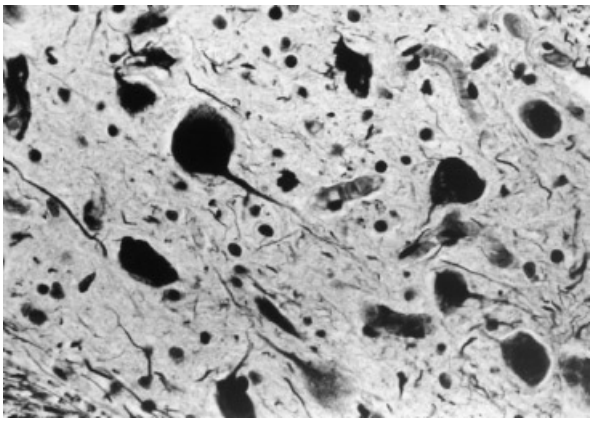

FIG. 1. This photomicrograph of substantia nigra with Bielschowsky silver stain (magnification ×200 before reduction) shows intracytoplasmic argyrophil intraneuronal inclusions.

Discussion

Prominent postural instability and falls at onset, severe axial rigidity, supranuclear ophthalmoplegia, and the surprised look suggested a diagnosis of PSP for this patient, and this clinical diagnosis was confirmed at autopsy. The clinical features met the criteria of probable PSP, which was proposed at the international workshop of the National Institute of Neurological Disorders and Stroke and the Society for Progressive Supranuclear Palsy.[4] The minimal response to levodopa was also consistent with PSP. However, the occurrence of LID in this patient was very unusual.

The pathology in PSP is wider than the nigrostriatal system. There are additional downstream lesions in the pallidum, pontomesencephalic nuclei, lower brainstem, and spinal cord, which explains no or minimal response to dopaminergic medication.[5–8] The time course of LID in our patient suggests peak-dose dyskinesia. Unlike PD, LID in our patient appeared rather early in the course of her illness and disappeared with disease progression. Limb dystonia can be an early sign of PSP[9]; however, it can be easily differentiated from LID by the drug history.

To our knowledge, there is only one previous report of an autopsy-proven PSP case with LID.[3] The dyskinesia in this case began 2 years after levodopa therapy, was confined to the face, and resolved following discontinuation of levodopa. LID in the autopsy-proven CBD case appeared at least 18 months after levodopa treatment.[1] Based on the description of relief from dyskinesia by reduction of levodopa, it appeared to be peak-dose dyskinesia, and to our knowledge there is no description of LID later in the course of the disease.

The basic mechanisms underlying LID are not completely understood. Several hypotheses regarding the pathophysiology of LID have been proposed. It is probably related to striatal dopamine receptor changes and the alterations in the neuronal firing pattern within the basal ganglia circuitry after dopaminergic denervation and chronic exposure to levodopa.[10–15] The receptor alterations include changes in sensitivity and relative balance between different dopamine receptor subtypes. In PSP, multiple levels in the nigrostriatal and striatopallidal systems are damaged; therefore, a neuronal system generating LID cannot work in PSP, which may explain why LID is very rare. Postmortem examination of the brain of our patient showed neuronal loss and gliosis in the striatum and pallidum as well as in the substantia nigra.

Legends to the Videotape

Segment 1. A 61-year-old woman's prominent postural instability is shown. She was unable to stand or walk without leaning against a wall or holding onto furniture, and she walked with both shoulders abducted. Her facial expression was impassive with markedly decreased blink frequency.

Segment 2. The patient's dyskinesia in the left leg, as observed 1 hour after the administration of levodopa 100 mg, is shown. The choreiform movements consisted of semirhythmic flexion–extension of the knee and internal rotation and adduction of the hip. Dystonic posturing of the left big toe was noted.

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Choreic Syndrome Due to Hashimoto's Encephalopathy

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Abstract: We report on the instructive case of an elderly woman who became encephalopathic and concurrently developed chorea. Thyroid antibody studies were abnormal. She responded extremely well to oral corticosteroids. © 2002 Movement Disorder Society

Key words: Hashimoto's encephalopathy; choreic movement; thyroidosis; subacute diffuse encephalopathy

Hashimoto's encephalopathy (HE) is a steroid-responsive, relapsing disease with pleomorphic clinical presentation, including strokelike repetition, myoclonic encephalopathy, partial complex or generalized tonicoclonic seizures, progressive neuropsychological impairment, and generalized hypertonia. Choreoathetotic movements in HE have not been previously described. The possibility of an autoimmune encephalopathy associated with Hashimoto's disease was first suggested by Brain and colleagues in 1966.[1] Chronic lymphocytic Hashimoto's thyroiditis is a commonly occurring (in 3–4% of the population), organ-specific, autoimmune disease accompanied by goiter, generally in middle-aged women. About one third of the patients are hypothyroid. In most cases, antibodies against thyroglobulin, thyroid peroxidase, or both are detectable.

