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Clinical/Scientific Notes

Severe Off-Period Facial Dystonia in Parkinson's Disease

Off-period dystonia is the most common type of levodopa-related dystonia encountered in Parkinson's disease.[1] One of the most important features of L-dopa-related off-period dystonia is an almost exclusive involvement of the feet, whereas peak-dose dystonia shows a clear predilection for the orofacial region and the neck, and biphasic dystonia usually involves the limbs but with a tendency to become more widespread.[1,2] Because marked involvement of the face has rarely been observed in off-period dystonia,[1] we consider it important to report a patient with Parkinson's disease who developed a disabling form of this dystonia affecting the face and leading to dental fractures.

Case Report

This 60-year-old man developed signs of Parkinson's disease in his right arm at the age of 47. He presented with mild resting tremor and decreased arm swing while walking. A year later he began taking 500 mg L-dopa with peripheral decarboxylase inhibitor with an excellent response. After 3 years he began to experience wearing-off phenomenon manifested by dystonic postures of the right foot and the reappearance of tremor which partially improved with the addition of 15 mg bromocriptine per day. After 6 years of treatment he developed painful dystonic spasms starting in his feet and progressing to involve the left arm and face, leading repeatedly to dental fractures resulting from severe tonic spasms of masseter muscles firmly closing the jaw. These spasms occurred regularly between 6 and 7 AM before the first dose of L-dopa and during wearing-off episodes throughout the day. During hospital observation, dystonia was confirmed to begin when the patient was still in bed with plantar flexion of the toes and extension of the great toe. Spasms usually started on the right and gradually became bilateral involving flexion of the proximal part of the legs, elevation of the left arm, and then affecting the face. During these episodes the patient was unable to speak, eat, or drink, and he even breathed with difficulty because of the severe dystonic spasms affecting the lower face and especially the jaw, on many occasions preventing him from opening or more infrequently closing the mouth (see the videotape segment). Dystonia could last for more than an hour while the patient remained markedly bradykinetic and rigid. The switch to on-phase occurred approximately 5 minutes after apomorphine administration. The dystonia subsided, the patient was able to leave the bed, speak, and eat without difficulty (see the videotape segment). It was noteworthy that he showed only mild peak-dose dyskinesias.

Initially, taking his first dose of L-dopa 1 hour earlier and the use of intermittent subcutaneous apomorphine injections during the day led to the resolution of dystonia in the patient. Subsequently, he obtained an equally effective and more practical control of motor fluctuations and dystonia with the use of a L-dopa solution containing 1 g L-dopa plus 2 g ascorbic acid per liter of tap water. He took 100–150 cc of this solution every 2 hours along with 15 mg bromocriptine per day. He has been free of dystonia for a year.

Discussion

Patients with Parkinson's disease may experience various forms of dystonia which may increase their disability. The most common are those related to long-term levodopa treatment and include, in order of prevalence, off-period, peak-dose, and biphasic dystonia.[1] Off-period dystonia usually occurs during the early morning and wearing-off episodes throughout the day.[1,3] It is generally assumed that this type of dystonia is caused by subtherapeutic levels of dopaminergic stimulation.[1–3] However, as McHale et al. have pointed out, there is not a strict correlation between the topographic distribution of dystonia and the L-dopa concentration, especially in patients with complex dystonia.[4] In fact, they studied plasma L-dopa levels in 33 patients with Parkinson's disease with complex patterns of L-dopa-associated dystonia and found more cases of foot dystonia as a peak-dose effect than at low-dose periods. Similarly, facial dystonia was more common with rising, falling, or trough L-dopa patterns than with peak concentrations. They mentioned three cases of facial dystonia as part of a severe generalized painful dystonia associated with trough L-dopa concentrations.

Other relevant studies have also analyzed the clinical features of off-period dystonia in a series of patients. Poewe et al.[1] studied the topography of L-dopa-induced dystonia in 46 patients with off-period dystonia, and they found only one patient who showed involvement of face. Similarly, Kidron and Melamed[5] reviewed a total of 53 patients with off-period dystonia and none showed facial dystonia. It is interesting to note that the mean age at onset of Parkinson's disease was below 50 in these series, which is in accordance with our observation and support the fact that these dyskinesias mainly affect subjects who are younger at onset.

It is also important to distinguish this form of off-period facial dystonia from that observed in patients with multiple system atrophy treated with L-dopa, which is usually asymmetric or unilateral and painless.[6]

The distinctions in the involvement of body areas reflect the somatotopic organization within the basal ganglia, as has been observed in autoradiographic studies of frontoputaminal pro-

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jections[7] and single cell recording studies in putamen and pallidum of primates,[8] and also in humans during stereotaxic surgery.[9] Also, it is important in this differing topography that the changes in dopaminergic input into the striatum in Parkinson's disease affect the caudate and putamen in a topographically distinct fashion; the degree of dopamine depletion shows a rostrocaudal gradient.[10]

We hypothesize that the more severe involvement of the face in our case may be explained by a more marked and widespread dopamine depletion in the striatum, particularly in the caudal segment of putamen where the orofacial region is represented.[9]

Our report documents a severe form of off-period dystonia, and it also points out that this type of dystonia can be as disabling as biphasic dyskinesias which are often considered the most severe dyskinesias affecting patients with Parkinson's disease.

Legends to the Videotape

Segment 1: This segment demonstrates the patient's facial dystonia: severe spasms involved the lower face, especially the jaw. Also, dystonia affecting the feet, proximal leg, and left arm is evident. In more severe off-periods than depicted here, the patient's jaw could clench strong enough to cause dental fractures.

Segment 2: This segment demonstrates the relief of dystonia after using subcutaneous apomorphine.

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Broad Bean (*Vicia Faba*)—A Natural Source of L-Dopa—Prolongs "On" Periods in Patients With Parkinson's Disease Who Have "On–Off" Fluctuations

In 1913, Guggenheim identified the chemical levodopa in the seedlings, pods, and beans of *Vicia faba,* commonly known as "broad bean."[1] It is a widely cultivated vegetable in the Mediterranean region. Its fresh green pods in the spring, and also dry seeds throughout the year, are consumed in Mediterranean cuisine as well as in Turkey. They are prepared by cooking with olive oil* and traditionally eaten after the main meal. Broad bean meal is regarded as being delicious, especially when eaten with yogurt, and it is often prepared for guests. Like most beans, *Vicia faba* has fibrous consistency, but despite this, it is very palatable.

Recently, in the context of our practice in our Movement Disorders Outpatient Clinic, several patients with Parkinson's disease (PD) who have motor fluctuations described to us the beneficial effect of ingesting cooked broad bean (*Vicia faba* seedlings and pods) on their PD motor symptoms. These levodopa-responsive patients reported that their "on" period was prolonged after consuming a broad bean meal, and stated that its effect was similar to that of Sinemet (Merck Sharp & Dohme) or Madopar (Roche) (levodopa and carbidopa or benserazide).

There is precedent for this effect on parkinsonian motor symptoms. Spengos and Vassilopoulos [2] described the antiparkinsonian effect of *Vicia faba* consumption and others have corroborated this finding.[3] Rabey et al.[4] documented a substantial increase in levodopa plasma levels following broad bean ingestion that correlated with substantial improvement in motor performance. In view of our patients' observations, we elected

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*Recipe of cooked broad bean: *Ingredients:* 1 kg fresh broad bean, 1 cup chopped fresh dill leaves (if desired), 2 medium-sized onions chopped, 8 tablespoons olive oil, ½ tablespoon salt, 1 cup cold water, ½ tablespoon sugar. The chopped onions are stirred with olive oil in a large saucepan for approximately 3 minutes on the stove. Then all other ingredients except dill are added and brought to a boil for approximately 1 hour. The meal is served by garnishing with dill. In Cyprus and Greece this meal is usually cooked with prestirred ground meat.

to assess their motor responses to broad bean through an outpatient open-label clinical trial.

Patients and Methods

The eight patients who previously had reported favorable motor effects from broad been ingestion agreed to participate in our clinical trial. They were asked to ingest one standard portion (approximately 250 g) of cooked broad bean at least twice a day without otherwise altering their dietary habits. The medical treatment was kept constant. Their predominant problems were disabling motor fluctuations (unpredictable or predictable) and dyskinesias, despite appropriate medical treatment with levodopa plus carbidopa or benserazide combined with other dopaminergic drugs. These patients with PD were asked to complete a daily diary recording the times and durations of "on" and "off" periods as well as sleep. We calculated the mean values of "on" and "off" times as well as nightly sleep durations for each patient during the 5–7 days of baseline assessment (without broad bean supplementation) and again corresponding to the 1–3 months during broad bean administration. Three of them filled out the diary cards appropriately, and these results and their case histories are summarized below.

