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Clinical/Scientific Notes

Speech Dysfluency Exacerbated by Levodopa in Parkinson's Disease

Abstract: The role of dopamine in the modulation of speech fluency is complex. In this report we describe two patients with Parkinson's disease whose speech dysfluency was exacerbated by the administration of levodopa. In doing so, we extend the observation that dopaminergic mechanisms may be involved in the regulation of speech fluency. It is important for clinicians to recognize that, in some instances, dopaminergic replacement therapy may exacerbate an underlying dysfluency syndrome in PD.

Dopaminergic pathways in the extrapyramidal system are involved in modulating the fluency of speech, yet the mechanisms are complex and poorly understood.[1–3] For example, there is evidence that dysfluency (disrupted speech flow and/or reiteration of previously spoken utterences)[4] may result from both over-activity and under-activity of central dopaminergic neurons.[1–3] Dysfluent speech may take a variety of forms, including stuttering, palilalia, freezing, and tachyphemia.

Stutterers are unable to articulate what they want to because of an involuntary and repetitive prolongation or cessation of sound.[5–9] Both developmental and acquired forms of stuttering exist. Acquired stuttering may result from infarcts or penetrating missile wounds in the putamen[10–13] and caudate,[10,11,13,14] and neuroleptics, particularly haloperidol, have been used successfully to treat stuttering,[1,15–18] leading several investigators to suggest that stuttering may be a consequence of hyperactive central dopaminergic systems.[1–3,17]

In contrast, in idiopathic Parkinson's disease (PD) and secondary forms of parkinsonism (i.e, disorders characterized by dopamine deficiency), dysfluency in the form of palilalia (repetition of syllables, words or phrases), freezing of speech (transient arrests in speech), and tachyphemia (tendency to speak more and more rapidly) have all been described.[19–21] These conditions may coexist within the same patient. Because the clinical phenomenology may overlap, some have questioned whether the underlying mechanisms could be similar.[13,19]

Our goal was to describe two PD patients with speech dysfluency that was exacerbated by the administration of levodopa, an agent which is centrally converted to dopamine. In doing so, we extend the observation that dopaminergic mechanisms may be involved in the regulation of speech fluency. In addition, we provide videotaped material of freezing of speech. To our knowledge, videotaped examples of this rare form of dysfluency have not been published.

A videotape accompanies this article.

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Case Reports

Case 1

In January 1997, at the age of 72 years, this man noted a flexed posture. Over the next 10 months, he noticed a left hand tremor and "some hesitancy of speech." He was a priest, and on one occasion, he involuntarily paused for several seconds during a sermon because he was unable to "get the words out." Because developmental stuttering may re-emerge with the onset of PD, detailed information was obtained regarding childhood stuttering. There was no history of childhood stuttering or any dysfluency prior to January 1997, and no family history of stuttering. In December 1997, he was seen by a neurologist, and was diagnosed with PD. He was started on levodopa (100 mg per day), and this was increased to 200 mg per day over the next 2–3 weeks. In January 1998, he was seen at the Center for Parkinson's Disease and Other Movement Disorders at Columbia-Presbyterian Medical Center. On examination, there was mild cognitive impairment, and mild hypomimia and hypophonia, but no dysfluency was noted. Tone was increased in all limbs without reinforcement, and rapid alternating movements were notable for loss of amplitude and occasional pauses. He took eight steps back on a pull test before recovering. Because of the absence of a rest tremor, a fluorodeoxyglucose PET scan was performed, revealing moderate bilateral lentiform hypermetabolism compatible with idiopathic PD. Over the ensuing one month, he reported that his speech dysfluency worsened to the point that he wrote: "[I have] great difficulty expressing myself or finishing a conversation. I'm conversing with a person and then I come to a complete stop and I begin to stutter." He was seen again in February 1998, and the decision was made to discontinue levodopa and to begin pramipexole (0.0625 mg per day). The pramipexole was increased gradually to 0.25 mg per day, and by late March 1998, he commented that his "stuttering" had "all but stopped." While there were occasional involuntary pauses, they were infrequent, occurring with approximately the same frequency as they had prior to levodopa therapy. Over the ensuing months, his pramipexole was increased to 1.125 mg/day. This was the highest dose he could tolerate without experiencing bothersome cognitive slowing and confusion. However, his gait continued to decline, and he began to experience occasional freezing while turning. In February 1999, the decision was made to admit him to the hospital. While in the hospital, pramipexole was discontinued, and he was placed on levodopa (initially started at 100 mg per day and gradually increased to 600 mg per day). Because there was evidence of mild cognitive impairment on levodopa in January 1998, olanzapine (2.5 mg twice daily) was started to attempt to lessen levodopa-induced confusion and cognitive impairment. His gait and freezing while turning improved. There was mild dysfluency in the hospital (videotape, while on levodopa 50 mg per day and olanzapine 2.5 mg per day). When questioned about his dysfluency, the patient noted that he did not have any difficulty finding the words he wanted to use, but rather, had occasional difficulty

producing the sounds he needed to make. This became much more severe over a two-week period following discharge. He wrote "I've had a big problem articulating. I'll start a conversation and then I'm short-circuiting. Answering a phone is an ordeal in itself. I wind up tongue-tied and stuttering. I tried delivering a sermon yesterday and it was a disaster. I cut the sermon short."

Case 2

In 1973, at the age of 40 years, this man noted a right hand tremor, soon followed by a tremor of the right foot. He was diagnosed with PD and started on levodopa (750 mg per day). He was initially seen in our Center in 1974, where he was noted to have hypomimia, rest tremor, and hypertonia and diminished arm swing on the right. Levodopa was discontinued, and over the next six years, he was treated with amantadine, dopamine agonists, or anticholinergic agents. In 1980, levodopa (300 mg per day) was resumed. It is unclear when his problem with speech really began, although the first mention of it in the medical record was in 1984, while he was taking 300 mg of levodopa per day. He was a university professor, and described a problem with frequently losing his train of speech and stuttering, particularly while delivering his academic lectures. There had been no prior history of stuttering as a child and no family history of stuttering. He had no cognitive impairment. His dysfluency gradually worsened over the ensuing years, and in 1988, he was referred for a speech evaluation, during which both pressured speech and sound repetition were noted. He eventually developed motor fluctuations, and complained that his dysfluency was markedly worse during his "on" periods. To assess this, in April 2000, he was evaluated in an "off" state (off of all medications for 13 hours), and again one hour after a 300 mg oral bolus of levodopa (videotape). His medications at that time were levodopa 1000 mg per day, pergolide 1.5 mg per day, and quetiapine 50 mg at bedtime (for auditory hallucinations). While "off", there was occasional palilalia and freezing of speech in addition to tremor at rest and mild torticollis. After the oral bolus of levodopa, while his tremor at rest improved, both the palilalia and freezing of speech worsened considerably, along with his torticollis.

Discussion

Certain types of speech dysfluency, including palilalia, stuttering, and freezing, may be the result of abnormalities in central dopaminergic activity, although both over- and underactivity of this neurotransmitter system have been hypothesized to be important, and the role of the dopaminergic system in these forms of dysfluency is still poorly understood. We describe two patients with speech dysfluency exacerbated by the administration of levodopa, an agent which is centrally converted to dopamine. The dysfluency had features of both freezing and palilalia. This extends the observations of others[1–3,13,17,22] that dopaminergic mechanisms are involved in the regulation of speech fluency, and that over-activity may be important in some situations.

Palilalia, which is commonly described in patients with parkinsonism, has been defined as a repetition of the first syllable of a word before the word is verbally expressed.[4,23–25] The term has also been used to describe the repetition of a phrase, word, or series of words at the end of a sentence, such that the patient reiterates with increasing rapidity and with decrements of voice and volume.[26,27] Palilalia has been contrasted with stuttering, with the following differences noted: (1) stutters repeat mainly initial syllables while patients with palilalia can repeat initial syllables, entire words, phrases, or parts of sentences,[27–29] (2) stutters are noted for the painful effort as they attempt to speak, whereas palilalics have more of a fluent output as if they cannot stop speaking,[27] and (3) stuttering may be characterized not only by repetition, but also by prolongation of word sounds.[27]

Freezing of speech has been defined as a transient speech arrest in the middle of talking, in which the sound is often sustained or repeated until it finally becomes unstuck.[19,25,30] As with palilalia and stuttering, there may be repetition of sounds, and similar to stuttering, there may be arrests in speech.[27] However, in contrast to stuttering, these arrests do not necessarily occur at the beginning of sentences.[27]

Our patients' speech contained examples of palilalia (e.g., "I hope that that" [Case 1], or "and its two ends and its two ends" [Case 2]) in which whole words or phrases were repeated. In addition, there was freezing, characterized by arrests in speech that occurred in the middle of sentences (e.g., in Case 1, "You step back into the [freeze]," and in Case 2 "[freeze on the word 'yes'] this morning [freeze on the word 'yes'] this morning.") At times, these arrests occurred in the beginning of sentences as well, making it difficult to distinguish between stuttering and freezing. Of interest was that after the bolus of levodopa (Case 2), freezing of spontaneous speech worsened to a greater degree than did freezing of speech while reading (i.e., when using an external visual cue to produce words). In other forms of freezing (e.g., start hesitation while walking) external cues (e.g., clapping, stepping over a line on the floor) can reduce the severity of freezing as well.[19]

We do not know of other reports of freezing and palilalia worsened by levodopa therapy. Peak dose changes in speech (described as a reduction in volume and poor articulation) have been described in several patients on chronic levodopa therapy, with these changes coinciding with the peak in plasma levels of levodopa,[31–33] and there is one report of a 68-year-old man with PD who would develop palilalia approximately 30 minutes after an oral dose of levodopa.[33]

Both of our patients were taking atypical neuroleptics in addition to levodopa at the time of the videotape, and these agents have been reported to cause stuttering.[34–36] Therefore, we can not fully exclude the possibility that these agents could have contributed to the speech problem. However, in both cases, by history, dysfluency had occurred when the patients were taking levodopa alone. In addition, these agents have been reported to cause stuttering rather than palilalia or freezing, and the stuttering occurs at high doses (e.g, 125–700 mg/day of clozapine).

The role of dopamine in the modulation of speech fluency is complex, and there are differences in the speech behaviors of PD patients with certain types of disfluency and stutterers. It is important for clinicians to recognize that, in some instances, dopaminergic replacement therapy may exacerbate an underlying dysfluency syndrome in PD.

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Legends to Videotape

Because the speech is at times difficult to understand, a transcript has been provided. The examiner's speech is written in *italics*, and the patient's in plain type. Repeated words or phrases are underlined. Freezing is denoted by [brackets].

