Movement Disorders
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Letters to the Editor Related to New Topics

REM Dependant Periodic Stereotypical Movements

Video 

The majority of motor parasomnias and almost all nocturnal seizures occur out of NREM sleep.[1,2] The only well-defined disorders that are exclusively REM related are REM sleep behavior disorder (RBD)[3] and painful nocturnal erections. Catathrenia is a disorder that arises mostly but not exclusively out of REM.[4] There is also a single case report of periodic movements in sleep (PMS) occurring predominantly in REM.[5] Otherwise, the medical literature is sparse on reports of REM dependant motor parasomnias. We report an unusual case of a stereotypical REM sleep motor parasomnia.

A 54-year-old man presented with a 5-year history of complex, stereotypical, and nocturnal movements that were disruptive to his wife's sleep and minimally to his as well. They tended to occur several times a week usually 4 hours into sleep and repeated approximately every 30 seconds for about an hour. Their semiology, according to his wife, did not change from night to night. He aroused easily from these and was immediately alert without any dream recall. These were not triggered either by sleep deprivation or stress. The next day he was not sleepy (Epworth sleepiness scale score 5/24), but fatigued and had sore upper extremities and neck muscles.

Medical and family histories were noncontributory. He was only on antihypertensives and allopurinol. Physical examination was unremarkable.

An MRI of the brain was normal. A polysomnogram (PSG) was done with 16 EEG channels, 2 EOG channels, 2 mentalis EMG channels, thermistor, pressure transducer, chest and abdomen effort belts, oximetry, 1 channel ECG, 2 bilateral tibialis anterior (TA) EMG channels, and a snore microphone. The PSG was significant only for mild positional obstructive sleep apnea with a total AHI of 10/hr, supine AHI of 22/hr, and lateral AHI of 1/hr. No PLMS occurred. No events occurred on the night of the PSG and his muscle tone was appropriately suppressed in REM sleep.

The patient was monitored overnight. The previous montage was replicated with the exception of the TA electrodes, snore microphone, and the thermistor. Thirteen distinct typical events, of 3 seconds duration each, were captured, all arising from REM sleep. Three of the events occurred in the first REM period of the night at a frequency of one every 30 seconds. Three of the second REM period with a frequency of 1 per minute, another two at the beginning of the third and last REM period one per 30-second epoch and finally five events in the middle of the third REM period 11 minutes after the previous two, with a frequency of one every 45 seconds. The clinical semiology was as follows: the subject was in the lateral position and there was no correlation to respiratory events. There was a rapid flexion of the neck with symmetrical adduction of both shoulders and flexion of both elbows (see Video). No lower extremity movements were associated with these events. These events were all associated with arousals. They were not associated with phasic REM. There was neither periodicity nor epileptiform abnormalities associated with them. In between the events, muscle tone remained suppressed and was only briefly elevated during the events themselves.

He was prescribed clonazepam at bedtime and this controlled his symptoms completely, including his wife's observations and his own fatigue, and continues to do so 2 years on.

It is highly unlikely that our subject's events are seizures because they occur exclusively out of REM sleep and are not associated with any EEG abnormalities. Sleep-related epilepsy never arises exclusively from REM sleep.[2] These events occurred independent of the patient's respiratory events. The lack of persistently increased muscle tone in REM on two separate nights makes RBD unlikely as the diagnostic criteria include demonstrating elevated chin muscle tone on a single overnight PSG.[3] This is not likely fragmentary hypnic myoclonus, a primarily NREM sleep phenomenon consisting of small myoclonic twitches and fasciculation unlike the complex stereotypical movements of our patient.[1] PLMD is unlikely because of the exclusivity in REM sleep, lack of the characteristic periodicity on PSG, and lack of involvement of the lower extremities.[6]

This unusual REM-dependant movement phenomenon most likely represents a more complex form of PMS as described by Mizuma and Sakamoto, with the difference being that in the latter case, the movements were only brief twitches and present to a lesser degree in NREM sleep.[5] In our case, the movements were complex, stereotypical, and exclusively out of REM sleep.

The paucity of events is unlikely to explain daytime fatigue but subjectively fatigue did improve after these events were controlled.

Further awareness of unusual REM phenomena may lead to better understanding of motor control in REM and the impact of REM disruption on daytime symptoms.