Case Reports

Patient No. 1

This 48-year-old man initially experienced left-sided bradykinesia and dystonic posturing of the left arm, which progressed to Hoehn & Yahr (H & Y) stage II[5] in 7 years. Carbidopa/levodopa was initiated shortly after the diagnosis, and he developed "wearing-off" and "on–off" phenomena within the next 4 years. He was admitted to our hospital 5 years after symptom onset and 20 mg bromocriptine per day and amantadine were added (with levodopa reduction), resulting in only limited benefit. At the time of the current assessments, he was receiving 150/600 mg benserazide/levodopa plus 5 mg pergolide mesylate per day. During "off" periods, his disability reached stage III. At baseline, without broad bean meal supplementation, the mean "on" duration was 3.5 hours; "off" periods were 14.5 hours per day and his mean sleep time was 5.5 hours. Supplementation with a 250 g broad bean meal three times a day, in addition to his medications, resulted in an increase of his mean "on" time to 12 hours. His "off" time was reduced to 3.5 hours and his sleep time increased to 8 hours during the 30-day study period.

Patient No. 2

This 40 year-old retired man had a 6-year history of PD, progressing to H & Y stage II when initially seen by us. He had undergone right pallidotomy 2 years previously. His medications at the time of this trial included 75/300 mg benserazide/levodopa and 1 mg pergolide mesylate three times per day plus 125 mg Madopar HBS twice per day. He had "wearing-off" and "on–off" fluctuations. During "off" periods, his disability reached stage III. His baseline diary card entries revealed a daily mean "on" duration of 8 hours; "off" periods averaged 10 hours and nightly sleep 6 hours. He initially consumed 250 g broad bean meals three times a day but when he noticed that its beneficial effect had been sustained during the following day, he reduced the broad bean intake to every other day. The follow-up period was 85 days. With broad bean meal supplementation, the mean duration of his "on" periods increased to 16 hours and "off" periods were reduced to 2–3 hours per day. The duration of his night sleep did not change.

Patient No. 3

This 56-year-old man had a 9-year history of PD, initially presenting as right-hand resting tremor. This progressed to involve both hands, followed by rigidity and bradykinesia within 1 year. Shortly after the diagnosis, he was started on levodopa and developed "wearing-off" phenomena, peak-dose dyskinesias, and right-hand dystonia within the next 2–3 years which have persisted. At age of 53, he underwent stereotaxic left thalamotomy resulting in resolution of the tremor of his right limbs. At baseline, he was on 50/500 mg carbidopa/levodopa and 2 mg pergolide mesylate per day, plus 15–30 mg buspirone per day for his dyskinesias. His mean baseline diary card values included a mean "on" duration of 6.5 hours, "off" periods of 9.5 hours, and nightly sleep of 8 hours per day. After initiating one broad bean meal (250 g) a day for 43 days, his mean daily duration of "on" time increased to 14 hours and "off" time decreased to 2.5 hours; his nightly sleep was similar to baseline at 7.5 hours. Impressed by the efficacy of broad bean supplementation, the patient reduced his carbidopa/levodopa doses to 37.5/375 mg per day, resulting in diminished "on"-period dyskinesias.

Discussion

Identifying levodopa from broad bean, Guggenheim attempted to eat 2.5 g levodopa himself and experienced marked nausea and vomiting. Subsequently, he administered 1-g doses to rabbits but failed to observe any effect; hence, he concluded that levodopa had no pharmacologic efficacy.[1] After the demonstration of dopamine deficiency in the striatum of patients with PD by Ehringer and Hornykiewicz in 1960,[6] and observation of the striking motor improvement with levodopa by Cotzias et al.[7] in patients with PD, levodopa has become the gold standard for the treatment of PD. However, this treatment is compromised by the subsequent development of motor fluctuations and dyskinesias in the majority of patients.

We observed a beneficial effect of *Vicia faba* in our patients manifested by strikingly prolonged "on" time and shortened "off" time. Previously, all these patients had been administered higher doses of levodopa up to 800–1000 mg per day, which failed to optimize their "on" time and resulted in peak-dose dyskinesias. Unfortunately, we did not have any documentation of the "on" periods of our patients with PD while they have been taking high doses of levodopa. We were surprised by the reported magnitude of our patients' responses, given the fact that previous trials of higher doses of carbidopa/levodopa seemed to provide no further benefit.

These observations are not readily explained by assuming that broad beans are simply a source of levodopa. For example, patient no. 2 was able to experience a sustained response from broad bean meals ingested on alternate days. This is reminiscent of the "long-duration response" of synthetic levodopa, but why this was not similarly experienced with higher benserazide/levodopa doses is unclear. Also, somewhat surprisingly, patient no. 3 experienced decreased dyskinesias with the addi-

tion of broad bean supplementation and reduction of carbidopa/levodopa therapy. He maintained taking buspirone as well, regularly 30 mg per day in contrast to prior irregular use, which could also contribute in diminished dyskinesias. This patient had previously failed to respond satisfactorily to carbidopa/levodopa adjustments which should have accomplished the same result if this was simply a levodopa effect. A placebo effect may have contributed in this unblinded trial, but the magnitude of the reported responses raises the possibility of other mechanisms. For example, the amino acid milieu generated from broad bean administration may favor the selective transport of levodopa across the blood–brain barrier.[8] Alternatively, other products derived from broad bean may complement the antiparkinsonian effect. These results suggest that a controlled trial with close monitoring of the clinical response is warranted.

In addition to these three reported patients, five other patients in our clinic experienced benefit from broad bean meals. We also attempted to enroll these patients in this study. Unfortunately, they were unable to complete the diary cards in a reliable manner presumably because they were from rural areas and literacy was limited.

Our experience with chronic broad bean administration complements that of Rabey et al.,[2] who described the acute responses following a single administration of broad bean to six patients with PD. They noted motor improvement of the same magnitude as seen following single doses of carbidopa/levodopa. They also documented substantially increased plasma levodopa concentrations following broad bean administration and the motor response tended to mirror these plasma levodopa levels. In contrast to this study, we assessed the effect of chronic broad bean meal supplementation as opposed to a single administration. Elevation of plasma levodopa following broad bean administration has also been confirmed by Vered et al.[9] They noted that 40 g of freshly chopped broad bean contained 120–130 mg levodopa.

Other natural sources of levodopa besides broad bean have also been reported such as *Stizolobium deeringianum*[10] and *Mucuna pruriens*.[11] According to Manyam and Parikh,[11] *Mucuna pruriens* beans contain levodopa and have been used as an efficacious herbal drug for PD treatment in India for many years. In a recent multicenter open trial in India, *Mucuna pruriens*, formulated as HP-200, was administered orally to 60 patients with PD for 12 weeks. It was extracted as a powder from the plant seeds and administered mixed with water. The authors observed significant improvement of parkinsonian motor scores, and speculated that HP-200 might contain other antiparkinsonian compounds besides levodopa.[11,12]

Our patients ingested their broad bean meals garnished with yogurt, which is rich in protein. It is well known that as a large neutral amino acid, levodopa competes with dietary protein amino acid breakdown products in crossing the brain–blood barrier; this competition potentially results in reduced levodopa motor effects.[13] Nonetheless, our patients still experienced a favorable motor response.

Some of our patients reported trying to cook and eat the dry seeds of broad bean (germination of *Vicia faba* seedling, which is available during all seasons) but did not experience any clinical benefit. Burbano et al.[14] showed that only the fresh green pods of broad bean were rich in levodopa content, in contrast to that of dry matter, apparently explaining the observations of our patients.

Broad bean is a widely cultivated and consumed vegetable of the Mediterranean region and Turkey. These preliminary results suggest that broad bean meals have efficacy as a means of reducing levodopa off-period disability. If confirmed in subsequent controlled clinical trials, the underlying mechanisms also need to be explored.

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Subcutaneous Apomorphine Injections as a Treatment for Intractable Pain in Parkinson's Disease

Distressing pain syndromes unassociated with dystonia are known to occur in Parkinson's disease (PD). Some form of pain is reported in approximately 46% of patients[1] and it usually occurs in the "off" state. It can be characterized as neuritic, radicular, chest pain, gastrointestinal distress, skin pain or burning.[1–4] In some patients, treatment is inadequate and prolonged "off" periods with pain can be so severe that withdrawal of levodopa is the only solution, sacrificing mobility.[4]

Apomorphine is a dopamine agonist with receptor affinity similar to dopamine, which is prescribed for subcutaneous use as bolus injections or continuous infusion. It has rapid onset (10–15 minutes) and a short duration of action (45–120 minutes). It is generally used as rescue therapy for severe intractable "off" periods in patients with fluctuating PD, and long-term efficacy up to 5 years has been demonstrated.[5,6] We report a patient with PD who has intractable "off" period pain and who ultimately only responded to subcutaneous bolus injections of apomorphine to abort the painful episodes.