Segment 1: Case 1 is describing his visit to Colonial Williamsburg, VA. The patient was videotaped 4–5 hours after the last dose of levodopa.

"It's like going baa back [freeze]. You step back into the [freeze]."

"Did it just happen?"

"Yes."

"OK."

"Um... It's walking back [freeze on the word "in"] back into the past centuries of [freeze on the word "of"] America....And I hope that [freeze] that all the tourism that does take place will not ruin it [freeze]."

Segment 2: Case 2 (off all medications for 13 hours).

"How do you how do you find your speech now?"

"Right now my speech is good."

"Do you ever have much tremor in the hands?"

"No, I I don't have too much tremor in the hands."

"OK."

"I I do have tremor though."

"You do, sometimes?"

"Yes."

"Which side?"

"The right side.... (reading) When the sunlight strikes raindrops in the air, they act like a prism and form a rainbow. The

rainbow is a division of white light into many beautiful colors. [Freeze] These take the shape of a [freeze] long round arch, with its path high above and its two ends and its two ends apparently beyond the [freeze] horizon. There is there is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds its. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow."

Case 2 (one hour after taking 300 mg of levodopa).

"So, how long ago did you take your medicines?"

"[Freeze on the word "About"] nine o'clock last night... [freeze on the word "eight"] o'clock".

"Eight o'clock?"

"[Freeze on the word "eight"] or nine"

"Eight pm?"

"Right."

"And then you didn't take medicine since then?"

"Yeh."

"Then you came here this morning?"

"[Freeze on the word "yes"] this morning [freeze on the word "yes"] this morning yes this morning."

"OK, and what happened this morning?"

"[Freeze on the word "I," then garble. Freeze again on the word "I," then garble]."

"And why did he do this test today?"

"[Freezing on the word "I"] had an appointment with him. I had an appointment with him. I had an appointment with him."

"Oh, OK."

"(Reading) When the sunlight sunlight strikes raindrops in the air, they act like a pr prism and form a rainbow [freeze on "rainbow"]. The rainbow is a division of white light into many beautiful colors. Take. These [freeze on "these"] take the shape of a long round arch, with its path high [freeze on "high"] above and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds its. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow."

Parkinsonism After Glycine-Derivate Exposure

Abstract: This 54-year-old man accidentally sprayed himself with the chemical agent glyphosate, a herbicide derived from the amino acid glycine. He developed disseminated skin lesions 6 hours after the accident. One month later, he developed a symmetrical parkinsonian syndrome. Two years after the initial exposure to glyphosate, magnetic resonance imaging revealed hyperintense signal in the globus pallidus and substantia nigra, bilaterally, on T2-weighted images. Levodopa/benserazide 500/125 mg daily provided satisfactory clinical outcome.

A videotape accompanies this article.

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Case Report

A previously healthy 54-year-old, man sustained a chemical exposure in July 1995 while he was spraying glyphosate in a garden. He was wearing no protection gear such as gloves or a face mask, and the exposure to the aforementioned chemical agent occurred as the breeze blew the spray back onto his trunk, arms, legs, and face. The substance was not washed off his body until 30 minutes later. Nonetheless, he was immediately brought to medical attention and 6 hours after the exposure, he developed severe conjunctival hyperemia and a generalized cutaneous rash.

One week after the chemical exposure, the skin lesions became blisters that persisted for approximately 15 days. After a short course of anti-histamine drugs, the skin lesions completely subsided. One month after the initial exposure, the patient displayed rigidity and slowness in all four limbs. One year later, he developed a resting slow tremor in the left hand and arm and complained of impaired short-term memory. Family history was unremarkable.

The patient was originally admitted to the Movement Disorders Clinic of the University of São Paulo General Hospital in July 1997. The recent past medical history disclosed that he was prescribed biperiden with a poor clinical response, but levodopa/benserazide (500/125 mg daily) yielded a good clinical outcome.

Physical examination performed under the influence of medication revealed a parkinsonian syndrome. There was facial hypomimia, semi-flexed posture of the trunk and arms, resting tremor in the left arm, global akinesia and rigidity with "cogwheel phenomenon" and postural instability. Severity was stage III Hoehn and Yahr [1] during "on" phase and stage IV during "off"phase. Deep tendon reflexes were diminished in all four limbs. No autonomic or eye movement abnormalities were detected, and the remainder of the neurologic examination was unremarkable. The patient scored 23 out of 30 points in the Mini-Mental State examination.[2] Deficits were detected in attention, memory, and calculation.

Blood chemistry and eletromyoneurography of the four limbs were unremarkable. The brain CT scan showed enlarged cerebral sulci and there was no pathological calcification in the basal ganglia. Brain magnetic resonance imaging (MRI) revealed hyperintense bilateral lesions on T2-weighted images in the globus pallidus (Figs. 1–3) and in the substantia nigra (Fig. 4), associated with sulci enlargement.

During a 2-year follow-up at the Movement Disorders Clinic, the patient had a reasonable clinical response to levodopa.

Discussion

The diagnosis of idiopathic Parkinson's disease (IPD) is based solely on clinical criteria, since there are no biological diagnostic tests to confirm this diagnosis. In this case, it is not possible to exclude the coincidence of IPD with exposure to glyphosate. However, the patient developed significant parkinsonian features only 30 days after exposure to glyphosate. Additionally, the MRI findings were not compatible with PD. A satisfactory clinical response to levodopa may sometimes be observed in secondary parkinsonism, so does not rule out this condition.

Exposure to numerous toxins has been associated with par-

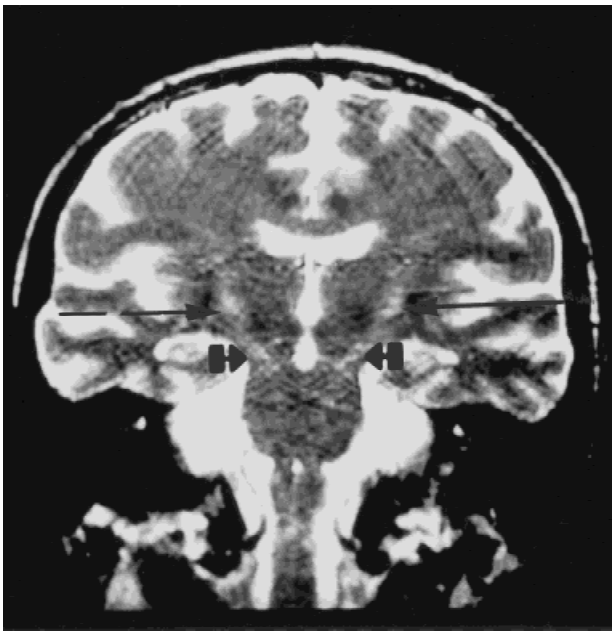

FIG. 1. Coronal T2-weighted magnetic resonance imaging (MRI) demonstrating increased signal intensity in the substantia nigra extending to basal ganglia bilaterally and enlargement of the cerebral sulci.

kinsonism Most of them are enviromental, such as manganese, carbon monoxide, carbon disulfide, cyanide, methanol, organophosphate insecticide, and herbicides as paraquat. [3–5] The discovery of the neurotoxin 1-methyl-4-phenyl-1-2-3-6-tetrahydropyridine (MPTP) as a cause of parkinsonism has benefitted almost every aspect of PD research, because it is the toxic agent that best mimics the clinical and pathological findings of PD in humans and animal experiments.[6] MPTP, an analog of meperidine, is a protoxin that is converted to 1-methyl-4-phenyl-pyridinium (MPP^+) by the enzyme monoamine oxidase B (MAO-B). More than 100 MPTP analogous

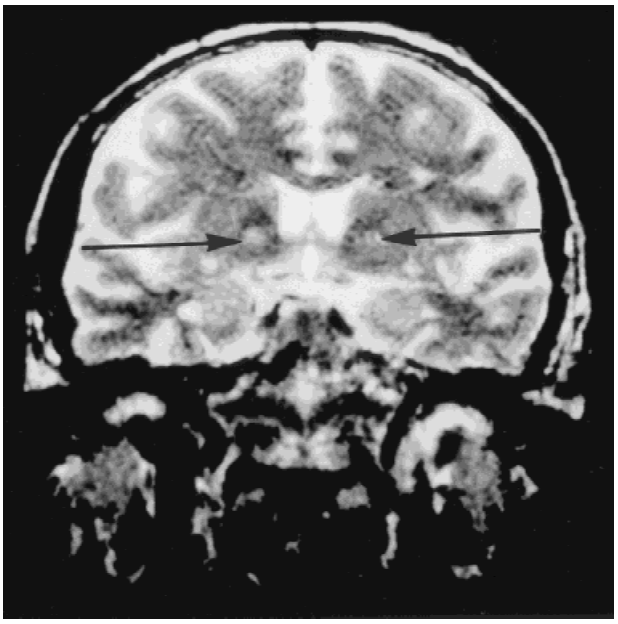

FIG. 2. Coronal T2-weighted MRI showing bilateral hypersignal lesion in the globus pallidus.

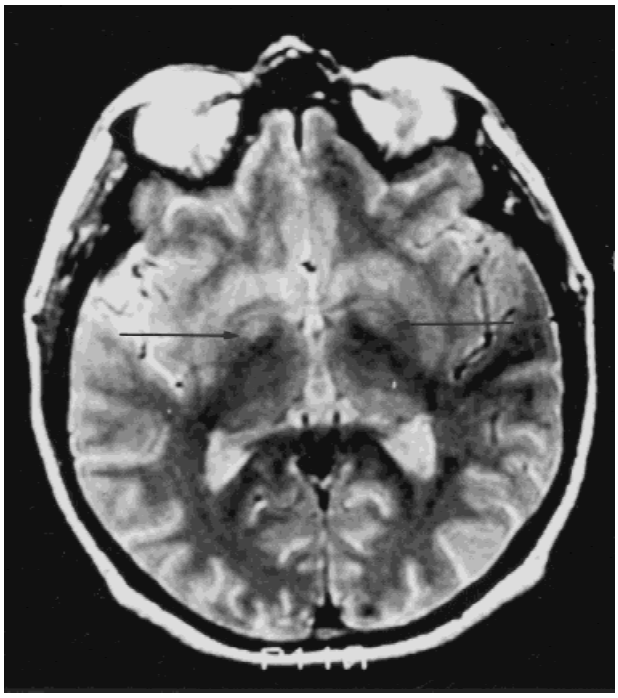

FIG. 3. Axial T2-weighted MRI showing bilateral hypersignal lesion in the globus pallidus.