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Deep Brain Stimulation of the Ventral Intermediate Thalamic Nucleus for Severe Tremor in Anti-MAG Neuropathy

Video

A 55-year-old left-handed man, without family history of tremor, was referred for distal limb paresthesias progressing for several weeks. Neurological examination showed sensory ataxia, distal sensory loss, distal lower limb weakness, abolished deep tendon reflexes, and slight postural tremor of upper limbs. Electrophysiological studies confirmed peripheral neuropathy with distal demyelination. CSF proteins were elevated (1.2 g/L). A monoclonal IgM gammopathy of undetermined significance was detected (normal bone marrow biopsy and chest and abdominal CT-scan). Sural nerve biopsy showed a demyelinating process, deposits of IgM on peripheral nerve myelin and peripheral myelin widening on electronic microscopy. Positive antimyelin-associated glycoprotein IgM antibodies (anti-MAG) confirmed the diagnosis of polyneuropathy associated with anti-MAG (PNMAG). Treatment by intravenous immunoglobulins, cyclophosphamide, and rituximab were administrated successively over the following years. Sensory ataxia and motor weakness improved slightly but the tremor progressively worsened. The tremor was present in upper limbs during posture and action, sometimes persisted during rest and was unchanged after consummation of alcoholic beverages. Tremor did not respond to symptomatic treatments including propanolol (up to 1200 mg/day), primidone (up to 500 mg/day), gabapentin (up to 2000 mg/day), pregabalin (up to 300 mg/L), topiramate (up to 150 mg/day), alprazolam (up to 1500 mg/day), and L-dopa (up to 300 mg/day) in monotherapy or combination. Only oral clonazepam (1.2 mg/day) led to some relief. Three years after disease onset, tremor had become severe and interfered with daily activities like feeding, dressing, and writing. Bilateral deep brain stimulation (DBS) of the ventral intermediate thalamic nucleus (VIM) was proposed. Electrodes (DBS 3389, Medtronic, Minneapolis, MN) were implanted stereotactically under local anesthesia after microelectrode recording (without specific rhythmic activities) and peroperative stimulation in the VIM, and connected to a subcutaneous stimulator (Kinetra, Medtronic). Postoperative MRI confirmed the location of the electrodes in the VIM. Chronic monopolar stimulation parameters were: 130 Hz, left: contact 1 negative, 3.0V, 90 microseconds; right: contact 4 negative, 3.0 V, 60 microseconds.

The tremor dramatically improved when stimulation was switched on (see Fig. 1, Supporting Information Video) leading to improvement of quality of life. The Overall Neuropathy Limitations Scale[1] score for upper limbs decreased from 3 to 1. Voltage increase was limited by the occurrence of

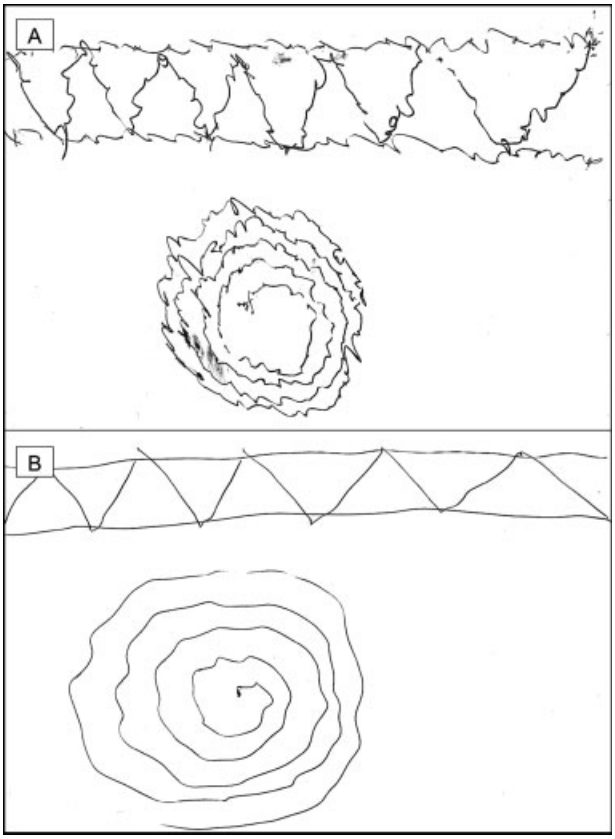

FIG. 1. Drawings with left (dominant) hand before (**A**, above), and 2 months after DBS (**B**, below), illustrating dramatic improvement of tremor.