Case Report

This 75-year-old woman was initially diagnosed with PD in 1982. Initial symptoms included micrographia, difficulties with manual dexterity (particularly typing), and mild bilateral tremor. Carbidopa/levodopa (C/L) was initiated in 1982 with significant improvement. In 1988 she began to experience wearing-off effect which was heralded by discomfort on the left side of the rib cage in the region of the diaphragm. She would have a fluttering-type sensation which turned into an ache and then a severe sharp pain. This would be followed by recurrence of micrographia, slowing, and shuffling gait. Also in 1988, mild peak-dose dyskinesia and off-period anxiety started. During the day the painful episodes could last 1.5 hours but in the morning and in the evening they were more prolonged, over 2 hours. It seemed that the middle-of-the-day episodes would improve after taking C/L whereas the morning and evening episodes were refractory. At that time she was on C/L 70/700 divided in doses every 3 hours and 2.5 mg bromocriptine three times a day.

Prior to our first evaluation in July 1988 she had been treated with clonazepam, alprazolam, amitriptyline, and lithium with little effect. Her examination at that first visit demonstrated mild head, neck, and upper extremity dyskinesias with no tremor or rigidity. She had mild impairment of finger tapping, mild masked face, decreased arm swing with walking, stooped posture, and some balance difficulty without retropulsion. We performed a videofluoroscopy during one of her episodes to determine the presence of involuntary movements of the diaphragm; there were none. She was "off" approximately 25% of the day and "on" time would occur 20 minutes after a C/L dose. Increases in bromocriptine to 15 mg per day, amitriptyline and C/L, and the addition of acetaminophen with codeine, anticholinergic medications (ethopromazine), and baclofen were ineffective in controlling the painful episodes.

By 1989 the episodes were worsening in severity. She would lay on her couch at home with her legs up, short of breath, holding her side, crying and fearful of death, suggesting the presence of panic symptoms concurrent with pain. After the placement of a pacemaker she fixated on that being the cause with fear that it may be malfunctioning. Controlled-release C/L was added that year and while it decreased the number of episodes, they became less predictable. The most prominent episodes were still in the morning and at night after the last dose of medication, and these would now last 3–4 hours. Pergolide at dosages of up to 2 mg per day replaced bromocriptine and while she had some mild transient improvement at low doses, the episodes continued. Other treatments used unsuccessfully that year were diazepam, cyclobenzaprine, and selegiline.

In January 1990 she was hospitalized for a drug holiday. The pain dissipated for 24–36 hours. However, she described some fluttering in the left diaphragmatic region and a tightness around her waist which were continuous. She became akinetic and rigid but had no tremor. The morning became the best time for her. Examination off medications demonstrated a severe akinetic rigid state. She had difficulty arising from a chair, a severely stooped posture, and impaired gait with no arm swing and three steps of retropulsion. She became depressed and tearful. She was placed on pergolide monotherapy after 3 days and amitriptyline for the depression. The pain recurred on pergolide and she continued to be much less mobile. While at home she continued to have the painful episodes along with the immobility. She was unable to perform activities of daily living independently and she continued to be depressed. By the end of that month, while on 3 mg pergolide per day, she restarted standard C/L therapy. There was a significant improvement of her mobility while taking 5½ tablets per day. The pain was less continuous but still severe at times, especially at night.

In March 1990 she was referred to a pain management program and treated with high doses of diazepam and hydrocodone with no effect. By September she had increased pergolide to 6 mg per day and still the pain was lasting at least 3 hours when it would occur. She sought out chiropractic therapy which was ineffective. In February 1992 she was started on up to 75 mg clozapine and codeine and while this combination was sedating, it had no effect on the painful episodes. She was also tried unsuccessfully on acetazolamide. By September 1992 dyskinesia was much worse involving the head and neck with blepharospasm, oculogyric crises. She was also experiencing some discomfort approximately 80% of the day. Acetaminophen with codeine and mineral ice were still used with minimal benefit. A TENS unit was ineffective. A second pain clinic evaluation in 1993 offered no other possible treatments. She was given flurazepam in an attempt to sleep through the nighttime episode and propranolol, neither of which was very helpful. In July 1993 she was hospitalized with delusions and visual and auditory hallucinations. She was confused, aggressive, combative, and suicidal. Pergolide was stopped and clozapine was reinstated with doses up to 150 mg per day. These psychiatric symptoms were much worse during the painful off-periods. Once the clozapine controlled the psychosis, it was found that

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she was depressed and she was placed on sertraline. While this combination helped her significantly from a psychiatric standpoint, there was no effect on the pain. At this point there was no obvious dementia.

In November 1993 she indicated that she actually dreaded each day because of the severity of the pain and her inability to cope. In addition, her parkinsonism was worsening with increased stooping of her posture and more difficulties with gait even when "on." Other treatments used unsuccessfully for pain included morphine sulfate controlled release, transdermal fentanyl, intercostal nerve blocks with bupivacaine, intravenous buprenorphine and meperidine, lorazepam in place of alprazolam, and nasal butorphanol.

In August 1995 she was on a total of 1500 mg levodopa and 150 mg clozapine per day when she was placed on 20 mg domperidone three times a day and, 3 days later, initiated on apomorphine (Draxis Health Inc, Mississaugua, Canada) subcutaneous injections. Her dose was titrated up by 1 mg every 20 minutes until she had improvement in her "off" time and pain (5 mg per injection). She was initially injected three times a day and when given at the onset of the pain and panic episodes they would be relieved within 10 minutes. At that time she was also experiencing diphasic dyskinesias which would also improve. Sometimes the pain would start at the same time as the diphasic dyskinesia. By December 1995 the apomorphine injections were 5.8 mg each and they were given 5 times per day. While she developed small skin nodules in some of the injection areas, she had no other side effects. The nighttime injection would sometimes shift the pain episode to a later time. When alprazolam would be given after that injection, the pain could be averted.

The effect of apomorphine injections was dramatic. Instead of 2–4-hour episodes, the pain would last only 10–15 minutes. She began socializing for the first time in 5 years. She stopped the domperidone after 5 months of therapy. Fourteen months after initiating the apomorphine her levodopa dose was decreased to 1050 mg per day. By March 1997 she was wearing off more frequently, requiring an increase in the number of injections to seven times per day.

In July 1997, pramipexole was initiated and increased to 4.5 mg per day. There was an increase in dyskinesia, the episodes of pain continued, but the panic attacks ceased. In February 1998 100 mg tolcapone three times a day was initiated and the number of injections were cut to five per day. By September 1998 her levodopa dose was down to 500 mg per day, pramipexole 2.25 mg per day, and tolcapone was increased to 200 mg three times a day. Pain episodes still occurred but the apomorphine continued to abort them within minutes, even after 3.5 years of therapy.

Discussion

This patient had a number of unusual features. The pain had a strange character starting in the end of dose as a sensation of diaphragmatic fluttering. This occurred initially without dyskinesia then, later, with diphasic choreiform dyskinesia. It was followed by a severe, sharp, boring pain in the "off" state which lasted hours and was, at times, present when motor features had not reached the "off" state. A drug holiday relieved the pain only briefly and it was made worse by pergolide monotherapy. The literature suggests that "off" period pain is relieved by drug holidays and is not provoked by dopamine agonists.[4] She had akinetic-rigid parkinsonism with minimal tremor. It is suggested that pain is most closely associated with this form of PD.[1] Finally, the patient had panic disorder which can be associated with pain and most commonly occurs in the "off" state.[7,8] In 24% of patients it is associated with depression. Like the pain, it can last many hours and did.

We treated her with extensive changes in antiparkinsonian medications to no avail. She was treated with antidepressants,[1] lithium,[9] clozapine,[10] acetazolamide,[11] propranolol, and anticholinergics, also to no avail. A drug holiday relieved symptoms for 1–2 days only. Finally, pain management with opiates, intercostal nerve blocks, and chiropractic manipulation were also unsuccessful. The apomorphine injections provided dramatic, immediate relief in an abortive fashion and this benefit has lasted over 3.5 years. A duration of effect this long is typical in treating intractable "off" periods.[5,6] Because the apomorphine is given early with onset of pain, it does not reach the same degree of severity. The apomorphine injections also improved the panic symptoms as well as the diphasic dyskinesia.