Case Report

In July 2000, a 77-year-old woman with an uneventful medical history was seen for very recent behavioral disorders. Over 1 week, she developed difficulty walking with uncontrollable asymmetric movements of the arms, feet, and head. She reported frightful visual hallucinations, with visions of a threatening wild boar, and alternated between inappropriate giggling, laughing, and crying. She was not febrile. Neurological examination showed diffuse hypotonia and bilateral and axial choreic movements. Tendon reflexes were normal. She had bilateral inflexion plantar responses. Blood investigations, including routine hematology, biochemistry, and erythrocyte sedimentation rate, were normal. Human immunodeficiency virus and syphilis serology and a titer for Lyme disease were negative. Serum B_{12} and folate concentrations were normal. Searches for antinuclear, anticytoplasm, and antiphospholipid antibodies, as well as all available paraneoplastic antibodies, were negative. There was no argument favoring a circulating lupus anticoagulant: platelet counts, activated partial thromboplastin time, and coagulation tests were normal. The patient had peripheral hypothyroidism with central correction: serum T4 was normal and thyroid-stimulating hormone (TSH) was elevated at 49 μU/ml. Antimicrosomal and antithyroglobulin antibody titers were markedly raised: antithyroglobulin antibodies were elevated at 374 IU/ml (normal, <100), antimicrosomal antibody titer was 3430 IU/ml (normal, <40). Cerebrospinal fluid (CSF) was acellular, with normal glucose and protein levels. CSF culture (including herpes simplex virus polymerase chain reaction) was negative. Electroencephalography (EEG) showed monomorphic, symmetrical, rhythmical theta activity. Brain computed tomography (CT) and magnetic resonance imaging (MRI) showed age-related enlargement of the ventricles and cortico–subcortical atrophy. The diagnosis of probable HE was proposed and treatment was initiated with prednisolone 60 mg per day, associated with levothyroxin substitution (75 μg/day). Within a few days, we noted an improvement in clinical symptomatology, but 6 days after the beginning of treatment the antimicrosomal and antithyroglobulin antibody levels were still elevated and choreic movements reappeared. The prednisolone dose was then increased to 80 mg per day. An improvement in clinical symptomatology was again observed, followed by a decrease in the antibody titers. At 3 weeks, the patient was clinically normal. She has not experienced a relapse during 8 months of follow-up.

Discussion

After the initial report by Brain and associates in 1966,[1] several other individual cases and series of patients with neurological extrapyramidal disorders associated with high titers of antithyroid antibodies were reported. None of these patients had choreic syndrome. We retained the diagnosis of Hashimoto's encephalopathy in our patient on the basis of the clinical signs of encephalitis with no other obvious cause, associated with markedly elevated antimicrosomal and antithyroglobulin antibody titers and subsequent improvement of the clinical presentation after prednisolone and levothyroxin substitution. The paraclinical features followed the characteristic course described in other cases of HE.

Typically, the EEG is normal or shows slowing of the background rhythm with monomorphic, rhythmical delta activity.[2–4] The CSF exhibits a high protein titer (in 65% of reported cases) without abnormal cellularity and rarely with a high leukocyte density. Intrathecal synthesis of immunoglobulin G (oligoclonal bands) has been described in 6% of cases.[5] CT and MRI are usually normal but slight brain atrophy is sometimes detected.[5] Thyroid function tests show normal or decreased free T4 levels and increased or normal TSH.[4] The encephalopathy tends to present with a subacute or abrupt onset of confusion, alteration of consciousness, and frequently focal and generalized seizures. The encephalopathy usually responds to steroid therapy. If the response to corticosteroids is incomplete, plasmapheresis can be used with efficacy.[2] The long-term prognosis is favorable.

The pathogenesis of HE remains unclear. Several hypotheses have been proposed, including a generalized abnormality of the immune system, cerebral vasculitis, recurrent demyelinization, and a toxic effect of thyrotropin-releasing hormone on the cen-

A videotape accompanies this article.

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Received 13 August 2001; Revised 13 February 2002; Accepted 22 February 2002

Published online 17 April 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10230

tral nervous system. The autoimmune mechanism is supported by our case, due to the prompt, favorable response to steroids and the parallel course of the clinical features and the antithyroglobulin titers, also reported by others.[1,4] In an autopsy case recently reported on by Nolte and coworkers,[3] with longstanding Hashimoto's thyroiditis and typical features of HE, pathology findings suggested a peculiar brainstem-dominated vasculitis characterized by T-cell infiltrates of the leptomeningeal venules. Despite these reports, the pathogenesis of HE remains to be fully elucidated.

Our case demonstrates that a diagnosis of HE should be considered for patients who develop diffuse encephalopathy of unknown origin concomitant with choreoathetosis. Screening for antithyroid antibodies might be useful, as efficient treatment with steroids can be proposed.

Legends to the Videotape

Segment 1. At age 77 years, this patient had bilateral and axial choreic movements predominantly affecting the face and right limbs. She was first filmed at rest; next, she was asked to raise both arms together, then open her mouth , and finally raise her right leg first and her left leg second.

Segment 2. Three weeks later, choreic movements were completely resolved. She was treated with steroids and levothyroxine substitution.

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Freezing of Shoulder Flexion Impeding Boule Throwing: A Form of Task-Specific Focal Dystonia in Petanque Players

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Received 14 August 2001; Revised 4 February 2002; Accepted 5 February 2002

Published online 6 May 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10228

Abstract: During a period of intensive practice, 2 petanque players developed freezing of shoulder flexion impeding boule throwing. This movement disorder was consistent with the diagnosis of task-specific focal dystonia. Polymyography showed that freezing was associated with bursts of low amplitude. In the absence of motor or sensory deficits, a motor apraxia could be considered. © 2002 Movement Disorder Society

Key words: task-specific focal dystonia; motor apraxia

Dystonia is characterized by involuntary, sustained, often repetitive muscle contractions causing twisting movements or abnormal postures.[1] When the dystonic movements are intensified by motor activity the dystonia is classified as an action dystonia, and when it occurs only during a specific activity it is referred to as a task-specific focal dystonia, also called "occupational" dystonia. The tasks are usually skilled actions, and the dystonia may be so disabling that the career of the affected person may be prematurely ended, notably in professional musicians.[2,3] Writer's cramp is the most typical example of task-specific focal dystonia in adulthood.[4,5] However, the clinical spectrum is very wide. In sport, task-specific focal dystonia is exemplified by the "yips" of golfers, consisting in sudden jerks, tremors, or freezing spasms while putting.[6,7] Here we report on 2 cases of petanque players who, during a period of intensive practice, developed freezing of shoulder flexion, preventing boule throwing.