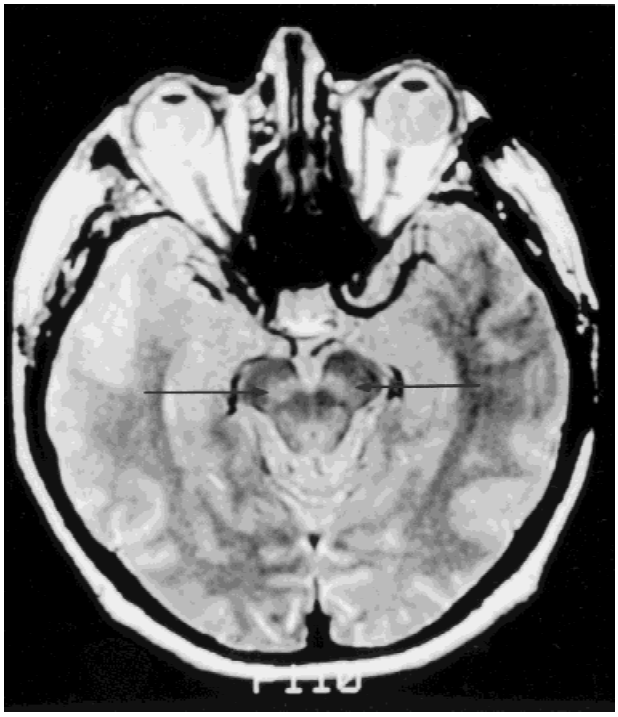

FIG. 4. Axial T2-weighted MRI showing bilateral hypersignal lesion in the substantia nigra.

compounds have been reported to this date, and some of them are substrates of MAO-B.[7,8]

Several toxins that interfere with the mitochondrial respiratory chain cause cell death. These toxins have been used as pesticides and herbicides for decades. Among them, paraquat is a specific herbicide that is chemically similar to MPTP. [9]

The low prevalence of PD in China, [10] Nigeria,[11] and Libya[12] as opposed to North America[13, 14] and Oriental Europe[15] suggests that environmental factors associated with industrialization and the use of agrotoxic agents play a role in the etiopathogenesis of PD.[16–18] Furthermore, Koller et al.[19] reported that early exposure to a non-urban environment and the exposure to treated water may also be involved in the etiopathogenesis of PD. Seidler et al., [20] in Germany, found an association between PD and pesticide use, especially organochlorines and alkylated phosphates, and exposure to wood preservatives. A similar study performed by Liou et al.,[21] in Taiwan, showed the following features as risk factors for PD: life in a non-urban community, work on a farm, use of herbicides (including paraquat) and pesticides. Recently, Caparros-Lefebvre et al.[22] reported patients with atypical parkinsonism in French West Indies and suggested that such a disorder could be linked to chronic exposure to benzyltetrahydroisoquinolines from tropical herbal teas and fruits. Therefore, there is an increasing tendency to believe that environmental toxins in genetically predisposed individuals play a role in the etiopathogenesis of PD.[20,23]

Glyphosate is a herbicide derived from glycine employed to control wormseed, and also employed to eliminate vegetation near rubber trees and in reforestation areas. Glyphosate can also be employed to control the growing vegetation around electric transmission towers, oil pipelines, water drainage channels, public squares, and streets.

Hammond et al.[24] evaluated the effect of glyphosate application in the newly genetically modified species of soil bean, which is usually employed to feed rodents, birds, fish, and cattle. The soil bean has been given to these animals for a 1-year period. The genetically modified soil bean kept its nutritional value and did not cause any biological changes.

No report of parkinsonism induced by glyphosate has been published to date. However, the neurotoxic effects of glycine have been described elsewhere in the literature.[25, 26]

Glycine is an inhibitory neurotransmitter whose active ionotropic receptors link the chlorine channels and inhibit antagonist muscles in the spinal cord. Additionally, glycine acts as a permissive cofactor required for activation of N-Methyl-D-Aspartate (NMDA) receptor.[27] The NMDA receptor is a glutamate receptor that controls the excitatory actions pertaining to the spinal cord and brain. This ionotropic receptor is a complex macromolecule with multiple specific sites for glutamate, glycine, zinc, and manganese linkage and regulates calcium, potassium, and sodium channels.[28] The unique glycine site on the NMDA receptor (strychnine-insensitive site), discovered by Johnson and Ascher[29] in 1987, represents an interesting target for the development of neuroprotective compounds.

NMDA receptor activation causes an influx of calcium to the neuron. In normal conditions, the NMDA receptor has an important role in neurotransmission as well as promoting neuroplasticity during central nervous system (CNS) development. It is also believed that this receptor is involved in memory and learning processes. However, hyperactivation of the NMDA receptor is thought to produce a neurotoxic effect, causing cell death in few hours.[25] High concentrations of glycine (10 mM) cause hyperexcitability and neurotoxicity in hyppocampus cell cultures, an effect that can be antagonized by NMDA receptor blockers.[25]

In MPTP experimental parkinsonism models, the use of systemic antagonists before exposure to the toxic agent for the glycine site on the NMDA receptor may decrease the dopamine depletion of the nigro-striatal circuity. These observations suggest that excitatory mechanisms of neurodegeneration may be involved in the pathogenesis of parkinsonism and also that NMDA-glycine site antagonists might prevent neurodegeneration in PD.[26, 27, 30]

In conclusion, we propose that the parkinsonian syndrome recorded in this patient might be related to the toxic effect of glyphosate, probably due to an excitotoxic mechanism. This hypothesis, supported by the findings of MRI, showed extensive lesions in the globus pallidus and substantia nigra, which receive massive excitatory glutamatergic projections from subthalamic nucleus.

Acknowledgment: This patient was kindly referred by Dr. Rogério Adas Ayres de Oliveira.

Legends to the Videotape

Segment 1. Patient during "off" phase.
Segment 2. Patient during "on" phase.

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Penicillamine-Induced Lethal Status Dystonicus in a Patient With Wilson's Disease

Abstract: A 37-year-old man with Wilson's disease is described, in whom the introduction of penicillamine therapy was followed after 3.5 weeks by the development of the status dystonicus with a fatal outcome.

Worsening of the clinical symptoms and signs after the introduction of penicillamine, especially when it is used as the initial treatment of the patients with Wilson's disease (WD) presenting with neurologic disease, has been frequently described.[1] However, the true risk with penicillamine treatment is still controversial.[2, 3] The penicillamine-induced deterioration is sudden and explosive, worsening within a few weeks, and does not appear to be a continuation of the more gradual progression prior to this treatment.[2]

Dystonia is a hallmark of the classic (dystonic) form of WD and was found at the first examination in 65% of 31 patients presenting with neurologic form of the disease.[4] The patients with primary and secondary dystonic syndromes infrequently develop severe, sometimes lethal episodes of generalized dystonia and rigidity (status dystonicus).[5] The most severe cases may develop bulbar and ventilatory complications, as well as acute renal failure due to rhabdomyolysis.

Herein, we present a case of WD in whom the introduction of penicillamine therapy was followed by the development of the status dystonicus with a fatal outcome.

Case Report

A 37-year-old man was admitted to our Institute for speech-related difficulties, hand tremor, gait instability, and "cramps" at initiation of arm and leg movements. The symptoms started a year before the admission with dysarthria and gait instability and gradual deterioration thereof. Exacerbation was recorded 4 months after the onset of the disease, after a surgery for inguinal hernia in general anesthesia, with dysphagia and frequent choking up. The patient had a 3-year-long history of insulin-dependent diabetes mellitus. His hypertension had been successfully managed by angiotensin 1-converting enzyme (ACE) inhibitors for 10 years.

Neurological findings on admission revealed dysarthria and dysphagia, with frequent choking up. Rigidity was found in both arms, somewhat more prominent to the left, with bilateral bradykinesia and postural tremor, with rough intentional tremor at the finger-to-nose test. The muscle tone on the legs was increased (rigidity), with dystonic posture (equinovarus) of the feet and intentional tremor on the heel-to-knee test with superimposed myoclonic jerks. The gait provoked action dystonia of the limbs, but in spite of that he walks unassisted. Lower ce-

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ruloplasmin serum level (0.13 g/L; normal range: 0.22–0.61 g/L) and elevated level of 24 hours copper excretion in the urine (4.48 μmol/L; normally up to 1.15 μmol/L) were found. Kayser-Fleischer's ring was positive. The platelet count was decreased (72–102 × 10^9/L) as well as the fibrinogen levels (1.6 g/l) and coagulation factors II, V, VII, and IX. Echographic examination evidenced hepatomegaly and the enlarged portal vein (16 mm). Only one brain magnetic resonance imaging (MRI) scan was performed and revealed precipitation of paramagnetic medium in globus pallidus, substantia nigra, and to a lesser degree in putamen, thalamus, and periaqueductal gray matter.

After WD had been diagnosed, penicillamine therapy was initiated with gradual increase of the daily dose, reaching 1,250 mg at the end of the fourth week. During this short period of the escalation of penicillamine dose, the urinary output of copper was not checked. However, the patient then manifested dramatic worsening with development of severe generalized dystonia with superimposed painful spasms of the limbs and trunk. He became bedridden, unable to speak, drink or eat, and required a nasogastric tube. All therapeutic measures (diazepam, clonazepam, pimozide, biperiden, carbamazepine, valproic acid, baclofen, levodopa/benserazide) failed. We had no possibility to perform bilateral pallidotomy. After 16 days, his dystonic movements deteriorated with diffuse sweating, hypotension, hypoglycemia, sinus tachycardia (100–140/min) followed by high fever (38.0–39.8°C) and leukocytosis (25 × 109/L). He developed rhabdomyolysis (creatine kinase 776 U/L; normally up to 134 U/L), a metabolic acidosis (pH 7.25) and a renal failure with a urea of 16.3 mmol/l and myoglobinuria. He was transferred to the intensive care unit, but despite all measures, oliguria developed and he died at the end of the third week of status dystonicus.

Discussion

We herein report a case of WD with neurologic presentation, in whom 3.5 weeks after the onset of penicillamine therapy, drastic deterioration ensued with status dystonicus resulting, in spite of all measures, in fatal outcome 3 weeks later. To the best of our knowledge, a similar case has not been reported in referential literature.

Penicillamine was first reported to be effective in treating WD by Walshe in 1956.[6] However, a significant detriment of this drug is the initial deterioration of the neurologic signs, commonly soon after treatment has been started. Walshe and Yealland [7] reported an initial deterioration in 22% of patients treated with penicillamine, but they further showed that this did not alter the final outcome unfavorably. Contrary to them, Brewer et al.,[1] in a retrospective survey of 25 patients with neurologic presentation who were treated initially with penicillamine, found that 13 of them experienced worsening of their neurologic symptoms, and even worse, that six never recovered to their pretreatment conditions. Therefore, Brewer [2] suggested that there was a major risk of permanent neurologic worsening after the initial introduction of penicillamine. The penicillamine-induced deterioration in our patient was sudden and rather dramatic, occurring after 3.5 weeks of treatment, similar to the cases previously described in the literature.[2] However, the case was most unusual not only for the fatal outcome, but also for the nature of specific clinical manifestations of the penicillamine-induced deterioration.