This is not the first report of apomorphine use for "off"-period pain. Frankel et al.[5] made passing reference to the ability of this drug to improve "off"-period limb and pelvic pain in three of 57 patients with fluctuating PD. They indicated that the effect was expected because the drug provides rapid relief of intractable "off" periods without pain. We wanted to emphasize the usefulness of apomorphine in these rather unusual patients who otherwise do not respond to standard anti-PD or pain remedies. In patients with PD who have intractable pain, apomorphine should be considered an important alternative in therapy. Frankel et al.[5] also demonstrated, as we observed, an improvement in diphasic involuntary movements. Apomorphine is currently available in Europe and Canada and is under investigation in the United States.

When pramipexole and tolcapone became available it was thought these agents might act to improve the motor fluctuations and therefore prevent the pain syndrome. Their effect on motor fluctuations is well known.[12,13] While the levodopa dose was lowered substantially on these medications, motor symptoms improved, and the panic attacks completely disappeared, the patient continued to require apomorphine injections for pain five to six times per day. These drugs did provide some benefit for pain but they could not replace the apomorphine injections. Why apomorphine could quickly alleviate pain while the other dopamine agonists could not is unclear but may relate to potency of the drug or its less selective dopamine receptor affinity.

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Extradural Motor Cortex Stimulation for Advanced Parkinson's Disease: Case Report

Extirpation of the motor cortex permanently abolishes parkinsonian tremor.[1] Stimulation of the motor cortex (MI) and occasionally of the sensory cortex (SI), at current values subthreshold for movement, caused cessation of the marked tremor and strong rigidity in two patients with severe Parkinson's disease (PD), making hand movements strong and easily executed.[2] Because voluntary movements were unaffected, those authors concluded that "the results suggest the possibility that subthreshold electrical stimulation through implanted electrodes might be used to control these symptoms in parkinsonian patients."[2] 5 Hz 10% subthreshold repetitive transcranial motor cortex stimulation (TCMS) at is known to improve motor performance in patients with PD without cognitive impairment. In 1994, a group suggested that their "findings might be extrapolated to suggest that subthreshold electric cortical stimulation through chronically implanted subdural electrodes may help improve these symptoms."[3]

Extradural motor cortex stimulation, a pain-relieving procedure, is a safe technique with a low-to-nil risk of kindling and no effects on the voluntary choice of movement.[4,5] It may also ameliorate post-stroke tremor and hemichorea.[6] Local anesthesia is the usual requirement.

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We tested extradural motor cortex stimulation (EMCS) on a patient with advanced PD. On the basis of Woolsey's results,[7] a role for ECMS in the setting of PD tremor was suggested (Dr. Benabid, personal communication, 1998).

Case Report

This 72-year-old woman gradually developed PD starting in the right upper limb in 1976. In 1998, despite adequate treatment (1056 mg levodopa–benserazide, 3 mg pergolide, 12.5 mg metixene, and benzodiazepine at bedtime), she rated IV–V on the Hoehn & Yahr scale. The following signs were present: postural tremor, severe bradykinesia, diffuse rigidity, upper arms and ocular cogwheeling, extreme difficulty in standing, Meyerson's sign, constipation, postural hypotension, dyspepsia, drooling, severe dysphagia (swallowing was impossible during off-periods), anteropulsion, and painful focal dystonias of the right foot in the morning. Gait was possible only with assistance. On–off periods were unpredictable. There was moderate-to-severe PD-associated dementia. Unified Parkinson's Disease Rating Scale (version 3.0) summary scores were as follows (on medication): section I: 10, section II: 41, section III: 44, and section IV: 13.

To avoid possible complications from stereotactic surgery, her husband, acting as a legal representative, gave permission for experimental EMCS, a routine pain-relieving procedure at our institution.[7,8] Review board approval and written informed consent were obtained.

Under general anesthesia, a quadripolar electrostimulator (model 3587A, Medtronic Inc, Minneapolis, MN, USA) was positioned in the extradural space overlying MI through two burr holes aligned anteriorly to the Rolandic fissure. This had been previously marked on the skin using Houghton-Taylor surface coordinates and neuroradiologic confirmation.[7] The target was the left arm area (Fig. 1). During a 2-week subthreshold test stimulation period, several parameters were assessed (amplitude: 3–7 V, impulse duration: 200–400 msec, frequency: 25–120 Hz). Although benefits were seen with other configurations also, best results were observed at a 3 V, 180 msec, 25 Hz, 3+/0− setting, off during sleep. The clinical improvement was bilateral in all limbs. The electrocatheter was thus connected to an implanted pulse generator (Itrel II, Medtronic Inc). Three months later, the patient could stand without assistance, climb the stairs, walk short distances, wash herself almost independently, and dress with some assistance. Rigidity was absent on the right side and slight on the left. Choreiform dyskinesias, cogwheeling, and dysphagia were absent. There was less thought impairment, better verbal understanding, recovery of spatial (but not temporal) orientation, correct person identification, and some recovery of reckoning. The husband was now regularly recognized. The patient even showed her gratitude with "thank you, doctor." Execution of movements was dramatically improved. Levodopa–benserazide was reduced to 625 mg (−45%). Tremor was absent. The Unified Parkinson's Disease Rating Scale (version 3.0) summary scores (on medication) were as follows: section I: 9, section II: 21, section III: 23, and section IV: 5.

Five months into implantation, direct injury resulted in wound dehiscence, local infection, and system failure. Clinical worsening started approximately 4 days later with a slow worsening of gait and postural stability over 2 weeks. The infection was successfully treated and the system replaced at a point

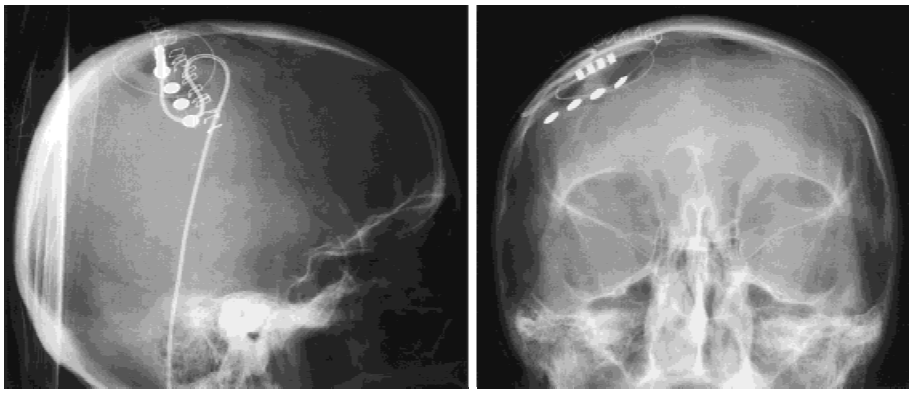

FIG. 1. Skull radiographs showing the stimulator in place.

when the prestimulation level was almost present. Benefit was as for the first implantation, and levodopa was reduced by 80%.

Discussion

Changes in MI following therapeutic surgery have been inconspicuous in several PET studies of PD.[8–11] However, a recent dynamic functional magnetic resonance study suggested that PD rigidity may be the result of diffuse disinhibition of MI/SI.[12] Electroencephalographic and TCMS studies also point to MI dysfunction in PD with evidence for reduced cortical inhibition.[13] Studies suggest that ECMS may increase cortical GABA,[4,5,14] EMCS thus improving PD by inhibiting cortical hyperactivity. Renormalization of MI activity subsequently downloads to the motor thalamus and subthalamic nucleus with clinical improvement. MI plays an important role in complex finger movement sequences and sequence organization, further explaining EMCS effects.[15]

Bilateral benefit from unilateral stimulation may be explained by interhemispheric transfer of activity through the corpus callosum (or subcortical sources with bilateral connections).[16,17] Moreover, both MI and supplementary motor areas share the control of bimanual coordination,[18] and MI is involved in ipsilateral movements.[19]

Sustained benefit after system failure may be the result of plastic phenomena: a few patients whose pain was relieved by EMCS did not relapse even for a long time after cessation of stimulation.[20]

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Bruxism in Huntington's Disease

Bruxism is a diurnal or nocturnal parafunctional activity manifested by clenching, grinding, bracing, and gnashing of the teeth.[1] Numerous possible causative factors have been suggested but not proven. These include occlusal discrepancies, psychological disturbance, stress, and disorders of sleep.[2–4] Bruxism has been reported in patients with anoxic encephalopathy,[5] coma,[6] cerebellar hemorrhage,[7] mental retardation,[8] Rett's syndrome,[9] and oromandibular dystonia.[10,11] This suggests that bruxism may be the result of central nervous system dysfunction.