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mild dysarthria. When stimulation was switched off, the tremor rapidly reappeared. Six months later, the effects remained unchanged.

Postural tremor is a common symptom in PNMAG[2] and occurs in up to 90%.[3] Although DBS of VIM is a well-established therapeutic option in disabling, drug-resistant tremor of central origin in Parkinson's disease and essential tremor (ET),[4] this treatment is not usually proposed for tremor associated with peripheral nervous system diseases. Tremor in PNMAG shares many clinical features with ET, including frequency, presence in posture and action and predominance in distal muscles.[2] In our patient, the close temporal association between the onset of the neuropathy and the appearance of the tremor suggested that the tremor was related to the neuropathy. Moreover, prevalence of postural tremor in patients with PNMAG is 10 to 200 times higher than the prevalence of ET in the general population.[3] The absence of family history of tremor and the absence of response to alcohol were additional arguments against the diagnosis of ET. However, an incidental association of ET and PNMAG cannot be excluded.

Pathophysiological mechanisms of tremor in PNMAG are unclear. As there is lack of correlation between slowing of nerve conduction and presence of tremor, and as tremor is not related to weakness or sensory loss, tremor could be generated in the CNS.[2] Tremor might be due to loss or modification of peripheral input to CNS.[3] The cerebellum could be implicated in both neuropathic tremor and ET.[5] The similarities between tremor associated to PNMAG and ET, and the disability due to the tremor despite immunoactive and symptomatic therapies justified to propose VIM-DBS to our patient.

To our knowledge, DBS has been reported for two patients with neuropathic tremor: one case of successful DBS for severe tremor due to a similar condition has been reported in your journal several years ago for a man with neuropathy with monoclonal IgM gammopathy.[6] Another patient with a hereditary neuropathy had a 30% improvement.[7] DBS of VIM could be useful for severe, drug-resistant neuropathic tremor, but larger studies are needed to prove its efficiency.

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Spinocerebellar Ataxia Type 1 Mimicking Stiff Person Syndrome

Video 

Spinocerebellar ataxias (SCA) comprise a number of autosomal dominant conditions characterized by slowly progressive cerebellar syndrome, with or without additional features e.g., pyramidal and extrapyramidal signs, ophthalmoplegia, cognitive disturbance, and retinopathy. We describe a SCA1 patient with features of stiff person syndrome (SPS).

A 47-year-old man was hospitalized for a week with liver and bowel damage, but no neurological problems, following a crush injury at work in 2004. A month later he complained of limb ache, unsteady gait with falls, headache, blurred vision, patchy sensory loss, jerky limb movements at night, and panic attacks. Cognitive examination was normal, but he was highly anxious and easily startled. Physical examination revealed mild cerebellar dysarthria with a breathy dysphonia, upper limb ataxia, and pronounced rigidity of abdominal, paraspinal, and lower limb muscles. Reflexes were brisk with flexor plantars. Gait was unsteady, stiff, robotic; with tendency to fall en bloc (video) (SCA1.wmv recorded 2006). Blood tests including full blood count, urea, electrolytes, liver function tests, glucose, vitamin B12, erythrocyte sedimentation rate, creatine kinase, thyroid function, syphilis serology, immunoglobulins, autoantibodies, anti-neutrophil cytoplasmic antibodies, lactate, vitamin E, HTLV-1 and 2, white cell enzymes, very long chain fatty acids, anti-neuronal antibodies, anti-glutamic acid decarboxylase (GAD) antibodies, and anti-amphiphysin antibodies were normal or negative (on blood only). 1.5 Tesla MRI brain and spinal cord was