Our patient, with only mild dystonic movements, developed increasingly frequent and dramatic episodes of generalized dystonia, with painful spasms and bulbar weakness during the fourth week of penicillamine therapy. The progressive deterioration led to exhaustion and metabolic derangement, while severe dystonic spasms induced rhabdomyolysis with renal failure, elevated levels of creatine kinase and urea, with acidosis. The presentation suggested the diagnosis of a rare clinical syndrome, status dystoniscus.[5] Manji et al.[5] described 12 cases with status dystonicus of various underlying etiologies (primary torsion dystonia, athetoid cerebral palsy, post-traumatic and post-encephalitic dystonia, infantile striatal necrosis, neuroacanthocytosis, etc.). Among the possible precipitating factors, the authors stressed intercurrent infection, which was not present in our patient, and changes of therapy, which, in our case was initiation of penicillamine itself. We were unable to find in the referential literature a similar case where status dystonicus was reported to be provoked by WD or precipitated by the introduction of penicillamine therapy. Recently, Huang and Chu [8] reported three patients who developed acute generalized dystonia and akinetic-rigid syndrome following an initial therapy with penicillamine (125–500 mg daily). One patient continued to receive the drug, while two changed to zinc-sulfate treatment, with improvement of generalized dystonia after 3 months and 3 years, respectively. Unfortunately, our patient was refractory to standard drug therapy and died after 3 weeks, despite discontinuation of penicillamine. Two out of 12 patients with status dystonicus from Manji et al.'s[5] series also died.

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Hemichorea, Moya-Moya, and Ulcerative Colitis

Abstract: This is a case report linking chorea, colitis, and moya-moya. The clear involvement in the vasculopathy of the basal ganglia offers an obvious substrate for the movement disorder.

Case History

An 18-year-old, right-handed student began to notice occasional involuntary movements of her right arm about 4 weeks prior to presentation. She described these movements as episodic writhing movements affecting her right forearm. On several occasions she had involuntary abduction of her arm while trying to write. She also complained of decreased dexterity in the right hand over the same period of time, which had made her writing less legible, and occasional slowness of her right leg, which occasionally interfered with walking. Her birth history and childhood had been unremarkable, and her cognition was normal with average performance at school. She did have a history of a single episode of loss of consciousness 6 years previously, which collateral history suggested was a seizure, and an EEG at that time showed a generalised epileptiform abnormality. She was commenced on sodium valproate and had no further seizures. This had been discontinued 3 years later with no recurrence. She had otherwise been very well. There was no family history of any illness, she was not taking any medication, and had no known allergies. Systematic questioning revealed a history of bloodstained bowel motions over the previous 2 weeks, with no associated pain, no change in stool frequency or consistency. She had not noted any mucous in her stools.

Examination on admission revealed occasional choreiform movements of her right arm. Gait appeared normal and steady, though some athetoid posturing of her right hand was noted as she walked. At rest she held her right hand in a flexed posture. She had marked reduction in the speed of rapidly alternating movements in her right (dominant) hand as compared to her left, but finger–nose coordination was unimpaired. Repeated tapping of her right foot was also significantly slower than on her left side. Her higher mental function was normal. All cranial nerves were normal. There was no evidence of cerebellar dysfunction. Tone, power, reflexes, coordination, and sensation were normal in all limbs. General physical examination was otherwise normal. She had no evidence of Kayser-Fleischer rings on ophthalmoscopy or subsequent slit-lamp examination.

Routine blood count, erythrocyte sedimentation rate (ESR), urea, creatinine, and electrolytes were all normal. Antistreptolysin O titres were normal. Coagulation studies (including proteins S and C, antithrombin III and anticardiolipin levels) were normal. Autoantibody screen was negative with the exception of anti-neutrophil cytoplasmic antibodies, which were positive in a titre of 1:1,280 with a perinuclear (p-ANCA) pattern. Cerebrospinal fluid examination was normal.

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Magnetic resonance imaging (MRI) brain (Fig. 1) showed multiple areas of signal void in the basal ganglia bilaterally, suggestive of vascular ectasia. Bilateral carotid and vertebral angiography showed non-filling of both anterior, middle, and posterior cerebral arteries with filling of numerous small collateral vessels basally. There was also evidence of marked dilatation of the external carotid circulation bilaterally. These findings were consistent with moya-moya syndrome (Figs. 2 and 3).

Colonoscopy showed evidence of proctitis but no other abnormality was seen to the caecum. Biopsies of the inflamed rectal mucosa showed evidence of diffuse cryptitis with focal crypt abscess formation, suggestive of ulcerative colitis. No granulomata were seen.

Following treatment with tetrabenazine 12.5 mg bd the choreo-athetoid movements improved considerably and her writing became much easier and clearer.

Discussion

Moya-moya is a rare disorder characterised by gradually progressive occlusion of arteries of the Circle of Willis with compensatory development of a network of dilated collateral vessels, which give rise to a characteristic angiographic appearance. Onset typically occurs in childhood or early adulthood and prognosis is variable. Neurological deficits may arise as a

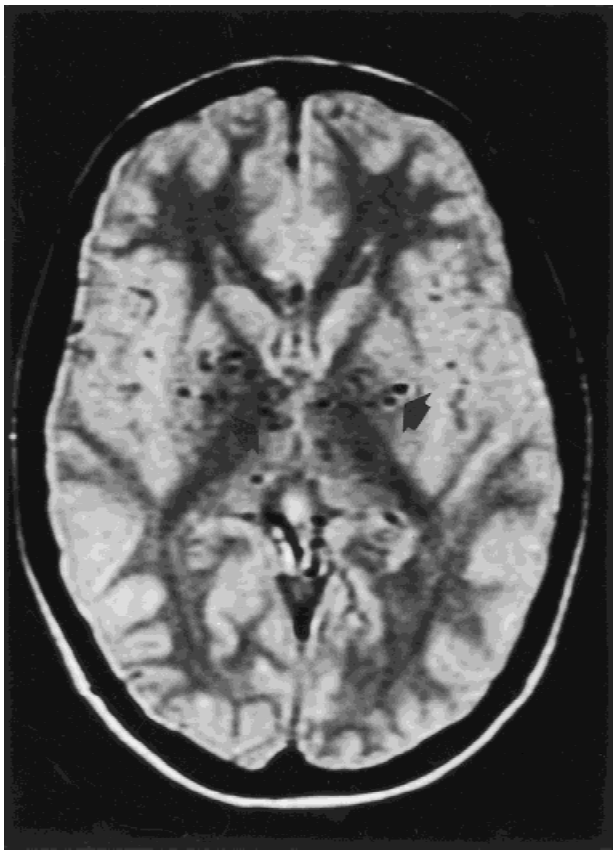

FIG. 1. T1-weighted axial magnetic resonance imaging (MRI) at the level of the basal ganglia showing multiple area of vascular ectasia (arrows).

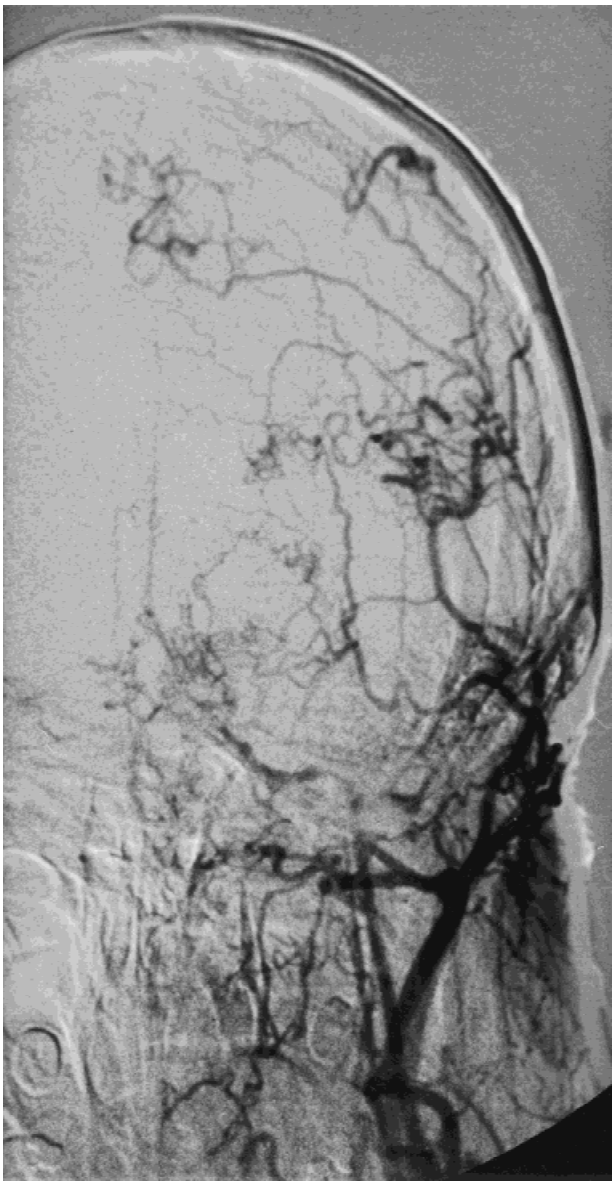

FIG. 2. Left carotid angiogram showing absence of filling of anterior or middle cerebral artery trunks and dilatation of external carotid circulation.

result of ischaemia from arterial occlusion, or haemorrhage from an ectatic collateral vessel. Neurological symptoms seen in moya-moya include cognitive decline, epilepsy, and stroke. Chorea has been described as a feature of moya-moya,[1,2] though involuntary movements are comparatively rare, occurring in two of 81 cases in one series.[3] Improvement of choreiform movements with steroid therapy has been described.[4] Moya-moya may occur as an idiopathic entity or secondary to systemic disease, and has been described in the setting of infection-related vasculitis (both leptospira-related[5] and tuberculous), systemic lupus erythematosus (SLE) with Sjogren's syndrome[6] and sarcoidosis.[7] Thrombophilia has also been found in cases of moya-moya,[8] but was not evident in this patient.