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder caused by a mutation in chromosome 4 and resulting in an unstable triplet CAG repeat expansion.[12,13] Cognitive impairment and motor symptoms such as chorea, dystonia, and bradykinesia are well-recognized clinical features in HD.[13,14] To our knowledge, bruxism associated with HD has not been previously highlighted. We describe three patients with HD who have severe bruxism, and discuss the possible underlying pathogenesis and its management.

Materials and Methods

The study patients were evaluated in a movement disorders clinic over 1½ years, and all had the following features: (1) audible tooth grinding, as corroborated by family members or caregivers; (2) jaw stiffness and pain; (3) tenderness and/or hypertrophy of masseters to clinical palpation; (4) dentist's diagnosis of tooth wear; (5) difficulty chewing, speaking, or swallowing; and (6) well-documented HD.

Case Reports

Case 1

This 35-year-old woman presented with insidious onset of choreic movements involving all four limbs and her face at the age of 16 years. Around that time, she was noted by her family members to be clenching and grinding her teeth. At age 21, she began to exhibit depression and irrational behavior, which was attributed to an adverse relationship with her stepfather. She was prescribed haloperidol and thioridazine, but these were subsequently discontinued when her involuntary movements progressed in severity. At age 27, her condition, particularly memory, cognitive function, and gait, continued to deteriorate. At age 31, her teeth grinding became so pronounced that the loud sounds began to disturb other family members. The grinding, which led to severe tooth attrition, was worse when she was awake and better during sleep. Two years later, a feeding gastrostomy tube was inserted because of severe dysphagia. She has since become wheelchair-bound. Her paternal grandmother died in a mental hospital and two paternal uncles had involuntary movements and bizarre gait. They have not been genetically tested for HD. The patient's mother is well and her father died in a drowning accident in his late 20s. She had 52 CAG repeats (17 repeats in the normal allele).

The patient was uncooperative during examination with evidence of severe dementia, choreic limb and facial movements, and was nonambulatory. Constant, audible tooth grinding could be heard when she was awake (see videotape segment 1). There was spasm and hypertrophy of the masseters bilaterally on palpation.

She was started on tetrabenazine which improved her choreic movements. However, the tooth grinding continued to progress. Subsequently, 60 units of botulinum toxin A (BTX) were injected into each masseter muscle. Within 3 days of injection, the patient reported marked relief of jaw pain and was able to open her jaw. Her family members noted total abolishment of the grinding. The improvement persisted for at least 2 months.

Case 2

This 18-year-old woman presented with stuttering speech and progressive mutism at age 5 years. Three years later she developed gait difficulties, and 4 years later she began to manifest involuntary limb movements and cognitive decline. By age 12, she was wheelchair-bound and completely mute. DNA test for HD revealed CAG repeat expansion with 82 repeats (17 repeats in the normal allele). The patient's father reportedly began to have involuntary movements and cognitive decline at age 34 and was institutionalized at age 45. Her mother is well, and her 16-year-old sister has not been tested. The patient was noticed to have clenching and grinding of her teeth for a number of years. She needed a feeding tube because of dysphagia. Neurologic examination revealed the presence of mutism, generalized chorea, blepharospasm, and dystonia of the left upper extremity. Three courses of BTX (mean dose per side, 73.3 units) were given over a mean time interval of 4 months. The latency of action of BTX was 2 days, and the mean total duration of action was 17.5 weeks. There was significant improvement of her grinding, with a mean peak effect of 3.5 weeks (range 0–4; 4, marked improvement in severity and function).

Case 3

This 35-year-old woman presented with cognitive decline, aggressive behavior, and involuntary limb movements at age 27 years and was clinically diagnosed as having HD. Subsequently, she was also noted to have clenching and grinding of her teeth. At age 32, she was treated with haloperidol for 7 months because of uncontrolled aggression. Her tooth grinding was markedly aggravated after the medication was started. Constant audible grinding was present whenever she was

A videotape accompanies this article.

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awake and less when she was asleep. She had severe tooth wear and lost several of her upper and lower molars. Dental braces were installed with minimal relief. Haloperidol was subsequently stopped and she was treated with clozapine. Clinical improvement of her grinding was noted for a few months. However, her grinding, as well as her cognitive and motor functions, deteriorated with time. Presently She is presently wheelchair-bound and needs assistance in feeding. She has a brother who has DNA-confirmed HD.

On examination, she was drowsy and slept for most of the day. Her neck was always in flexion. She could be momentarily awakened by passively lifting her head. Loud grinding sounds could be heard whenever she was aroused. Constant clenching of jaw muscles could be seen on inspection, and there was bilateral masseter hypertrophy to palpation. She was also severely demented, unable even to obey one step command, and exhibited parkinsonian features and generalized chorea. She was injected with 60 units of BTX each to her masseter muscles. Marked improvement of her grinding was noted a few days after the injections and this has lasted at least 1 month. She is awaiting further follow up.

Discussion

In this report we seek to highlight our clinical observation of the constant unremitting, loud grinding sounds in three patients with HD. This appears to be different from the intermittent nocturnal grinding usually reported in the "normal" population. Our report is not an epidemiologic study or a clinical trial evaluating the severity of bruxism in a HD population. Hence, we did not consistently inquire about history of grinding in all our patients with HD and cannot provide its prevalence rates. The three patients were seen recently in our movement disorder clinic. Although it can be argued that the bruxism noted in our patients with HD could be coincidental, the history and clinical presentation strongly suggest it is likely the result of the disease process. First, teeth grinding in all three patients started with the other symptoms and signs of HD. Second, the severity of patients' teeth grinding (increased frequency and duration as reported by caregivers) appeared to correlate with the progression of the disease. The symptom created much distress to the patients and their caregivers as a result of which they aggressively pursued medical attention. Third, our patients had severe grinding of teeth as evidenced by constant, loud grinding sounds complicated by severe tooth wear and jaw pain, and difficulty with speech or swallowing.

Although "tardive bruxism" is possible, the history of bruxism before exposure to neuroleptics argues in favor of HD-related bruxism. We recognize that self-reporting of bruxism is subject to recall bias; however, the history of onset of grinding was corroborated by their family members and caregivers. Furthermore, the exposure to neuroleptics in each patient was limited. Importantly, teeth grinding in HD could be aggravated by neuroleptics, as evidenced in patient 3, and therefore these drugs must be used with caution in these patients. Bruxism has previously been reported as a result of neuroleptic use. Micheli et al.[15] described eight cases of "tardive bruxism" and drew attention to the observation that teeth clenching and grinding in "tardive bruxism" disappeared during sleep in contrast to the nocturnal bruxism often reported in dental literature. They postulate that this might represent a form of focal dystonia. We agree that there are similarities between bruxism as seen in our patients and oromandibular jaw-closing dystonia.[11] However, the latter group of patients commonly presents with jaw clenching and is associated with dystonia in other anatomic areas. Loud grinding is the predominant symptom in our patients and only patient 2 had associated blepharospasm and dystonic posturing of her left upper extremity. Incidentally, jaw-closing dystonia has not been detected in a recent clinic survey of dytonia in HD in which the extremities were the most frequently involved regions.[14]

Estimates of the prevalence of bruxism in the adult population varies between 5% and 96%.[4,16–18] The reasons for the marked range include differences in the methodology and diagnostic criteria. Based on historical data and clinical assessment of tooth wear, Richmond et al.[8] have found bruxism to be present in approximately half of a large institutionalized, mentally retarded population. Bruxism has also been noted to be present in the majority of patients with Rett's syndrome, a neurodegenerative disorder manifested by a young age-onset and wide spectrum of behavioral and motor abnormalities.[9] We do not know the pathophysiological significance of the relatively early age of onset of bruxism in two of our patients. Whereas the pathogenesis of bruxism has not been clearly elucidated, we speculate that the cortical and striatal degeneration associated with HD might result in disinhibition of the trigeminal-facial motor pathways and produce involuntary contraction of the jaw and facial muscles. No specific structure in the brain has been identified as the site of the "bruxism generator." However, both animal and human studies suggest that both the dopaminergic and norepinephric systems may be involved.[19–22] It has been hypothesized that interactions of the motor, autonomic, and limbic systems activate the jaw muscles either directly or through facilitation by a "bruxism generator" in the brain.[3] There is evidence of interaction between trigeminal sensory stimulation and basal ganglia structures.[23,24] Huston et al.,[25] using electrical stimulation of the substantia nigra in rats, demonstrated the presence of bidirectional links between the orofacial systems and the basal ganglia. Bromocriptine, a dopamine agonist, was found to decrease the number of bruxing episodes per hour of sleep. This supports the hypothesis that the central dopaminergic system may be involved in the modulation of sleep bruxism.[20]

Treatment of bruxism consists of occlusal, psychological, biofeedback, and drug therapies,[26] none of which has been demonstrated to be consistently effective.[2] L-Dopa was shown to attenuate sleep bruxism in a recent controlled trial.[27] However, its effect on diurnal bruxism needs to be further evaluated. We have previously described the use of BTX in the treatment of bruxism.[11] In all three patients, BTX provided significant relief of grinding, leading to improvement in chewing, swallowing, and speech. We suggest such treatment be considered only for those who are distressed by their symptoms (such as severe jaw pain), those with associated dental complications, and those with unremitting grinding.