Case Reports

Patient 1

This 52-year-old, right-handed man had played petanque regularly since he was 20 years old. He played for the first time in competitions when he was 30. For 15 years he had participated in tournaments without any problems throwing the boules. Then he stopped playing because of a disagreement with the team manager. After an interruption of 3 years, he trained himself intensively to reach the level he had attained before he stopped playing. After about 3 months of training, he started competitions again, but progressively he experienced difficulties throwing. He had the feeling that his arm was blocked and that he could not open his hand to release the boule. After several unsuccessful and disheartening attempts, he threw the boule without taking aim at the target and missed it. In contrast, he had no difficulties throwing when there was no target. His motor difficulties were sometimes accompanied by sweats and difficulties in breathing. Social phobia was diagnosed by a psychiatrist, and he was treated by cognitive–behavioral psychotherapy that was ineffective regarding the movement disorder. With the increasing number of tournaments, his problems worsened. They appeared increasingly earlier in the course of a tournament, and he could no longer take part in competitions. He had no difficulties in other tasks, notably in his job as a bus driver. There were no known problems of dystonia in his family members. He had never previously received treatment for mood disturbances. He said that, during his youth, he had played knucklebones and that, after several years of practise without problems he experienced difficulties throwing the knucklebones, so he stopped playing.

Results of the neurological examination were normal. More particularly, in the right upper limb, there was no atrophy or hypertrophy, no abnormal posture at rest, and tone and strength were normal. Dexterity in the right hand was normal. Active

and passive movements of the right shoulder could be performed freely and without pain.

A videotape recording of a training session (consisting of shooting at a target at a distance of 10 m) showed freezing of shoulder flexion from the very first throw. Shoulder extension was apparently normal. After a series of approximately 10 unsuccessful attempts due to the freezing, he threw the boule with a flexion of normal amplitude but without staring at the target and he missed. Sometimes, between the attempts, he was breathing hard. Mirror movements of the left shoulder accompanied the repetitive movements of the right shoulder (see Video, Segment 1).

Patient 2

This 56-year-old, right-handed man had played petanque in competitions every year for approximately 20 years without any problems, when he started to experience difficulties throwing during a period of intensive competition. The difficulties increased as the games went on, and after about 50 throws, he had the feeling that "his arm was spring-driven." However, he did not have difficulties when he threw the boule without taking aim at the target. In the same period, he developed a right lateral epicondylitis. An electrophysiological study of the right upper limb and a computed tomographic scan of the head showed no abnormalities. He stopped playing for the rest of the season. After a 6-month break, the epicondylitis was no longer present but when he started to play again, the difficulties returned. He was a manual worker and had never experienced difficulties in his professional tasks. There were no problems of dystonia in his family. The only treatment that he was undergoing when his difficulties occurred was a beta-blocker (Tenormin) for hypertension. He had never taken drugs for anxiety or depression. Results of the clinical examination was normal. More particularly in the right upper limb, there was no abnormal posture at rest, no joint pain or limitation in active and passive movements, and no tender points at the elbow. Strength and tone were normal.

A videotape recording and simultaneous polymyography during a session of shooting at a target showed that the first throws were performed without difficulty but after about 30 throws, the freezing of shoulder flexion started to occur (see Video, Segment 2). The freezings became more frequent as throwing continued. Between the attempts, sometimes he handled the boule in a sort of ritual usual among petanque players. After several unsuccessful attempts due to the freezing, he threw the boule with a shoulder flexion of normal amplitude but often missed the target.

In the 2 patients, polymyography was performed using an eight-channel Keypoint apparatus during throwing movements by recording the rectified integrated EMG signals from the shoulder joint flexors: deltoid (anterior), coracobrachialis, pectoralis major (upper), biceps brachii, and from the antagonistic shoulder joint extensors: deltoid (posterior), teres major, latissimus dorsi, triceps brachii (long head) with surface electrodes. Recordings were successively performed in the following conditions: (1) performing the throwing gesture with nothing in the hand; (2) throwing at the target with the boule from a distance of 8 m; (3) throwing at the target from the same distance with a tennis ball; and (4) throwing at the target with the boule and with the eyes closed. In both patients, between 5 and 10 successive trials were recorded for each condition. In condition 1, polymyography during throwing showed no abnormal co-contractions between the agonists and antagonists (Fig. 1A). In condition 2, during freezing, the bursts were of smaller amplitude and shorter duration than those recorded in condition 1 (Fig. 1B). During throwing the EMG pattern was the same as in condition 1. In conditions 3 and 4, freezing was also present with the same EMG patterns as in condition 2, but the total number of bursts per muscle accompanying freezing was lower than in condition 2. The EMG patterns were the same in both patients, although freezing was more marked in Patient 1 than in Patient 2.

Discussion

Our 2 petanque players developed freezing of shoulder flexion, which impeded throwing. The type of motion and the circumstances of this pathological condition suggest an idiopathic, task-specific focal dystonia. First, boule throwing is a repetitive, stereotypic, skilled motion, and idiopathic task-specific focal dystonia usually occurs during this type of mo-