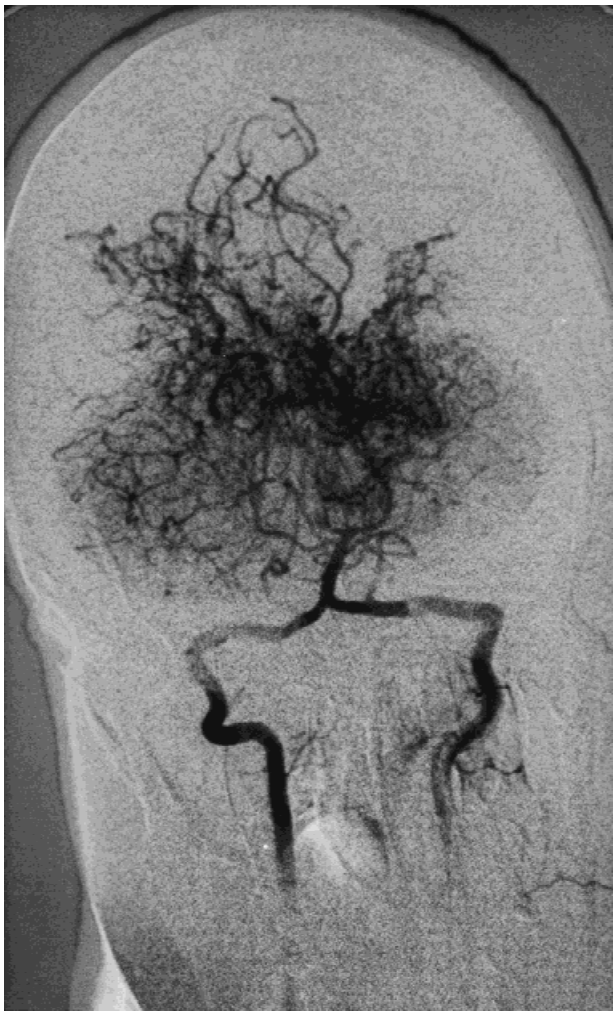

FIG. 3. Left vertebral angiogram showing poor filling of main vessels and extensive network of collaterals.

Ulcerative colitis may be associated with neurological manifestations in approximately 3% of cases.[9] The most common neurological sequelae are cerebrovascular accidents, epilepsy, and occasionally myelopathy. The increased incidence of stroke may be multifactorial, with hypercoagulability and possibly dehydration playing a part.[10] However, ulcerative colitis also has well-recognised associations with both systemic[11] and cerebral[12] vasculitis. Ulcerative colitis is associated with the presence of perinuclear antineutrophil cytoplasmic antibodies (pANCA) in 40–80% of cases.[13] The correlation between ANCA titres and disease activity in ulcerative colitis is not sufficient to be useful as a marker of disease activity. These antibodies target a variety of antigens, and it has been suggested that the autoantigens targeted by these antibodies differ from the target antigens seen in ANCA-associated necrotising vasculitis,[14] which would suggest the they are not necessarily a marker of systemic vasculitis. Cytoplasmic ANCA (cANCA) positivity in ulcerative colitis has been reported in a case with evidence of systemic vasculitis.[15]

No cases of moya-moya have previously been reported in association with ulcerative colitis, but the coexistence of these

two conditions suggests the possibility of a pathological process common to both. However, while it would be tempting to suggest that the vascular pathology underlying moya-moya in this woman was a vasculitis, we really have no evidence to support this.

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Deep Brain Stimulation of the Internal Pallidum did not Improve Chorea in a Patient With Neuro-Acanthocytosis

Abstract: We report the failure of bilateral globus pallidus internus deep brain stimulation to improve chorea in a patient with chorea-acanthocytosis. Prior to this surgery the patient had experienced a striking but short lived amelioration of symptoms with clozapine therapy.

Chorea-acanthocytosis is a rare familial and sporadic progressive neurological disease characterized by a wide variety of clinical features such as generalized chorea, orofaciolingual dyskinesias with dysphagia and dysarthria, muscle wasting, hyporeflexia, seizures, and behavioral and psychiatric disturbances.[1] The hallmark of the disorder is the presence of abnormal erythrocytes with spiky projections in the peripheral blood film and was first reported as a syndrome of chorea in 1967.[2,3]

Standard medical treatment with neuroleptics is very restricted and offers no satisfactory long-term benefit. Therefore, functional neurosurgical treatment can be considered an alternative for selected patients.

There is one case report in the literature describing successful treatment of hyperkinesias in chorea-acanthocytosis with bilateral posteroventral pallidotomy.[4] Unlike pallidotomy deep brain stimulation is safe in bilateral procedures, reversible, adaptable to the clinical situation[5,6] and therefore especially suited for a therapeutic trial in disorders of unknown responsiveness to functional stereotactic procedures.

Here we report a patient with chorea-acanthocytosis who initially responded dramatically to clozapine after failure of standard neuroleptic treatment. After limits of this therapy became evident, we performed stereotactic bilateral implantation of stimulation electrodes into the internal globus pallidus (GPi).

Case Report

A 38-year-old previously healthy male was referred to our unit with hyperkinesias of the lower limbs leading to progressive gait disturbance with frequent falls at the age of 35 years. In parallel, he developed difficulties eating due to frequent involuntary protrusions of the tongue forcing food out of the mouth during mastication. A few months later, a rapidly generalized chorea emerged with extensive oromandibular hyperkinesias leading to increasing self-mutilating behavior of the tongue and buccal mucosa. Within 1 year of onset of the symp-

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toms, the patient had lost 47 kg of weight due to severe dyskinesias and difficulties eating.

There was no history of seizures and no evidence for dementia or cognitive impairment. Involuntary vocalizations occurred, comprising grunting and whistling which the patient described to have begun around the age of 17, but which sharply increased after the emergence of chorea at the age of 35 years. Coprolalia was not reported.

The patient was the third child of healthy unrelated parents. Pregnancy, birth, and developmental milestones were unremarkable. Both parents died of unrelated causes in their seventh decade with medical records unavailable. An older brother of the patient was born with bilateral hearing impairment and died at the age of 33 years from an unclear sudden cardiac arrest. However, the patient remembers that his brother had similar vocalization tics starting at young age, but never developed involuntary hyperkinesias before death. An older sister of the patient is said to be unaffected, although contact was lost many years ago. The patient himself is not married and does not have children.

Neurological examination of the cachectic patient revealed infrequent involuntary vocalizations such as grunting and showed marked generalized chorea predominantly of the trunk with back arching and severe oromandibular hyperkinesias. The anterior parts of the tongue displayed signs of frequent biting, and feeding dystonia was present. Dysphagia and dysarthria were absent. The gait was hyperkinetic with dystonic posturing of both feet and poor balance. Postural reflexes were markedly impaired with retropulsion. There was generalized wasting of muscles with equinovarus deformity of both feet. Examination of the limbs revealed generalized chorea and mild bradykinesia. Tendon reflexes of the lower limbs were absent and plantar responses were silent. The right arm was ataxic and dysmetric. Sensory examination was normal.

Neuropsychological assessment showed a marked reactive depression. The patient performed well in the cognitive tests and no mental deficits were found. A progressive personality disorder evolved with obsessive-compulsive features and moderate distractability.

The diagnosis of chorea-acanthocytosis was made on clinical grounds with fresh blood smears containing between 20% and 25% acanthocytes compared to less than 3% in unaffected controls. This feature increased to over 90% after 6 hours aging. Blood group serology testing for Kell-antigene status was carried out according to standard techniques confirming the patient was McLeod phenotype-negative.

Genetic testing for Chorea Huntington and Dentato-Rubro-Pallido-Luysian-Atrophy (DRPLA) was negative. The creatinine kinase (CK) plasma level was elevated to 334 U/l (normal range <80 U/l) without any history of recent muscle trauma or seizures. Plasma lipid profiles and serum lipoprotein electrophoresis were in the normal range, thus excluding hypo- or abetalipoproteinaemia. Serum copper and coeruloplasmin levels were normal, making Wilson's disease unlikely.

CT and MRI scans showed no signs of generalized atrophy and no signal alterations within basal ganglia. However, mild dilatation of the lateral ventricles with slight bilateral atrophy of the head of the caudate was evident. Nerve conduction studies revealed a mild axonal neuropathy in the lower extremities. electrocardiography (ECG) and cardiac ultrasound were normal, thus excluding ventricular hypertrophy and cardiomyopathy.

Before admission to our hospital, the patient had been treated successively with a variety of neuroleptic drugs, including haloperidol, risperidone, olanzapine, sulpiride (600 mg/day), tiapride and perphenazine, buspirone (up to 60 mg/day) and diazepam, without any significant symptomatic improvement. He was then started on clozapine (200 mg/day) which initially almost completely suppressed the hyperkinesias. The feeding dystonia and tongue biting ceased with total restitution of the tongue, enabling the patient to masticate food in an undisturbed manner and allowing him to gain 40 kg weight in the following weeks. After 2 months almost free of symptoms, the chorea gradually returned without responding to an increased dosage of 300 mg/day clozapine and after another 10 weeks the symptoms had returned to the preclozapine status.

Surgical Procedure

The patient then gave informed consent for a therapeutic trial of pallidal stimulation to alleviate the hyperkinesias. He underwent bilateral implantation of a quadrupolar electrode (model DBS 3387, Medtronic Inc., Minneapolis, MN) into the GPi under local anesthesia using the Leibinger stereotactic system. The regular spaced (1.5 mm) quadrupolar electrode, which we also routinely use for pallidal stimulation in Parkinson's disease, was chosen to cover a larger tissue volume. Targeting and electrode implantation were performed as described elsewhere.[6] For physiological target verification we used electrical macrostimulation along the electrode trajectory, starting 6 mm above the intended target and extending up to 4 mm below. No microelectrode recordings were performed intraoperatively. As an immediate effect after placement of the electrodes at the target point (GPi right: 3.2 mm anterior to the midcommisural point [MCP], 5 mm inferior to the intercommisural line [ICL], 19.4 mm lateral to the midline of the third ventricle; GPi left: 3.2 mm anterior to MCP, 5 mm inferior to ICL, 19.7 mm lateral to the midline of the third ventricle) according to the atlas of Schaltenbrand and Wahren[7] the generalized chorea almost completely disappeared. One to 2 mm below the target point, stimulation with 0.1 ms pulse width, 130 Hz and up to 3.5 V started to elicit phosphene sensations in the contralateral visual field without producing capsular responses. Postoperatively, the benefit from microlesioning due to the electrode placement faded within less than 1 week and the bilateral stimulation via the provisional external lead was initiated.