In conclusion, we think our experience with bruxism in HD is not unique, and bruxism may be underdiagnosed in HD. Recognition and treatment of severe bruxism is clinically relevant because the grinding is likely to further compromise the poor dentition and swallowing difficulty frequently associated with the progression of HD. Neuroleptics can exacerbate or cause bruxism in patients with HD. Epidemiologic studies, systematically evaluating for bruxism in HD, using objective measurement parameters, would be useful in determining the preva-

lence of bruxism in patients with HD. BTX provides safe and effective relief for severe bruxism.

Legend to the Videotape

This 35-year-old woman (patient 3) with HD, presenting with cognitive decline, aggressive behavior, chorcic limb movements, and tooth grinding. On examination, she exhibited marked clenching of her masseters and loud tooth grinding sounds.

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Donepezil for Huntington's Disease

Huntington's disease (HD) is a progressive, autosomal-dominant neurodegenerative disorder characterized by dementia, behavioral disturbance, and choreiform movements. Drug trials performed to reverse cognitive decline in patients with HD have shown minimal or no improvement.[1–4]

Involuntary movements in patients with HD may be related to cholinergic hypofunction in the striatum.[5–7] The few procholinergic drugs tested have met with little success in improving choreiform movements in patients with HD.[6–9]

Donepezil HCl is a piperidine-based reversible acetylcholinesterase inhibitor used to treat mild to moderate dementia in patients with Alzheimer's disease.[10–12] It has also been reported to improve cognition in patients with traumatic brain injury and dementia with Lewy bodies.[13–16]

We hypothesized that the procholinergic properties of donepezil could improve cognitive dysfunction and involuntary movements in patients with HD.

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Method

Eight patients, two women and six men, aged 39–77 years with HD, participated in this open-label study. The study was limited to genetically confirmed symptomatic patients with HD. Excluded were patients with HD who were presently taking, or having recently taken, anticholinergic medications such as benztropine, trihexyphenidyl, or tricyclic antidepressants. Other classes of antidepressants without major anticholinergic effects were permitted as long as there was no clinical evidence of depression at the time of the study. Antipsychotic drugs such as haloperidol and olanzapine were also permitted but were kept fixed during the study. All patients gave their written consent. The protocol was approved by the hospital's institutional review board. Baseline evaluation using the motor, cognitive, behavioral, and functional assessment of the Unified Huntington's Disease Rating Scale (UHDRS) was performed prior to administration of donepezil. In addition, a battery of other neuropsychological tests were done at baseline. These included the Folstein Mini-Mental Status Examination for assessment of global cognitive function; the Wechsler Memory Scale-III (including Information and Orientation, Digit Span Forward and Backward, Mental Control, and Letter Number Sequencing) to measure attention; the Symbol Digit, Stroop Test, and Odd Man Out Test to assess executive function; and the Hopkins Verbal Learning Test to measure learning ability and recognition memory. Donepezil was administered to all patients at 5 mg per day for 6 weeks, then 10 mg per day for another 6 weeks. All subjects were instructed to take the medication in the morning to give both the patients and the evaluator the best chance of appreciating the drug's antichoreic effect in case the benefit was transient or short-lived. Compliance was monitored at each visit. Repeat motor evaluation was done by the same neurologist and cognitive assessment by the same neuropsychologist at 6-week intervals.

Paired *t* test was used to compare baseline values from 6- and 12-week assessments. Wilcoxon signed rank test was used when the normality test failed because of the small sample.

Results

Eight of eight patients, with a mean age of 58 years, tolerated 5 mg donepezil per day for 6 weeks but only half finished the study on 10 mg per day (Table 1). Four of eight withdrew from the study as a result of side effects—two patients developed worsened chorea with increased falls, three had moderate to severe diarrhea, and one experienced increased anxiety and irritability. All side effects were noted within 4 days from increasing the donepezil dose to 10 mg per day. Other side effects such as sedation, nausea, fatigue, vomiting, and anorexia were not noted.

Only one patient remained on 10 mg donepezil per day claiming improved swallowing function. Although no appreciable benefit in motor performance was noted by the patients, the improvement in total score of the motor portion of the UHDRS from baseline to 6 weeks (36 versus 32.9; $p = 0.031$; $n = 8$) and 12 weeks (32.5 versus 28.7; $p = 0.004$; $n = 4$) was statistically significant. However, there was no statistical difference or even a trend in the motor subsets of UHDRS, namely, eye abnormalities, rigidity, bradykinesia, dystonia, and chorea (8.5 versus 8.5, $p = 0.88$; 2.0 versus 2.0, $p = 0.25$; 1.5 versus 1.5, $p = 0.50$; 2.1 versus 2.1, $p = 1.00$; 7.4 versus 7.1, $p = 0.63$, respectively).

Two patients had a slight improvement in memory and concentration at 5 mg per day. However, no statistically significant difference was noted between mean scores at baseline and 6 weeks on all neuropsychological tests performed (Table 2). Because the normality test failed for the paired *t* test analysis as a result of the low number of subjects, Wilcoxon signed rank test was used in more than half of the statistical analyses. Hence, standard deviation was not provided. Likewise, there was no clinically or statistically significant improvement in behavioral and functional assessments, independence scale, or functional capacity at 6 weeks (Table 2). Only four patients were available for neuropsychological testing at 12 weeks, not achieving enough statistical power to permit analysis.

Discussion

Involuntary movements of patients with HD may be related to increased activity of the dopaminergic system or insufficiency of the cholinergic system.[5–7] Haloperidol, a dopamine-blocking agent, for example, has been a standard treatment for chorea in patients with HD. Earlier pharmacological investigations using physostigmine, an anticholinesterase inhibitor, and choline chloride, a central procholinergic agent, transiently improved chorea in patients with HD.[5] However, succeeding trials using various cholinergic agonists have failed to reproduce this effect.[6–10] Donepezil is the latest central procholinergic agent approved by the Food and Drug Administration and has not been tested for patients with HD.

TABLE 1. *Demographics and drug tolerability*

Patient no.	Sex	Age (yrs)	Genetic test	Duration of HD*	Medications	5 mg D†	10 mg D‡
1	F	45	+	?15	Fluoxetine, clonazepam, trazodone	yes	no
2	M	77	+	7	Aspirin, vitamins C, E, B complex	yes	yes
3	M	56	+	10	Sertraline, carbamezepine, olanzapine	yes	yes
4	M	46	+	10	Venlafaxine, clonazepam, haloperidol	yes	no
5	F	47	+	3	Bupropion, venlafaxine, thioridazine	yes	no
6	M	48	+	4	Valproate, clonazepam, venlafaxine	yes	yes
7	M	62	+	3	Sertraline	yes	yes
8	M	39	+	8	Haloperidol, sertraline	yes	no

* Onset of psychiatric/cognitive/motor symptoms in years.
† Tolerated 5 mg donepezil per day.
‡ Tolerated 10 mg donepezil per day.