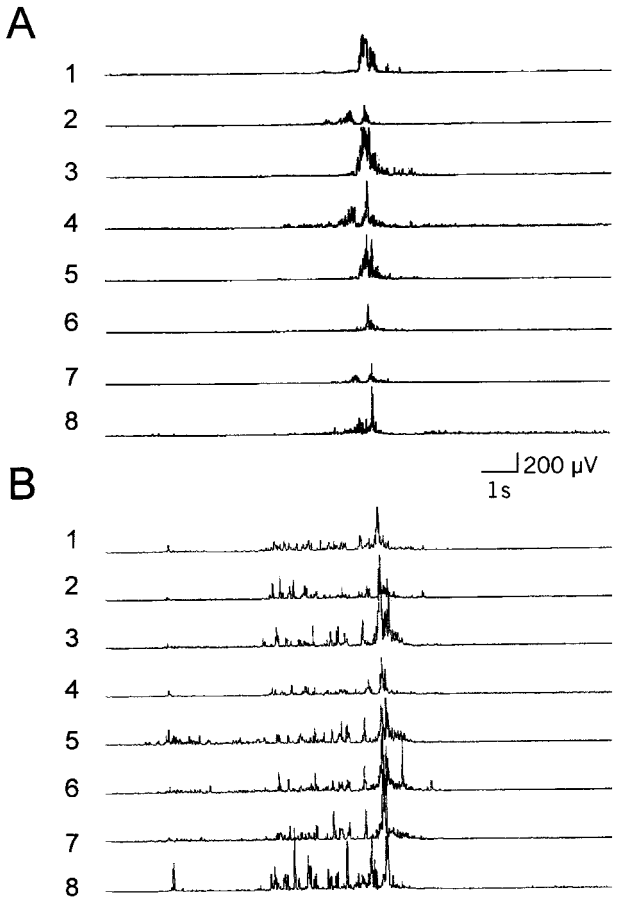

FIG. 1. Polymyography: 1, pectoralis major (upper); 2, teres major; 3, deltoid (anterior); 4, deltoid (posterior); 5, coracobrachialis; 6, latissimus dorsi; 7, biceps brachii; 8, triceps brachii (long head). **A:** During the throwing gesture with nothing in the hand, there were no obvious abnormal co-contractions between agonists and antagonists. **B:** During the freezing, a series of bursts of small amplitude compared with A were recorded. During throwing, the electromyography pattern was the same as in condition 1 with bursts of larger amplitude.

tion.[8] Petanque is a target sport with a ballistic motion like golf, cricket, or dart throwing where task-specific dystonia has been reported.[9] Like golfers affected by yips, our 2 patients were of middle age and had practised their sport for more than 20 years without problems when their movement disorder occurred. Second, the patients developed their movement disorders during a period of intensive practice, and the internal epicondylitis in Patient 2 suggests an overuse syndrome that can induce the occurrence of a task-specific focal dystonia. Experimentally, Byl and colleagues[10] demonstrated that repetitive movements of the distal upper limb in two nonhuman primates produced a disorganization of the cortical sensory representation of the distal upper limb with motor dysfunction. Additionally, Topp and Byl[11] demonstrated that the monkey which developed the motor dysfunction in the shortest time after repetitive, rapid, stereotypical hand-squeezing movements, had a preexisting anatomical restriction of the flexor profundus tendon on the fourth digit. These abnormalities in nonhuman primates may represent a model of task-specific focal dystonia in human beings. Indeed, a disorganization of the cortical sensory representation of distal upper limbs has been found in focal hand dystonia.[12,13] Moreover, in Patient 1, the difficulties throwing the knucklebones during his youth may have been the first expression of a task-specific focal dystonia, and the sign of an individual predisposition for developing this type of dystonia.

In our patients, the absence of freezing when they performed the throwing gesture with nothing in the hand and when they threw the boule without taking aim at the target suggests that the somatosensory and visual inputs played a role in the occurrence of their motor dysfunction. In line with this, it is noteworthy that golfers affected by yips try to reduce it not only by modifying hand position but also by altering their visual fixation.[6] The role of sensory inputs in the occurrence of dystonia has been suggested by Kaji and associates, who induced a dystonic posture in patients with writer's cramp by a tonic vibration reflex manoeuvre, which is known to increase muscle spindle activity. The dystonic posture was significantly improved by local injection of lidocaine, which decreases muscle spindle activity.[14] However, during boule throwing with their eyes closed, freezing occurred if our patients were thinking about the target. In petanque players who had played regularly for many years, this finding suggests a dysfunction in the production of automated sequences performed from memory. This is in keeping with the finding of Greene and Bressman in dystonia, where they demonstrated that thinking about a specific task triggering dystonia had the same effect as really performing the task.[15] The SMA-basal ganglia system might be recruited preferentially in the production of automated sequences performed from memory.[16]

During freezing, polymyography showed repetitive bursts of smaller amplitudes and shorter duration than those recorded during the ballistic movement accompanying boule throwing. Thus, the recruitment of the muscles required to perform throwing correctly was insufficient during freezing. This pattern is not typical of primary dystonia.[17] However, Berardelli and coworkers mentioned that in some instances, bradykinesia in patients with dystonia is the result of inadequate activation of the agonist muscles.[17] In our patients, in the absence of motor or sensory deficits, the muscular inhibition could be the result of motor apraxia. Such a mechanism could be considered at least in some task-specific focal dystonia and could result from a dysfunction in the parietofrontal circuits and their subcortical connections subserving the transformation of sensory information into action.[16]

In Patient 1, mirrored movements of the left shoulder accompanied freezing (see Video, Segment 1). In healthy adults, mirrored movements are electrophysiologically present but usually clinically invisible, because they probably undergo interhemispheric inhibitory control through the myelinated callosal fibers.[18] Their presence in our patient could be due to the loss of inhibitory control.

As in other task-specific focal dystonias, overuse is likely implicated in the occurrence of the movement disorder in our 2 petanque players. When electromyography shows an excessive co-contraction, local treatment by botulinum toxin can improve the dystonia. We cannot rule out an excessive co-contraction from the nonrecorded forearm muscles, but the results of the polymyography clearly showed that the incomplete achievement of the ballistic movement of shoulder flexion was more related to a muscular inhibition than to an excessive co-contraction.

Legend to the Videotape

Segment 1. Patient 1: Recorded during a training session consisting of shooting at a target 10 m away. Freezing of the shoulder flexion was present from the first attempt and was usually accompanied by mirror movements of the left shoulder. Sometimes, he stopped the attempts and breathed hard. After a series of about 10 unsuccessful attempts due freezing, he threw the boule with a shoulder flexion of normal amplitude but missed the target.

Segment 2. Patient 2: The first throws were performed without difficulty. After about 30 throws, the freezing of the shoulder flexion started to occur. The freezing became more and more frequent as the throws continued. After several unsuccessful attempts due to freezing, he threw the boule with a shoulder flexion of normal amplitude but often missed the target.