Effects of Acute and Chronic Gpi Stimulation

In contrast to the excellent perioperative result with marked reduction of the hyperkinesias due to the microlesioning effect after bilateral electrode implantation, neither acute nor prolonged high-frequency stimulation of the GPi could reproduce the initial benefit. Each electrode contact was tested as active cathode in a bipolar setting. Raising the stimulation amplitude and pulse width up to a maximum of 10 V and 450 μsec (185 Hz), as far as tolerated with respect to side effects, did not reveal a reproducible reduction of chorea for any bipolar electrode combination during acute testing. Instead, increasing side effects such as pyramidal signs (facial hemispasms), optic sensations, scotoma, and psychovegetative phenomena (nausea and epigastric sensations) were noted, and confirmed physiologically the correct positioning of the stimulating electrodes. Increasing the frequency of stimulation up to 1,000 Hz within the therapeutic amplitude range resulted in deterioration of the

choreatic movements without inducing other side effects. An alternatively performed low-frequency stimulation (10–50 Hz) did not show any reproducible positive effects on the hyperkinesia either, but led to reproducible deterioration of speech and gait. We then tried chronic stimulation with the bipolar electrode combination on each side, eliciting phosphene sensations at lowest threshold and using stimulation parameters just below induction of visual side effects. The trial was terminated after 20 days of continuous stimulation without notable reduction of chorea.

In conclusion, there was no benefit from high- or low-frequency stimulation of the GPi. In contrast stimulation at frequencies >500 Hz led to deterioration of the symptoms. Consequently the leads were explanted after 3 weeks of extensive testing because no consistent clinical effect could be elicited.

Since microlesioning due to the electrode implantation initially improved the hyperkinesias, we discussed the possibility of a staged bilateral pallidotomy with the patient as final treatment option. The patient was reluctant to repeated surgical intervention at that time and therapy with clozapine was restituted but proved to be insufficient. Choreatiform hyperkinesias deteriorated and lip biting and vocalizations reoccurred. The patient was then started on tetrabenazine 75 mg/day as an add-on therapy with a mild additional benefit. Currently the patient is almost to the point of needing permanent medical and nursing care due to his severe gait disorder and feeding problems.

Discussion

To our knowledge, this is the first report of drug-resistant chorea-acanthocytosis treated with bilateral high-frequency stimulation of the Gpi. Pallidotomy and pallidal deep brain stimulation are highly effective treatments for levodopa-induced dyskinesias in Parkinson's disease, which may present with ballistic, choreatic, athetoid and dystonic features.[6,8] The benefical effect of both procedures is possibly due to releasing the motor thalamus from abnormal neuronal discharge patterns in GPi associated with the dyskinetic "on"-state in Parkinson's disease.[9] The importance of the internal pallidum in the pathophysiology of hyperkinesias in general is supported by recent reports on the improvement of idiopathic dystonia with pallidotomy or pallidal stimulation.[10,11] A case report of successful treatment of hyperkinesias in chorea-acanthocytosis by posteroventral pallidotomy suggested that also symptomatic chorea might benefit from pallidal surgery.[4] Since the advantages of stimulation compared to pallidotomy lie in its potential reversibility, adaptability to the clinical course, and reduced likelihood of permanent side effects, we performed high-frequency stimulation of the GPi in a patient with severe chorea-acanthocytosis whose symptoms were drug-resistant, although he initially had obtained substantial benefit from the application of clozapine. The positioning of quadrupolar electrodes according to standard protocols described by Volkmann et al.[6]

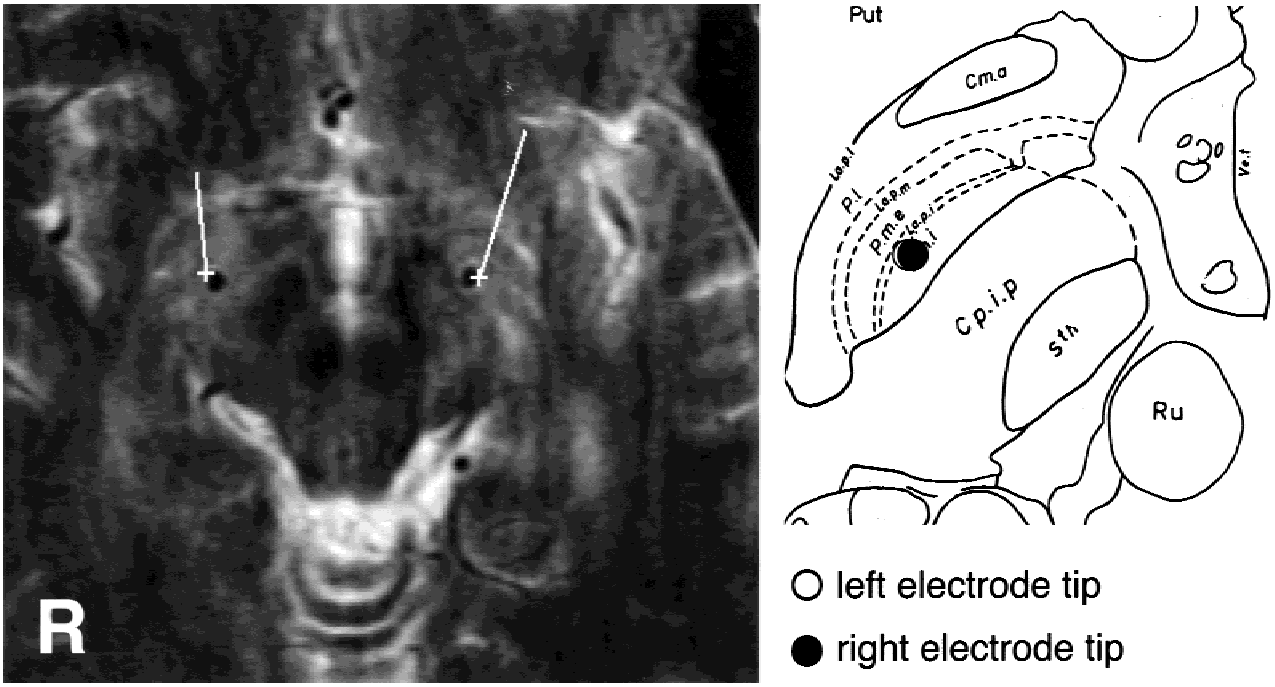

FIG. 1. Left: Postoperative axial magnetic resonance imaging (MRI) parallel to the anterior commissure-posterior commissure (AC-PC) plane displaying the position of the electrode tips. Superimposed are the planned trajectories of the leads with a crosses indicating the target point and a line indicating direction of the lead. **Right:** Corresponding horizontal plate of the atlas of Schaltenbrand and Wahren (4.5 mm below the AC-PC plane). The position of left and right distal electrode pole is indicated based on stereotactic coordinates derived from intraoperative teleradiographic X-ray controls and ventriculography. Cp.i.p, capsula interna, posterior; Cm.a, commissura anterior; La.p.m, lamina pallidum mediale; La.p.i., lamina pallidum internum; P.l, pallidum laterale; P.m.e, pallidum mediale externum; P.m.i, pallidum mediale internum; Put, putamen; Ru, nucleus ruber; Sth, nucleus subthalamicus; Ve.t, ventriculus.

was performed without any adverse effects and the immediate intraoperative arrest of hyperkinesias demonstrated the correct targeting.

It remains unclear why postoperative high-frequency stimulation could not reproduce the initial benefit. An electrode dislocation could be excluded by matching a postoperative MRI with the intraoperative CT and ventriculography based surgical plan (Fig. 1). A possible explantation would be that effective treatment of chorea requires a rather large lesion within the GPi and that the field of stimulation was not sufficiently large to chronically suppress the hyperkinesias. For several reasons, we did not believe that prolonged stimulation over several weeks would have changed the clinical picture. Delayed responses of hyperkinetic symptoms to pallidotomy or chronic stimulation have been described in dystonia.[12,13] In our own experience, however, mobile (choreatic or myoclonic) features of dystonia promptly respond to pallidal stimulation very much the same way as choreatic or ballistic dyskinesias in Parkinson's disease. The remaining fixed dystonic component may improve over a longer time period. Moreover, a different time course of clinical responses to microlesioning and stimulation appeared unlikely to us. Hence, we saw no rationale to implant internal pulse generators, after 3 weeks of extensive testing failed to demonstrate beneficial effects; moreover, chronic low- and high-frequency stimulation (>500 Hz) led to deterioration of the symptoms.

In conclusion, this is a single case report of a patient with chorea-acanthocytosis who failed to respond to deep brain stimulation of the internal globus pallidus.

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Permanent Cerebellar Toxicity of Cytosine Arabinoside (Ara C) in a Young Woman

Abstract: This report provides the first videotape example of a patient with permanent cerebellar ataxia from high dose cytosine arabinoside. This case was unusual in that the patient was young, the effects are seemingly permanent and severe, and corticospinal tract damage also occurred. Early recognition to stop drug administration remains the only method to reduce risk.

High dose cysosine arabinoside therapy (HDAC) given for acute nonlymphocytic leukemia has been well known to cause cerebellar toxicity.[1]This is usually transient and mild but may be severe and permanent. Autopsies have revealed Purkinje cells as the most vulnerable brain cell, but minor and patchy loss in molecular and granular layers of the cerebellum occurs as well. The deep cerebellar nuclei are only minimally affected.[1] Several neurological complications have been described with both intravenous(IV) and intrathecal administration of Ara C (Tables 1,2). No case has been published with videotape, nor has any case with permanent corticospinal tract signs from IV HDAC been reported. We believe this report also describes the longest follow-up of a case of HDAC neurological toxicity.

Case

At the age of 29, in 1991, this previously healthy woman was diagnosed with acute myelogenous leukemia. Renal and liver

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A videotape accompanies this article.

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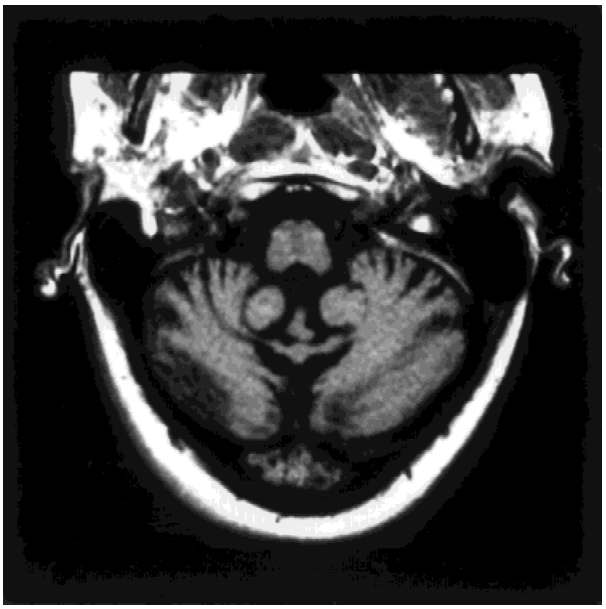

Fig. 1. 1999 MRI of brain showing cerebellar atrophy.

functions were normal. Her neurological examination was normal. Baseline neuroimaging was not obtained. Her body surface area was 1.7 m^2. She was treated with adriamycin 76 mg IV on days 1–3, and intravenous Ara C 340 mg per day via continuous infusion for five days. Twenty-seven days after her last Ara C dose she was started on Ara C 5.1gms every 12 hours on alternate days (3gm/m2). After five doses (total dose of 27.2 gms) she developed blurred vision, slurred speech, dysmetria, dysphagia, nystagmus, and photo phobia, and her Ara C was stopped.