TABLE 2. *Comparison of cognitive, behavioral, and functional assessments at baseline and 6 weeks in patients with HD on donepezil (n = 8)*

Test	Normal references (for age 56)	Baseline (range)	6 weeks (range)	p value
Verbal Fluency Test	39	19 (6–32)	23 (7–38)	0.10
Symbol Digit Modalities Test	43	18 (6–35)	16 (5–46)	0.74
Stroop Interference Test				
a. Color naming	69	42 (26–89)	37 (19–61)	0.30
b. Word reading	97	53 (36–82)	55 (32–87)	0.66
c. Interference	36	15 (1–21)	17 (4–36)	0.36
Mini-Mental Status Examination	28	23 (17–29)	24 (14–30)	0.36
Wechsler Memory Scale				
a. Information and orientation	14	12 (9–14)	12 (8–14)	0.29
b. Digit span forward	*	8 (7–11)	9 (7–11)	0.29
c. Digit span backward	*	4 (0–6)	4 (0–8)	0.57
d. Mental control	28	14 (6–30)	14 (7–28)	0.86
e. Letter number sequencing	9	7 (0–9)	7 (0–15)	1.0
Odd Man Out Test				
a. Trails 1 and 3	none	15 (5–19)	16 (11–20)	0.39
b. Trails 2 and 4	none	12 (8–17)	11 (4–17)	0.30
Hopkins Verbal Learning				
a. Learning (Trial 1,2,3)	28	15 (10–19)	16 (9–22)	0.27
b. Memory (Delay)	10	5 (0–9)	4 (1–7)	0.73
c. Recognition (true and false positives)	12	11 (3–13)	11 (6–13)	0.26
Behavioral Assessment (UHDRS) Severity × frequency	N/A	47 (1–270)	53 (1–357)	0.66
Functional Assessment (UHDRS)	N/A	32 (25–38)	28 (25–39)	0.31
Independence Scale (UHDRS)	N/A	80 (60–90)	80 (60–80)	1.0
Functional Capacity (UHDRS)	N/A	7.0 (2–11)	7 (2–11)	0.75

N/A, not available.

* Normative reference for Total Digit Span (forward and backward) for mean age of 56 is 16. Our group's mean score was 11.9.

A high drop-out rate (50%) was noted in our patients with HD. This was the result of drug side effects which developed in patients taking 10 mg donepezil per day. However, intolerability with increased dosing as a "placebo side effect" cannot be discounted in an open-label study such as this. Although a statistically significant improvement in the total UHDRS motor score was achieved, there was no significant change in the motor subsets and only one patient remained on the drug as a result of improved swallowing function. Two patients developed worsening of chorea while on the drug, which resolved with drug withdrawal.

Although two patients admitted to slight improvement in memory and concentration, neither patient opted to stay on the drug. No clinical or statistical improvement was noted in the cognitive, behavioral, and functional assessments. The patient group was moderately to severely impaired on all cognitive measures, thus there was ample opportunity for measurable improvement on cognitive tasks. Normative age-matched references are provided (see Table 2). Nonetheless, because the desired power for the performed statistical test was not achieved as a result of the small sample, the negative results should be interpreted cautiously.

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An Unusual Cause of Gait Disturbance in an Elite Sprinter

Idiopathic hypoparathyroidism is a rare disorder that can present with a variety of neurologic and neuropsychiatric complications.[1–4] In this case, the primary diagnosis was made after an elite athlete presented with a movement disorder that was interfering with his race performance.

Case Report

A 17-year-old elite middle distance runner presented with a 6-month history of a progressive exercise-related movement disturbance affecting his left arm and leg. Initially the problem occurred intermittently during strenuous training sessions. Over the 6-month period prior to presentation, the episodes increased in frequency and severity to the point where they occurred three to four times per training session as well as during races. This problem reached the stage in which his race performance times deteriorated, prompting his coach and parents to seek a medical referral.

The patient described an unusual sensation of muscular "tightness" while running, which originated in the left side of his neck and shoulder, spreading distally down his arm and then to his trunk, hip, and leg on that side. He noted that the affected muscles would suddenly "stiffen" and his gait stride became abruptly restricted at that point. No ballistic or choreiform movements occurred. The episodes usually resolved spontaneously over 30 seconds if he ceased running. He retains full awareness throughout the episodes. The episodes did not occur during other sports or at rest. His training partners have adapted themselves to the episodes by running on his non-involved side during sprints.

His history was unremarkable, in particular, there was no history of head trauma. He had an uncomplicated vaginal delivery with no neonatal problems. There was no family history of neuromuscular disease. His parents and two younger siblings (both of whom are also track athletes) are alive and well.

Neurologic and physical examination at rest was unremarkable. There were no Kayser-Fleischer rings or corneal calcification. Eye movements were normal. Hyperventilation did not reproduce any abnormal movements. He was then exercised on a running track and performed several 100-m sprints. After two sprints, he developed a typical episode (see the videotape) with the left arm being primarily affected. The arm was held in a dystonic posture in an abducted position with the head and neck turned to the contralateral side with facial grimacing evident. The hand and fingers were in a dystonic position. After 30 seconds' rest, the limb returned to normal. Repeated sprint run-throughs again brought out the problem in this stereotypical manner. The contralateral side remained normal to examination throughout.

Initial investigations were unrevealing, including full blood examination, erythrocyte sedimentation rate, thyroid function tests, serum electrolytes, liver function tests, ceruloplasmin, serum and 24 hr urinary copper excretion. An electroencephalogram was normal, including with hyperventilation. His computed tomography and magnetic resonance brain scan were normal, in particular, there was no evidence of basal ganglia calcification.

Reviewing the videotape of the arm movements, the resemblance of his hand position to Trousseau's sign, which is seen in hypocalcemic tetany, was noted. Detailed calcium studies were then performed pre- and post-exercise. The results are as follows:

- Serum calcium (resting): 2.24 mmol/L (normal range, 2.30–2.65 mmol/L)
- Serum calcium (post-exercise): 2.20 mmol/L (normal range, 2.30–2.65 mmol/L)
- Phosphate: 1.16 mmol/L (normal range, 0.8–1.4 mmol/L)
- Serum albumin: 48 g/L (normal range, 35–50 g/L)
- Parathyroid hormone (intact molecule): 1.2 ng/L (normal range, 10–65 ng/L)
- Parathyroid hormone (mid-molecule): <10 pmol/mL (normal, >95 pmol/mL)
- Urinary calcium excretion: 21.6 mmol/24 hr (normal range, 2.5–7.5 mmol/24 hr)
- Vitamin D (1,25 diOH): Normal

A videotape accompanies this article.

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Although initially thought to have paroxysmal kinesogenic dystonia, the clinical picture in addition to the calcium and PTH levels suggested a diagnosis of idiopathic primary hypoparathyroidism causing hypocalcemic tetanic spasms. He was started on a daily calcium supplement (600 mg calcium carbonate and 3.1 μg vitamin D) and advised to increase his dietary calcium intake to a minimum of 1000 mg per day. His abnormal movement episodes ceased completely within 2 days of beginning the medication. On a number of subsequent occasions he forgot to take his medications and the exercise-related episodes rapidly returned. He has been followed for 7 years and has remained well to date. He continues to compete at an international level. While on therapy he has no abnormal movements and so far has had no evidence of renal calculi.

Discussion

There have been a handful of case reports documenting paroxysmal dystonia or choreoathetosis in hypoparathyroidism.[5–9] In addition to these cases, there have been other reports of movement disorders associated with basal ganglia calcification in the absence of hypocalcemia[10] as well as with hypocalcemia from other causes.[11,12] In this case, the videotape clearly shows the onset of his hypocalcemic tetanic symptoms during a 100-m sprint.

In the published reports of hypoparathyroidism-induced movement disorders, the patients may describe a subjective "tightness" of affected limbs prior to the dystonic posturing, which is usually brief and similar to that described by our patient.[5] Rarely, dystonic posturing may be prolonged, lasting hours.[9,12] Interestingly, the onset of the movement disorder often precedes the diagnosis of hypoparathyroidism by months or years and treatment using calcium supplementation and vitamin D (cholecalciferol) therapy is usually successful.[5,7] In this case, the triggering factor to his episodes was race sprinting, rather than gentle jogging, suggesting that acute changes in serum calcium levels induced by acid-base changes accompanying strenuous exercise were then the principal factor.