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Generalised Dystonia with an Abnormal Magnetic Resonance Imaging Signal in the Basal Ganglia: A Case of Adult-Onset GM1 Gangliosidosis

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Abstract: We describe a 46-year-old woman with adult-onset generalised dystonia and a severe speech disorder with an abnormal magnetic resonance imaging signal in the basal ganglia. A storage disease study demonstrated the presence of a GM1 gangliosidosis. This rare condition should be investigated in cases of generalised dystonia, especially in those cases with other features suggesting symptomatic dystonia. © 2002 Movement Disorder Society

A videotape accompanies this article.

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Received 13 November 2001; Revised 3 March 2002; Accepted 12 March 2002

Published online 7 May 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10247

GM1 gangliosidosis is a lysosomal disease of autosomal recessive inheritance caused by a deficit in the β-galactosidase enzyme.[1] Two different forms have been described: GM1 gangliosidosis, which is basically a neurovisceral disease, and Morquio's disease, which is a predominantly skeletal disorder. Different mutations have been described in the β-galactosidase gene,[2–4] leading to different phenotypes (Morquio's disease and the infantile, juvenile, and adult-onset forms of GM1 gangliosidosis). It has been reported that the infantile form of GM1 gangliosidosis shows very low β-galactosidase activity, while the juvenile and adult-onset forms have residual enzymatic activity.[1] The adult-onset form occurs very infrequently but could be underdiagnosed.

Case Report

A 46-year-old woman had presented at the age of 11 years with left hip subluxation after a minor trauma. She underwent surgery when it was realised that there were bilateral degenerative signs in both hips. Two years later, the patient required surgical correction of the right hip because her joint problems became aggravated. After surgery and intensive rehabilitation, the patient regained a relatively normal gait. However, at the age of 21, after a new hip subluxation, she underwent left hip arthrodesis. At the age of 26, she started to have abnormal postures in both lower limbs and hands with progressive deformation of the fingers. Progressive speech difficulty and involuntary orofacial movements also appeared. She was admitted to another hospital, and at that time slight cognitive impairment, difficulty in speech articulation, dystonic postures of the limbs, and hyperreflexia with left Babinski's sign were observed. Cranial magnetic resonance imaging (MRI) was normal, but cervical MRI showed important vertebral degenerative signs and flattening of vertebral bodies, although there were no spinal cord abnormalities. Levels of blood copper, ceruloplasmin, and long-chain fatty acids were normal, as was urinary quantification of amino acids. No diagnosis was made and the clinical picture evolved to include marked gait and speech disorders, making it impossible for the patient to walk or speak by the age of 40. The family history disclosed consanguinity in her parents, who were very distant relatives.

The patient was admitted to our hospital when she was 45 years old. On neurological examination she was alert and collaborative. She could hardly speak, being able to articulate only a few simple words. Her ocular motility was normal but she showed an enhanced blinking rate. Fundoscopy examination was normal. Voluntary tongue motility was diminished. Slow, involuntary orofacial movements were observed, with abnormal, fixed postures of the hands and feet. Her hands showed a deformity in flexion of the distal interphalangeal joints that could be passively corrected. A posture in hyperflexion with inward deviation was seen in both feet. She showed increased tone in all four extremities, especially the legs, but dystonic spasms were not observed. She also exhibited generalised limb weakness with markedly slow voluntary movements. Sensory examination was apparently normal. Deep tendon reflexes were abolished in the lower limbs and plantar responses were equivocal. She could stand up with help but gait was impossible. Abdominal examination did not disclose visceromegaly.

A new MRI of the brain showed high signal intensities in the caudate and putamen nuclei on both proton-density and T2-weighted images (Fig. 1). These nuclei were of small size, and

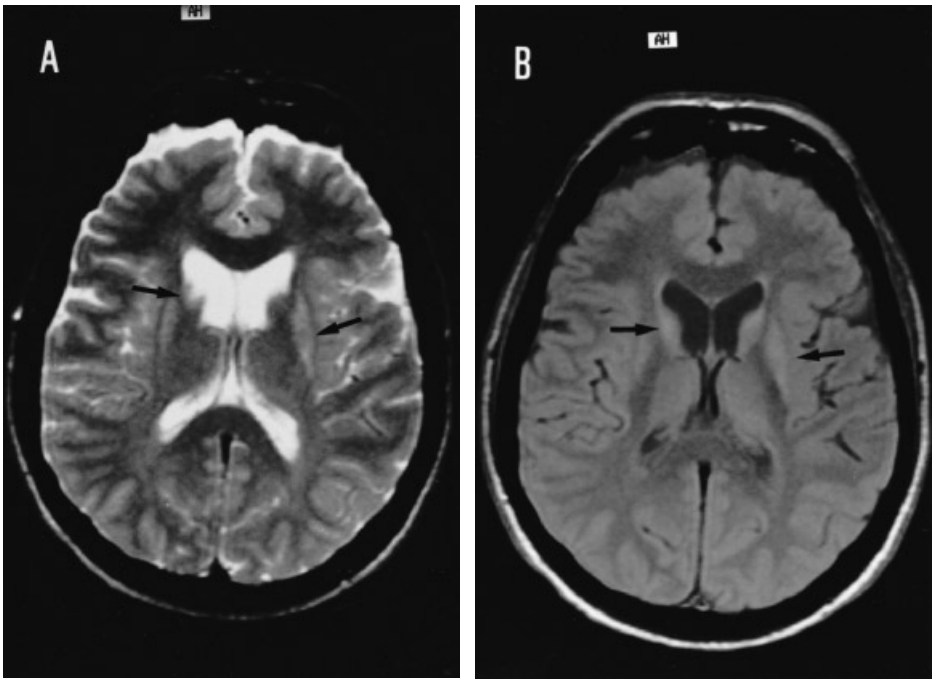

FIG. 1. T2-weighted (**A**) and proton-density (**B**) magnetic images of the brain show bilateral hyperintensities in both the putamen and the caudate nuclei (arrows).

the frontal horns of the lateral ventricles appeared dilated. There was cortical atrophy, predominantly in the frontal and temporal regions. Storage disease study revealed a marked deficiency in β-galactosidase activity in the patient's fibroblasts (patient, 45.5 nmol/hour/mg of protein; control subject, 1802 nmol/hour/mg of protein), supporting a diagnosis of GM1 gangliosidosis.