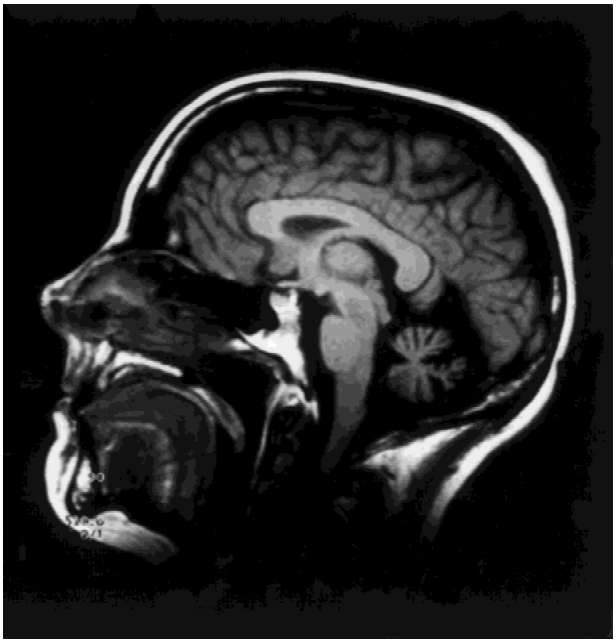

Fig. 2. 1999 MRI of brain showing cerebellar atrophy.

TABLE 1. *Neurologic toxicity of high dose systemic ARA-C*

Blindness[8]
Cerebellar Syndrome[1–3]
Encephalopathy (lethargy, confusion, aphasia)[9]
Generalized Myoclonus[4]
Oculomotor Weakness[10]
Painful Legs & Moving Toes[11]
Parkinsonism[2]
Seizures[9]

During her chemotherapy she also received: metoclopramide 50mg IV given on four occasions over five weeks; prochlorperazine 10 mg IM on three occasions and 10mg PO once over six weeks; trifluoperazine 5.0 mg IV once. No extrapyramidal reactions occurred. Brain CT, MRI, and spinal fluid analysis were all normal. She also reported the development of episodic flurries of involuntary jaw closure occurring for seconds at a time, once or twice daily on the average. She improved gradually until reaching a plateau, with stable ataxia and jaw movements, after about three months. The jaw movements were seen by another neurologist who described them as myoclonic. These were never seen by the author. On examination at age 37 her mental status was normal aside from cerebellar ataxic speech. Cranial nerves were normal except for saccadic pursuit and difficulty initiating eye movements without blinking. There was no nystagmus. The limbs were of normal strength. There was spastic tone in the legs. Ataxia was moderate in the arms and severe in the legs. Reflexes were brisk and symmetric. There was a Babinski reflex on the left. Sensory exam was normal. She required Canadian crutches to walk due to severe ataxia and spasticity. Adventitious jaw movements were not present. A trial of buspirone 30 mg twice daily did not improve gait. Valproic acid improved the jaw closures.

Discussion

This case is unusual because of the young age of the patient. Most patients with cerebellar toxicity from HDAC are older.[2,3] It is also unusual in its severity.[2,3] The presence of corticospinal signs and involuntary focal movements, presumably jaw myoclonus, have not been described, although a single case of generalized myoclonus was reported.[4] Since the abnormal jaw movements were present only rarely, they were not seen. No evidence of tardive dyskinesia or tardive dystonia was present. While tardive myoclonus is a consideration, the low cumulative dose, the brief exposure to a neuroleptic, and the rarity of the syndrome make this unlikely. Risk factors for the development of this syndrome, other than older age, are debated.[5] Possible risk factors include: cumulative dose, previous neurologic abnormalities, and liver and renal dysfunction.[5,6] Since Ara C is still required for the treatment of certain malignancies, and the mechanism of the toxicity is unknown, future cases of Ara-C

TABLE 2. *Neurologic toxicity of intrathecal (IV) ARA-C*

Cauda Equina Syndrome[13]
Encephalopathy[14]
Myelopathy[13]
Seizures[15]

toxicity are to be anticipated. Early recognition to forestall further toxicity is crucial if cumulative dose increases risk. SPECT scanning has been reported to be more sensitive than MRI in identifying abnormalities,[7] but may reveal abnormalities in clinically normal subjects who do not develop toxicity. It is therefore unclear if neurological examination or SPECT scanning is the screening test of choice.

Legend to the Videotape

1999 Videotape. Note that the patient has gum in her mouth. She had no adventitious jaw or tongue movements at the time.

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Restless Legs Syndrome in an Asian Population: A Study in Singapore

Abstract: In face-to-face interviews, we examined 157 consecutive individuals aged 55 years and older, selected from the general population in Singapore, and 1,000 consecutive individuals aged 21 years and older, from a primary healthcare center. Based on the IRLSSG criteria, the prevalence of restless leg syndrome (RLS) was 0.6% and 0.1%, respectively.

Restless legs syndrome (RLS), characterised by an irresistible urge to move the lower extremities at night,[1,2] is often a poorly recognised and underdiagnosed condition. Walters et al.[3] highlighted that more than half of RLS patients were previously misdiagnosed or given no diagnosis. Studies suggest that the prevalence of RLS varies amongst different populations.[4–12] Two recent population-based studies estimated a prevalence of about 10% in Caucasian populations.[4,5] While no "RLS genes" have been found, familial RLS demonstrating autosomal dominant inheritance has been reported.[13,14] This suggests that there may be potential genetic predisposition and/or gene-enviromental interactions leading to RLS. Hence, study of prevalence and risk factors in different ethnic populations could further our understanding of the underlying pathogenesis. To our knowledge, there has been no epidemiologic data on the prevalence and risk factors of RLS in an Asian population. The aim of this study was to determine the prevalence and risk factors in Singapore, a republic in South East Asia with a 3.5 million population.

Methods

This study was conducted in two parts. The first involved individuals who participated in our local Health Screening for The Elderly Programme. Only those who were 55 years of age and above, and with no past medical history of hypertension, diabetes mellitus, chronic heart disease, and cerebrovascular accident were eligible for this programme. Out of 20,000 people resident in a new town (BN), 5,713 were of age 55 years and above. An estimated 500 satisfied the inclusion criteria for this programme, which included a general clinical examination, body mass index determination, blood pressure assessment, fasting blood sugar level and lipids, a neurological examination, and an ophthalmic examination. Based on previous experiences, an estimated 200 selected individuals were expected to participate in this programme. A total of 157 out of the 500

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eligible participated. All participants underwent a neurological examination and were interviewed by RLS-trained neurologists. The four minimal criteria recommended by the International Restless Legs Syndrome Study Group (IRLSSG) were used in the assessment for RLS: (1) desire to move the legs associated with paresthesias; (2) motor restlessness; (3) worse at rest with relief by activity; and (4) worse at night.[2] Only those who gave positive answers to all four questions were classified as having RLS. Information of prior psychiatric illness, exposure to neuroleptics, alcohol intake, smoking, and past medical illnesses was obtained. The second part of the study was carried out in a separate town (T). One thousand consecutive individuals of age 21 years and above who attended a primary outpatient healthcare center in this town were studied with similar clinical examination and interviews, as described above.

Results

Out of the 157 participants in the Health Screening for The Elderly Programme in town BN, there were 69 men (44%) and 88 women (56%), with mean age of 64.2 ± 7.3 (standard deviation) years (range 55 to 93). The prevalence of hypertension, diabetes mellitus, and smoking was: 33%, 1.5%, and 1.5%, respectively. Only one (0.6%) of the 157 participants had RLS. He was 69 years of age, and did not have diabetes mellitus, hypertension, anaemia, or clinical evidence of peripheral neuropathy or parkinsonism.

There were 480 men (48%) and 520 women (52%), with mean age of 41 ± 14.9 years (range 22 to 91) who were examined in town T. The prevalence of hypertension, diabetes mellitus, and smoking was: 16.6%, 5.1%, and 11.0%, respectively. Seven hundred and seventy-three (77.3%) of the 1,000 study population did not have any chronic medical illness determined by history and physical examination. Only one (0.1%) individual satisfied the criteria for RLS. She was 36 years of age and did not have any associated medical problems, except hyperlipidaemia.

Due to the low prevalence of RLS, risk factor analysis could not be meaningfully performed.

Discussion

We found a prevalence of 0.6% of RLS in a healthy general population 55 years of age and older. Separately, we found a prevalence of 0.1% of RLS in a primary healthcare centre population aged 21 years and older.

Published prevalence estimations of RLS have varied considerably between 2.5% and 29%.[4–12] The main reasons are likely due to differences in the study populations and the use of different diagnostic criteria and methodology. To date, there has only been one "face-to-face" population-based study which utilised the minimal diagnostic criteria for RLS as recommended by the IRLSSG.[2] We support the use of standardized methodology, which can facilitate investigators to meaningfully compare the prevalence and risk factors of RLS between different populations and geographical locations.

In a recent telephone survey of a predominantly Caucasian population in Kentucky (USA), Phillips et al.[5] found an age-adjusted prevalence of restless leg symptoms to be 10%. In a population "face-to-face" study by Rothdach et al.,[4] the prevalence of RLS was 9.8% in a German population aged 65 years and older. Our study, utilising similar methodology, revealed a much lower prevalence in both a healthy general population (0.6%) and a primary healthcare patient population (0.1%). The low prevalence of RLS in our study population precluded analysis of predisposing risk factors or associations. None of the RLS-positive individuals in our study had concurrent diabetes, hypertension, anaemia, or parkinsonism, and none gave a history of cigarette smoking or significant alcohol intake.

The presence of RLS familial clustering consistent with an autosomal dominant inheritance with varying degree of penetration suggests a genetic predisposition to RLS in some individuals. This observation is reinforced by reports of RLS in certain familial forms of diseases such as Charcot-Marie-Tooth (CMT2)[15] and autosomal dominant cerebellar ataxia.[16] While no susceptibility genes have been mapped, the possibility of gene-enviromental interactions leading to RLS cannot be excluded. This is supported by our findings, and by others,[4–12] that race and geographical locations can contribute to a vast difference in the prevalence of RLS.