The pathophysiological basis of hypoparathyroid-induced movement disorders remains speculative, although the presence of basal ganglia calcification in some published cases is suggestive of an extrapyramidal origin. In hypoparathyroidism, neurologic conditions such as parkinsonism, dystonia, hemiballismus, torticollis, and oculogyric spasms have been reported.[7,10,13–16] This hypothesis does not fully explain the situations in which identical phenomena are observed in hypocalcemia without basal ganglia calcification or where these phenomena are reversed by pharmacologic treatment despite the ongoing presence of the basal ganglia calcification. Whether microscopic basal ganglial calcification is present or perhaps a coexistent neuronal circuit dysfunction is present remains speculative.[17]

It is possible that the clinical symptoms have a peripheral rather than central origin. Calcium is a key component of cell membranes and hypocalcemia is known to increase membrane permeability. This in turn may increase neuromuscular excitability resulting in clinical symptoms. Why a generalized pathophysiological process such as hypocalcemia should produce strictly unilateral symptoms, as demonstrated in this case, is unclear although this phenomenon has been observed before.[7,12]

Alternative etiologic possibilities to explain this clinical presentation include paroxysmal exercise-induced dystonia[17] and epilepsy. Hypoparathyroidism is a known cause of both focal[10] and generalized seizures.[16] There is no conclusive way of differentiating paroxysmal exercise-induced dystonia from hypocalcemic tetanic spasms; however, the clinical features, investigative findings, and response to calcium supplementation was more in keeping with hypocalcemic tetany.[18]

This case stresses the need for screening of exercise-induced movement phenomena for hypocalcemia and hypoparathyroidism. This is an important diagnosis for the patient because therapy may be curative. In addition, the use of videotape to phenomenologically describe the episode was the critical step in the diagnostic pathway in this case. Although many movement disorders can be videotaped in the surgery or hospital clinic, the demands of sporting patients require a more lateral approach to achieve this goal.

Legend to the Videotape

The videotape demonstrates the patient performing a 100-m sprint on an Olympic running track. The dystonic episode commences with arm abduction followed by facial grimacing and versive head movements. The leg then stiffens and the running gait is disturbed. As the patient nears the camera, the typical Trousseau sign of hypocalcemic tetany is evident.

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Hemichoreoathetosis Following Posterior Parietal Watershed Infarction: Was Striatal Hypoperfusion Really to Blame?

Watershed infarction consists of approximately 5%–10% of brain infarction.[1,2] Focal jerks or shakings are observed in 12% of patients with watershed infarction.[3] However, detailed clinical characteristics of these dyskinesias have not been described.

We present a patient who developed hemichoreoathetosis. T2-weighted and diffusion brain magnetic resonance imaging (MRI) studies showed a recent infarction involving the right posterior parietal lobe. However, magnetic resonance cerebral angiography (MRA) study showed an occlusion at the proximal portion of the right middle cerebral artery. [^{99m}Tc]-HMPAO brain single photon emission computed tomography (SPECT) study showed decreased cerebral blood flow at the right striatum and posterior border zone.

Case History

An 81-year-old woman suddenly developed choreoathetosis involving her left face, arm, and leg. The dyskinesias were suppressed markedly while she was moving and maintaining a posture. She had no history of cardiac disease or syncope. Her blood pressure was normal. On neurologic examinations, she was inattentive but her judgment and orientation to time, place, and person were intact. She had no apraxia, agnosia, anosognosia, or agraphesthesia. There was no sensory extinction. She had left homonymous hemianopia. Manual motor function tests revealed minimal weakness in her left limbs. Pain, light touch, position, and vibration sensations were normal. Deep tendon reflexes were hypoactive but symmetric bilaterally. Planter reflexes were flexor bilaterally. Finger-to-nose tests and rapid alternating hand movements of her left arm were normal. She

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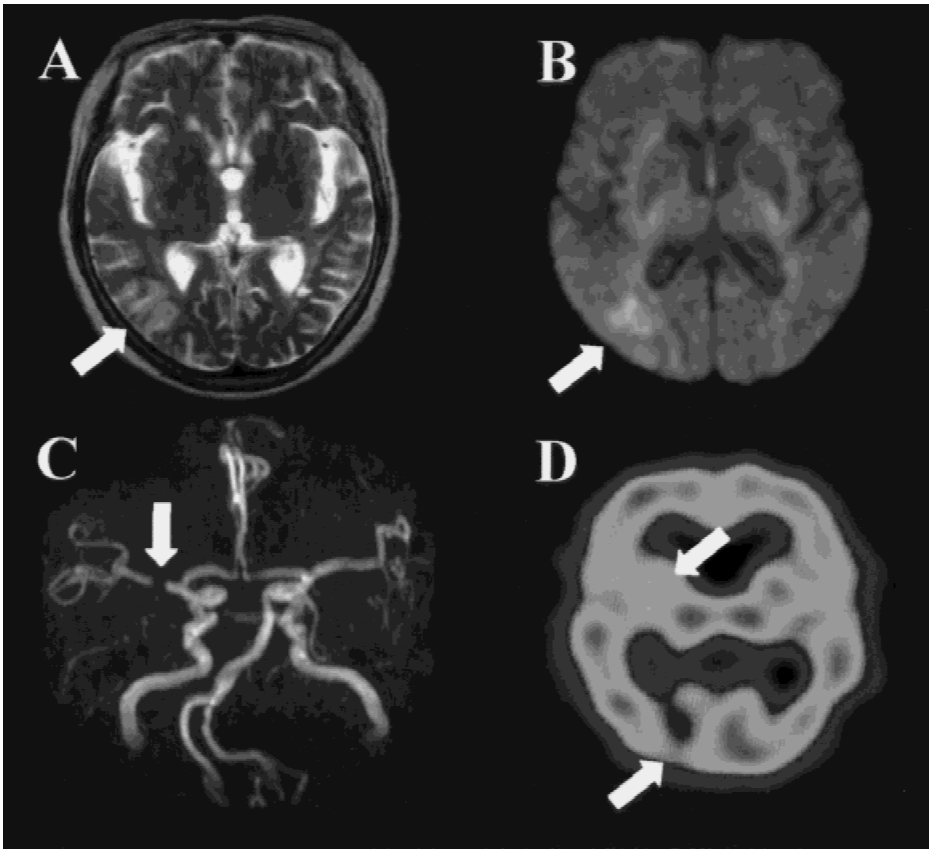

FIG. 1. (**A**) T2-weighted and (**B**) diffusion magnetic resonance axial brain imaging studies show a high signal intensity lesion (arrows) at the right posterior parietal lobe corresponding to the posterior border zone. (**C**) Magnetic resonance cerebral angiography study shows nearly complete obstruction at the M1 portion of the right middle cerebral artery (arrows). The right basilar communicating artery is not visualized. (**D**) [^{99m}Tc]-HMPAO brain SPECT study shows decreased cerebral perfusion at the right striatum and posterior border zone (arrows).

swayed to the left on tandem gait. Routine laboratory examinations and thyroid function tests were normal. Serum total cholesterol (7.60 mmol/L) and LDL-cholesterol (5.87 mmol/L) levels were increased. Serum antiphospholipid antibody and serologic tests for syphilis were negative. T2-weighted brain MRI study showed a high signal intensity lesion at the right posterior parietal region corresponding to the border zone between the middle and posterior cerebral artery territories (Fig. 1A). Diffusion MRI study of the brain also showed a high signal intensity lesion at the same area (Fig. 1B). MRA study showed nearly complete obstruction at the M1 portion of the right middle cerebral artery. The connecting segment from the basilar artery to the right posterior cerebral artery was not visualized on MRA study (Fig. 1C). There were multiple partial stenoses at both internal carotid arteries. [^{99m}Tc]-HMPAO brain SPECT study showed decreased cerebral blood flow at the right posterior parietal region and striatum (Fig. 1D). The dyskinesia lasted for 10 days and disappeared spontaneously.

Discussion

Watershed infarctions can be divided into three groups (anterior, posterior, and subcortical) according to the locations. Most patients with watershed infarction have severe obstruction of the internal carotid artery.[3] Syncope or iatrogenic hypotension frequently precedes the onset. Therefore, additional hemodynamic changes to the preexisting carotid circulation defect have been frequently attributed to watershed infarction.[2] In some patients, emboli from a carotid plaque to the major cerebral vessel may cause watershed infarction.[2,4]

Our patient did not have a right basilar communicating artery. Such anatomic variation might further compromise the reduced posterior parietal cerebral blood perfusion through the occluded right middle cerebral artery.

Patients with parietal lobe lesion may develop hemichoreoathetosis in association with abnormalities in somatic sensations, graphesthesia, and detecting direction of tactile movements. Integration of defective sensory information with motor processing in the striatum may lead to such pseudochoreoathetosis.[5] Patients with the right posterior border zone infarction may have anosognosia and abnormal cortical sensations (two-point discrimination and stereognosis).[3] However, our patient had no sensory abnormalities. Therefore, the term "pseudochoreoathetosis" cannot be used for the dyskinesias seen in our patient.

In our patient, MRA and brain SPECT studies provided evidence suggesting functional changes of the right striatum. We suspect collaterals from the penetrating branches of the right anterior cerebral and anterior communicating arteries rescued the right striatum from ischemic necrosis. Functional brain imaging and MRA studies are needed to clarify the origin of neurologic deficits that cannot be explained by a lesion observed in structural brain imaging studies.

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