Discussion

Our patient developed a progressive disease characterised by generalised dystonia, skeletal abnormalities, and a severe speech disorder. After many years she was diagnosed with adult-onset GM1 gangliosidosis. The infantile form of GM1 gangliosidosis begins at birth and has a rapidly progressive course characterised by feeding and respiratory dysfunction, hepatosplenomegaly, blindness, seizures, and marked spasticity. The age of onset of the juvenile form ranges from 6 months to 3 years, and the disease is characterised by ataxia, pyramidal and extrapyramidal signs, mental impairment, and seizures. Cherry-red spots may appear in both the infantile and juvenile forms. The onset of the adult form ranges from 3 to 30 years, and the disease is clinically characterised by dysarthria, gait disturbance, and dystonia.[5–7] There are usually no cerebellar signs, cognitive impairment, myoclonus, dysmorphism, visceromegaly, or cherry-red spots. In a series of 16 Japanese patients with adult-onset GM1 gangliosidosis,[5] all had speech disturbance; extrapyramidal signs, such as dystonia, rigidity, and bradykinesia; and gait disorder. Dystonic postures, such as torticollis, facial grimacing, and blepharospasm, were commonly observed. Our patient did not exhibit torticollis or blepharospasm, but an excessive blinking rate and orofacial grimacing were prominent signs. Classically, skeletal abnormalities are not considered to be prominent features in GM1 gangliosidosis; however, our patient's initial symptoms were related to hip dysfunction, with later degenerative signs of the vertebral bodies. Bone abnormalities, such as flattening of the vertebral bodies similar to those found in our patient, were reported in 12 of 16 Japanese patients with adult-onset GM1 gangliosidosis.[5]

MRI alterations in the basal ganglia have been reported in only a few patients with adult-onset GM1 gangliosidosis. The main finding consists of bilateral, symmetrical, high-intensity signal on proton-density and T2-weighted sequences in the putamen.[5,6] Our patient showed this signal alteration in the MRI, but the caudate nuclei were also involved. Dilation of the anterior horns of the lateral ventricles and cortical atrophy have been also described in the adult-onset form.[5] Other metabolic diseases with extrapyramidal symptoms and basal ganglia alterations in the MRI are the glutaric and hydroxyglutaric aciduries and Leigh disease.[8–10] However, these forms usually begin in childhood, and scans show involvement of the white matter, dentate nuclei, and brainstem. Unlike early-onset GM1 gangliosidosis, pathological studies of the adult form have found that cortical neurons are little affected by storage, which is limited almost exclusively to the basal ganglia.[7,11,12] The pattern of distribution of the lesions, involving predominantly the putamen nuclei, as observed on MRI and in pathological studies, could account for the finding that dystonia is the predominant symptom in the adult form. Moreover, marked neuronal loss with secondary gliosis in the putamen and the head of the caudate nuclei[7] could be responsible for MRI findings.

We conclude that adult-onset GM1 gangliosidosis can present as a generalised dystonic syndrome and should be investigated in patients with dystonia beginning under the age of 30 years, particularly if there are other features suggesting symptomatic dystonia. Vertebral body abnormalities and basal ganglia signal hyperintensities on MRI may be highly suggestive of the disease.

Legend to the Videotape

A 46-year-old woman shows generalized dystonia with involuntary perioral movements (facial grimacing). Ocular motility is normal. She has severe difficulty with tongue motility. A severe deformity of the hands, secondary to dystonia, is also prominent.

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Focal Dystonia as the Presenting Sign in Creutzfeldt-Jakob Disease

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Received 26 October 2001; Revised 13 February 2002; Accepted 25 February 2002

Published online 25 April 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10232

Abstract: A variety of movement disorders may occur during the course of prion disease. We describe a unique patient who had focal upper limb dystonia as the presenting symptom of familial codon 200 mutation-positive Creutzfeldt-Jakob disease. © 2002 Movement Disorder Society

Key words: focal dystonia; Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease (CJD) is a transmissible spongiform encephalopathy (prion disease). One third of patients present with a nonspecific prodromal syndrome of fatigue or disorders of sleeping and eating. Another third initially have cognitive symptoms such as memory loss, confusion, or behavioral changes. The others present with focal neurological signs such as ataxia, aphasia, visual loss, or hemiparesis.[1] Myoclonic jerks are common and occur in approximately 90% of patients with CJD. Other movement disorders, including dystonia and hemiballismus, may also appear during the course of the disease. However, a movement disorder as an initial presentation is very rare and, if it does occur, is usually choreoathetoid in nature.[2]

We report on an unusual case of familial Creutzfeldt-Jakob disease. The patient presented with focal dystonia that remained as an isolated phenomenon for a period of approximately 2 months. Thereafter, other symptoms and signs rapidly emerged and became predominant. This may be the first case of such a unique presentation.

Case Report

A 59-year-old, Jewish woman presented with a 2-month history of progressive, continuous painful dystonia of her left hand. She had been previously diagnosed as suffering from probable Sjögren's syndrome because of xerostomia and dry eyes. However, rheumatoid factor, anti-Ro(SS-A), anti-La(SS-B), and antinuclear antibodies were negative, and a salivary gland biopsy was normal. There were no other previous medical illnesses.

Other than dry oral mucosa, her general examination was normal. Neurological examination revealed a severely dystonic left wrist and hand. The arm was flexed and abducted, and the wrist was permanently extended and ulnar deviated, while the fingers and thumb were flexed. The fingers and wrist could be actively extended but returned to the dystonic position at rest. The dystonia precluded testing of power in the left hand. There were no limb apraxia or alien hand phenomenon. There was also occasional jerking of the hand. The deep tendon reflexes were brisker in the left arm and leg. The remainder of the neurological examination, including higher mental functions, was completely normal. Complete blood count and differential, biochemistry, serum copper and ceruloplasmin levels were all normal. Magnetic resonance imaging (MRI) of the head on T2-weighted image, revealed two increased intensity, small, nonspecific, left frontal white matter lesions. MRI of the cervical spine was normal. An electroencephalogram (EEG) was normal. Cerebrospinal fluid (CSF) examination showed a mildly elevated protein of 70 mg/dl, normal sugar, and 15 mononuclear cells/ml.