One potential limitation in generalising our study results is that the participants were selected from a relatively healthy population based study group, and those with medical conditions such as diabetes, hypertension, and ischaemic heart disease were not included. This may have contributed to the lower than expected RLS prevalence. However, the association of RLS with these conditions has not been proven. Furthermore, the low RLS prevalence was supported by our study of a large primary healthcare adult population-based group, wherein every study subject was personally examined in a face-to-face interview, reducing the risk of underdiagnosis. It must be highlighted that the primary healthcare population was relatively young, with mean and median age of 41 and 35 years, respectively. This is consistent with the average age of our adult population.[17] In addition, the prevalence of hypertension (16.6%), diabetes mellitus (5.1%), and smoking (11.0%) was similar to that in the 30- to 49-year age group of our general population,[18] indicating a good sampling of this age group in the general population. The much lower prevalence (0.1%) in our healthcare patient population compared to our older general population (55 years and above; 0.6%) was compatible with studies which showed a higher prevalence of RLS in the elderly.[6]

In conclusion, the prevalence of RLS is low in Singapore, supporting a frequently held observation that RLS is relatively uncommon in Asians. Studies in other Asian populations would be useful to confirm our findings. Further research could examine for genetic differences, and gene-enviromental factors which underpin this lower prevalence of RLS.

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Piribedil for Restless Legs Syndrome: A Pilot Study

Abstract: Thirteen consecutive patients with restless legs syndrome (RLS) were treated with piribedil and were rated using an RLS rating scale (0–10) and subjective response (0–100%); 11/13 (85%) had improvement of their mean RLS scores with subjective response ranging from 30% to 100% (mean 74.6%). This pilot study suggests that piribedil is effective for RLS.

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Background

The restless legs syndrome (RLS) is characterized by paresthesias or dysesthesias, a desire to move the limbs, nocturnal exacerbation or appearance of symptoms, motor restlessness, periodic limb movements, and sleep disturbance.[1] Dopamine deficiency is postulated based on the effectiveness of dopaminergic drugs.[2] Levodopa benefits RLS, but often leads to augmentation and rebound. Piribedil is a direct-acting, selective D_2/D_3 dopamine agonist that is useful in early and advanced Parkinson's disease (PD).[3] This paper aims to describe the therapeutic effects of piribedil in 13 patients with RLS.

Methods

Patients

Thirteen consecutive RLS patients (seven males, six females) were recruited and followed up in this open label trial from February 1999 to May 2000 (Table 1). All 13 fulfilled the minimal criteria for RLS set by the International RLS Study Group.[1] The mean age was 66 (range 39–87); 3/13 (23%) had idiopathic RLS; 4/13 (31%) had PD; and 6/13 (46%) had clinical signs of neuropathy (sensory deficits in the lower limbs). Of the six with neuropathy, one had uremia and was on regular dialysis, and two had electromyography done (one showed bilateral L5-S1 radiculopathy, while the other had findings suggestive of a diffuse, symmetric, sensorimotor, axonal polyneuropathy). No patient had iron deficiency. Five out of 13 were de novo cases of RLS (no past or current treatment for RLS); 3/13 were taking levodopa preparations (for PD), with insufficient benefits for RLS; 2/13 were receiving clonazepam, while 1/13 was taking zolpidem with still significant symptoms.

Medications

For patients with only nocturnal symptoms, piribedil (Trivastal retard 50) was administered as one tablet at bedtime, and was increased by one tablet every 5–7 days until significant benefits were perceived, or intolerable side effects were noted. If the patient is unable to tolerate one tablet per day, a dose of half a tablet at bedtime was used. For patients with daytime symptoms as well, piribedil was given one hour before typical onset of symptoms. In order to prevent nausea and vomiting, 10–20 mg of domperidone was given 30 minutes before every dose of piribedil. Those who were taking other RLS medications at the initiation of the study were instructed to maintain a constant dose of these drugs all throughout the trial.

Outcome Variables

The patients were rated using an RLS scale (0–10) pre- and post-treatment with piribedil. [4] This RLS scale evaluates the following factors: frequency of symptoms (0 = never; 1 = less than once a month; 2 = less than once a week; 3 = at least once a week; 4 = almost every night); severity (0 = no distress; 1 = mild; 2 = moderate; 3 = severe); and duration of symptoms (0 = no time or a few seconds; 1 = < 30 minutes; 2 = > 30 minutes but <1 hour; 3 = > 1 hour). The patient's subjective improvement was also assessed using a continuous numerical scale from 0% (no response) to 100% (complete resolution of symptoms).

TABLE 1. *Summary of patient data*

Patient no.	Pre-tx RLS score	Post-tx RLS score	Duration of response (months)	Percent subjective response	Piribedil dose (mg/day)	Cause of RLS	Remarks	Concurrent treatment
Responders								
1	10	3	8+	90	100	PD		Levodopa
2	9	0	14+	100	100	PD		
3	10	0	5	100	25	PD		Levodopa
4	10	0	14+	100	50	Neuropathy	PN on exam	
5	10	0	13+	100	150	Idiopathic		
6	10	0	4.5+	100	50	Polyradiculopathy	LSPR on exam and on EMG	
7	8	5	1	30	50	Neuropathy	PN on exam	
8	10	0	9+	100	50	Neuropathy	PN on exam	Clonazepam
9	10	0	14+	100	100	Idiopathic		
10	10	0	13+	100	350	Neuropathy	Severe PN exam; (+)uremia	
11	10	6	15	50	150	PD		Levodopa
Nonresponders								
12	10	10	0	0	50	Idiopathic	On clonazepam	Clonazepam
13	10	10	0	0	50	Neuropathy	Severe PN on exam and on EMG	Zolpidem

PD, Parkinson's disease; PN, Peripheral neuropathy; LSPR, Lumbosacral polyradiculopathy; Pre-Tx, pretreatment; Post-Tx, post-treatment; +, denotes continuing response; EMG, .

Statistical Analyses

The primary outcome variables were the change in RLS scores post-treatment, and the subjective RLS improvement rating. Pre- and post-treatment RLS scores were compared using Wilcoxon's signed rank test. The association between the subjective improvement and RLS score was assessed using Spearman's rank correlation. The relationship between RLS scores or subjective improvement with the presence of neuropathy or PD was ascertained using the Mann-Whitney U-test.

Results

Eleven of 13 patients (85%) reported subjective benefit from piribedil, with a mean subjective improvement of 74.6% (range 0–100%); 8/13 (62%) had 100% response (Table 1). The RLS score dropped from a mean of 9.97 pretreatment to 2.62 post-treatment ($P = 0.003$); 11/13 had a pretreatment score of 10, while 8/13 had a post-treatment score of zero. There was a strong correlation between subjective improvement and RLS score (Rs = 0.9533; $P < 0.001$). There was no association between RLS scores and neuropathy ($P = 0.697$) or *P*D ($P = 0.614$), nor between subjective improvement and neuropathy ($P = 0.935$) or PD ($P = 1.0$). The effective dose ranged from 25 to 350 mg/day (mean dose of 120 mg/day). Ten out of 11 responders benefited from low dose piribedil (150 mg/day or less), while 1/11 (with severe uremia and neuropathy) needed 350 mg/day. The duration of response for the 11 responders has ranged from 1 to 15 months (mean 10 months); 7/11 continue to have sustained benefit as of last follow-up. No patient presented with augmentation (earlier onset of RLS symptoms during the evening, shorter latency to onset after assuming a restful position, increased intensity, or extension of the symptoms to the upper body). Two of the 11 responders stopped piribedil (patient no. 3 after 5 months of treatment, and patient no. 7 after 1 month) despite positive results (and no side effects) because of financial reasons. They decided to try alternative treatment (herbs) or physical measures (massage, elastic stockings, or vibration devices) for their RLS symptoms. Another responder (patient no. 11) ceased to benefit from piribedil after 15 months of therapy, and was switched to other medications.

Three of the 13 patients experienced side effects with piribedil; two decided to stop the medication. Patient no. 12 (a non-responder) experienced sleepiness and mental clouding at a dose of 50 mg/day of piribedil and stopped the study medication. This patient, however, did not report sudden sleep attacks. Patient no. 8 (a responder) stopped the drug after 9 months of therapy due to chest pain and palpitations despite a low dose of piribedil (50 mg/day). None experienced nausea or vomiting when piribedil was preceded by treatment with domperidone (10–20 mg before every dose of piribedil).

Discussion

This open label trial shows that the dopamine agonist piribedil is effective in RLS, even at 25 mg per day. The majority have responded to 50 to 100 mg/day. Only one individual (patient no. 10) needed a high dose (of 350 mg/day); he had the most severe RLS symptoms, severe uremic polyneuropathy, and was receiving dialysis twice weekly. The benefit is long-term in most individuals. Six responders have had more than a year of sustained response from the drug. In general, piribedil is well tolerated by RLS patients. Nausea and vomiting are effectively prevented by pretreatment with 10–20 mg of domperidone.

Currently, nonlevodopa dopaminergic agents are the treatment of choice for RLS because of their effectiveness at low doses, favorable side effect profiles at such doses, long-term efficacy, and very low (or nil) occurrence of rebound and augmentation with chronic use. Pergolide[5] (a D_1/D_2 dopamine agonist) and pramipexole[6] (a D_2/D_3 dopamine agonist) have been shown to improve RLS symptoms in double-blind, placebo-controlled studies. Ropinirole[7] (a D_2 agonist) was shown to be effective in RLS in an open label trial. Amantadine was recently reported to have long-term benefits in idiopathic and neuropathic RLS, even in patients with severe symptoms.[8] Although its mechanism of action is unclear, amantadine is postulated to enhance presynaptic release of dopamine. Nocturnal subcutaneous infusion of apomorphine may offer dramatic improvement of RLS symptoms and sleep, but is inconvenient and impractical to administer chronically.[9] Pramipexole is thought by some experts to be the most potent and most efficacious dopaminergic agent ever tested for RLS.[6] Unlike other dopa-

mine agonists, pramipexole stimulates dopamine D_3 receptors; this suggests that D_3 receptors may play a major role in the pathophysiology of RLS. Piribedil, like pramipexole, is also a dopamine D_3 receptor agonist.[3] Thus, this pilot study appears to corroborate the hypothesis that D_3 receptors may play an important role in RLS. In some countries, like the Philippines, piribedil is the only readily available dopamine agonist. Thus, piribedil can be used as a first-line drug for the treatment of RLS.

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