After a single report of a case of dystonia associated with Sjögren's syndrome,[3] the patient received an empirical trial of oral prednisone (60 mg/day). The dystonia did not respond to this therapy.

Approximately 2 weeks later, the patient developed insomnia and behavioral changes, including irritability, aggression, anxiety, and inattentiveness. Within the next 2 months, dysarthria and dysphagia developed, the dystonic arm became plegic along with paresis of the left leg and signs of bilateral upper and lower limb ataxia. The patient became bedridden due to a combination of severe left hemiparesis, ataxia, and rigidity of all four limbs. At this stage, generalized myoclonic jerks developed. Her level of consciousness gradually deteriorated until she became unresponsive to external stimuli. Remarkably, other than diffuse slow theta waves, no periodic paroxysmal sharp waves were demonstrated on repeated EEG recordings. A blood test for the prion protein (PRNP) point mutation at codon 200 was positive, confirming the diagnosis of familial Creutzfeldt-Jakob disease. On further questioning, it was found that the patient had a paternal Jewish grandparent of Libyan descent. Her paternal uncle had died in his late fifties of a progressive neurological disease. The patient's father had died in his fifties of heart disease, and her mother had died in her thirties from tuberculosis. She has two daughters in their early thirties who are healthy and have no neurological disease.

Discussion

Movement disorders are a common manifestation of Creutzfeldt-Jakob disease. Approximately 90% of patients develop myoclonic jerks in the course of the disease.[2] Other movement disorders, including chorea, athetosis, dystonia and hemiballismus develop in approximately one quarter of patients during the course of the disease.[2,4]

Movement disorders as a presenting symptom are very rare. Only 1 of 230 French CJD cases reported by Brown and colleagues presented with a movement disorder, i.e., choreoathetosis.[2] In another epidemiological study of CJD cases in England and Wales, 5% presented with involuntary movements. Myoclonus, however, was included in this five percent.[4] Sethi and Hess (1991) reported a case of CJD that presented with both ataxia and dystonia.[5] Cannard and associates describe a case of CJD presenting and evolving as rapidly progressive corticobasilar degeneration (CBD). The initial symptoms were stiffness and loss of dexterity in the left hand, which were then followed by all other features of CBD. Our case presented with unilateral dystonia, postural tremor, and pyramidal signs. Lacking, however, were the other features of CBD such as parkinsonism, alien hand phenomenon, cortical sensory loss, and limb apraxia. The MRI did not show any cortical atrophy.[6]

Familial CJD in Libyan Jews is caused by the mutation at codon 200 in the prion gene. The mutation is autosomal dominant and has an age-dependent penetrance reaching nearly a hundred percent by age 85 years.[7] Thus, the mutation in this patient confirms the diagnosis of CJD, obviating the need for a brain biopsy.

Meiner and coworkers reviewed familial CJD in Libyan Jews with the mutation at codon 200 in the prion gene PRNP.[7] The clinical manifestations in sporadic and familial CJD are very similar. Approximately 12% of patients with the codon 200 mutation present with myoclonic jerks. There are no reported cases of familial CJD in Libyan Jews that presented with movement disorder other than myoclonus.

Pleocytosis (15 mononuclear cells/ml) is an unusual finding in CJD. However, blood and CSF serology, and MRI imaging were negative for infective and autoimmune causes of dystonia. The rapid progression of the neurological illness along with the presence of the mutation at codon 200 confirm the diagnosis of CJD.

Conclusion

Creutzfeldt-Jakob disease should be considered as part of the differential diagnosis of a patient presenting with a focal movement disorder, including dystonia.

Legends to the Videotape

Segment 1. The patient is seen with a severely dystonic left arm, fingers flexed, and wrist extended. The arm is flexed and abducted. There are two episodes of jerking of the hand followed by a more prolonged muscle contraction. She is able to extend her fingers, which return to flexion at rest. Her gait, including tip toe and heel gait, is normal. Deep tendon reflexes are more brisk on the left side.

Segment 2. Six weeks later, the patient is bedridden, somnolent, and bradykinetic. There is now dystonic posturing of the right hand. The left arm has become plegic with spasticity. The left leg is weak. Deep tendon reflexes are brisk, more on the left side. There are bilateral extensor plantar responses.

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Secondary Nonresponsiveness to New Bulk Botulinum Toxin A (BCB2024)

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Received 25 September 2001; Revised 14 January 2002; Accepted 15 February 2002

Published online 10 April 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/msd.10209

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Abstract: We report on a patient with cranio–cervical dystonia injected with the new, lower protein formulation of botulinum toxin A who developed secondary resistance to this toxin. Subsequent injections with botulinum toxin B provided substantial reduction of blepharospasm. This is the first reported case of secondary resistance to the new preparation of botulinum toxin A.

Key words: botulinum toxin A; secondary resistance

A single production of bulk toxin designated 79-11 was the source of all botulinum toxin A (BTX-A) distributed by Allergan (Botox; Irvine, CA) until November 1997. Allergan, however, received approval in November 1997 to market BTX-A manufactured from a new bulk toxin (BCB2024). The two toxins have comparable pharmacological, chemical, and toxicological features.[1–3] The new bulk toxin, however, contains a lower protein lode potentially reducing the risk of developing immunological resistance.[1] Since the widespread use of the BCB2024 toxin, there have been no reports of secondary nonresponsiveness to BTX-A. We have encountered one patient with primary cranio–cervical dystonia injected only with the new BCB2024 toxin that developed resistance.

Patient Report

The patient is a 55-year-old woman who first noted difficulty with excessive blinking and involuntary squeezing of the right eyelid in early 1998 and within 2 months experienced similar problems with the left eye. The symptoms worsened over several months and she had to hold her eyes open to see. She was unable to drive, work, or cook. She developed mild neck pain about this same time but had no change in handwriting or her voice. There was a history of Parkinson's disease in her mother and a maternal aunt.

On examination she had increased blinking with intermittent sustained squeezing of the lids of both eyes. Her eyes were closed for more than 75% of the evaluation. There was no ptosis or apraxia of eyelid opening. She had cervical dystonia characterized by mild torticollis and retrocollis. A modified Tsui dystonia rating scale score was 11.[3,4] The remainder of her neurological examination was normal.

She began treatment for blepharospasm with BTX-A injections using 70 U of the BCB2024 strain of Botulinum toxin A (Botox; Allergan). She initially had good benefit that lasted 2.5 months and no side effects. When the benefit from her injections abated, she could not drive, work, or perform many activities of daily living. Subsequent injections provided incomplete peak benefit for the eyelids and neck pain increased and the dose of BTX-A at each treatment session was increased. This strategy relieved blepharospasm and pain from cervical dystonia. She was injected eight times at approximately 9 to 16 week intervals exclusively using BCB2024 bulk botulinum toxin. Doses ranged from 70 to 180 U (average, 114 U) per session (Table 1). For the last two sets of injections she reported no benefit for either neck discomfort or blepharospasm despite increased doses of botulinum toxin. A unilateral frontalis injection[5] performed with 20 U of BTX-A demonstrated no weakening of the frontalis. A mouse protection bioassay (Northview Pacific Laboratories, Berkeley, CA) failed to demonstrate neutralizing antibodies. Trials of oral medications trihexyphenidyl, baclofen, carbidopa–levodopa, and mexiletine provided minimal benefit. Subsequently, BTX-B (Myobloc; Elan Pharmaceuticals, San Francisco, CA) 6,000 U injected into the orbicularis oculi provided benefit lasting 2 months. We assumed a 50:1 efficacy ratio between BTX-B and BTX-A for these initial injections based upon available data from cervical dystonia trials.[6,7] BTX-B injections continue to reduce her blepharospasm, although a slight dose increase was necessary to provide adequate peak benefit (Table 1).

TABLE 1. *Botulinum toxin injection locations and doses*

Toxin	Total dose (U)	Dilution (cc)	Units injected per muscle			Interval (wk)
			Proc	OO	SA	
BTX-A	70	2	5 U × 2	5 U × 12		N/A
BTX-A	70	2	5 U × 2	5 U × 12		10
BTX-A	105	2	7.5 U × 2	7.5 U × 12		16
BTX-A	105	2	7.5 U × 2	7.5 U × 12		10
BTX-A	120	1	10 U × 2	10 U × 10		9
BTX-A	160	1	10 U × 2	10 U × 10	20 U × 2	10
BTX-A	120	1	10 U × 2	10 U × 10 10 U × 6		9
BTX-A	180	1	15 U × 2	12.5 U × 4[a]	20 U × 2	10
BTX-B	6,000	1	500 U × 2	500 U × 10		N/A
BTX-B	7,200	1	600 U × 2	600 U × 10		12
BTX-B	7,200	1	600 U × 2	600 U × 10		17

[a]These injections were in the medial and lateral eyelid bilaterally.
Proc, procerus; OO, orbicularis oculi, SA, scalenus anterior.

Discussion

Resistance to botulinum toxin can be primary or secondary.[8] Primary resistance is rare and may be due to genetic mutations for botulinum toxin docking proteins or target molecule proteins. We report on the first case of BTX-A secondary resistance using only the new BCB2024 bulk toxin preparation. Initially, BTX-A injections provided a robust response, but the benefit waned after repeated treatments. A standard functional test, the frontalis injection[5] documented lack of response to BTX-A, but a mouse protection bioassay did not identify BTX-A neutralizing antibodies. This assay is highly specific (100%) but has a low sensitivity of 40% compared to the frontalis injection.[5] The subsequent response to BTX-B makes BTX-A resistance the most likely diagnosis.

Immunoresistance to BTX-A as measured by the mouse protection bioassay is associated with larger doses of BTX-A and younger age at onset of symptoms.[9] Clinical nonresponsiveness, however, is associated with shorter interval between injections, higher number of booster sessions, higher dose per 3-month period, and higher dose per non-booster injection.[8] Our patient is unusual because she appears to have developed neutralizing antibodies despite being injected with relatively modest doses of botulinum toxin. The short interval between injections (9–16 weeks) may have contributed to her resistance to BTX-A but her severe recurring blepharospasm prohibited daily activities and she preferred to take this risk rather than suffer extra disability. Continued observations will determine if

BTX-A resistance predisposes to the development of cross reacting antibodies to other neurotoxins.

The absence of reports of BTX-A resistance to the BCB2024 toxin preparation may be due to the lower protein content of this toxin preparation.[10] The BCB2024 toxin contains 4.8 ng of protein per 100 U compared to 25 ng in the 79-11 toxin preparation.[1] Rabbits injected with the BCB2024 preparation demonstrate a lower frequency of botulinum toxin neutralizing antibodies supporting the concept that lower protein content reduces the incidence of clinically important botulinum toxin neutralizing antibodies.[10]

We suggest that the same precautions to avoid development of resistance to 79-11 toxin should be followed with the BCB2024 toxin. Specifically, only the lowest necessary dose should be used with as long of an interval as possible between injections. Our observation emphasizes the need for a prospective study to determine the risk of development of botulinum toxin neutralizing antibodies with each specific neurotoxin to help development management guidelines for these patients.

Acknowledgments: This work was supported by the National Institutes of Health (NS31001), the Sam and Barbara Murphy Foundation, and a donation from Ruth Kopolow. Dr. Racette has served as a paid consultant for both Allergan and Elan Pharmaceuticals in the last year.

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