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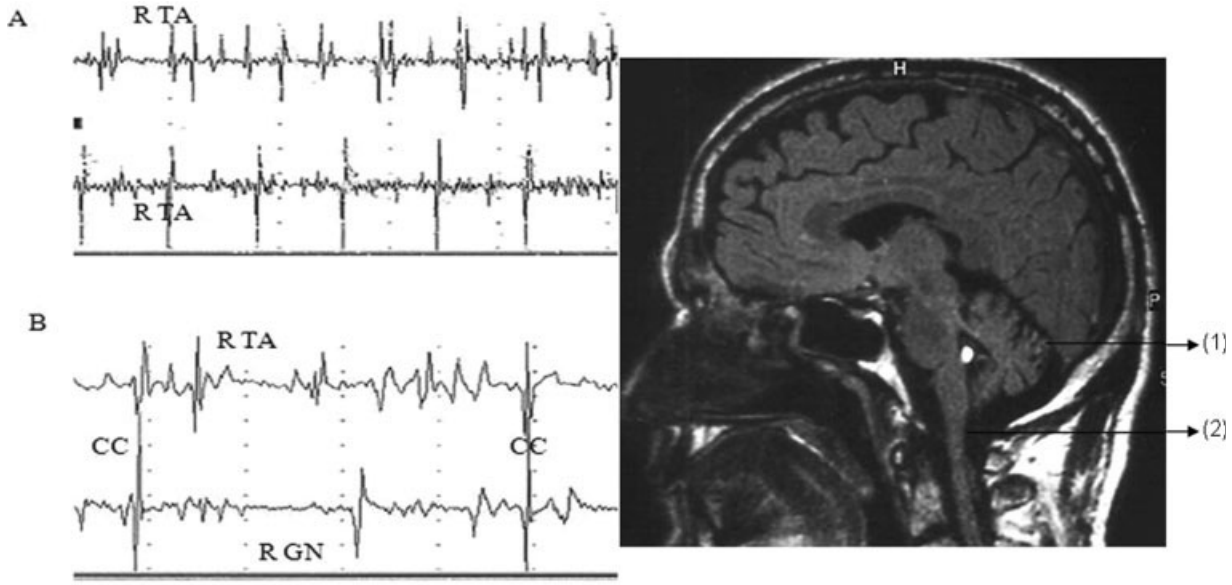

FIG. 1. EMG showing continuous motor unit activity in Right Tibialis Anterior (RTA) in (**A**) and co-contraction (CC) of RTA with gastrocnemius (R GN) in (**B**). 3T MRI showing Cerebellar (**1**) and Brain stem/ Cervical Cord (**2**) atrophy.

normal (11, 2004). Somatosensory evoked potentials (SSEP) and central motor conduction times were delayed from the lower limbs. CSF was acellular with marginally elevated protein of 0.43 g/L, normal glucose and absent oligoclonal bands. Nasendoscopy was unremarkable. Nerve conduction studies (NCS) were normal, but electromyography (EMG) revealed continuous motor unit activity and co-contraction in paraspinal and proximal limb muscles (Figure 1). Genetic testing on two occasions (2006, 2008) revealed at least 41 pure uninterrupted CAG repeats on one allele of SCA1 gene. Known family members in Fiji were clinically unaffected; none were genetically tested. Serial 3 Tesla MRI (02, 2006) showed progressive atrophy of the cerebellum, lower brainstem, and cervical cord (Figure 1). Clonazepam 2 mg od, Tizanidine 12 mg od, and Baclofen 90 mg/day have helped the stiffness albeit with prominent sedative side-effects.

Clinical progression between 2004 and 2006 was rapid with subsequent plateau in stiffness but continued reduction in mobility.

SCA1 makes up about 10% of autosomal dominant ataxias worldwide. It is due to trinucleotide repeat expansion in the ATXN1 gene, with the wild-type gene showing 6-44 interrupted CAG repeats and disease gene showing 39-91 usually uninterrupted CAG repeats. It typically presents in early adulthood with a cerebellar syndrome and hyperreflexia, but patients can later develop cognitive impairment, choreoathetosis, dystonia, and bulbar failure. MRI usually shows atrophy of the anterior lobe of cerebellum, basis pontis and cervical cord. Neurophysiology is often abnormal, with one study of 17 patients showing abnormal SSEP in 100% and abnormal NCS in 94% of cases.[1]

SPS is a rare, acquired disorder of fluctuating muscle stiffness with episodic spasms, hypothesised to arise following excitation of spinal and supraspinal circuits, perhaps due to reduced GABAergic activity.[2] It can occur as a paraneoplastic phenomenon in association with anti-amphiphysin antibodies, and as an autoimmune condition in the presence of anti-GAD antibodies. Clinical features in GAD-positive subjects include paraspinal rigidity, and prominent abdominal and thoracolumbar muscle co-contraction.[3] Hypersensitivity with spasms provoked by unexpected stimuli or stress, marked anxiety and breathing difficulties from a combination of panic and chest wall restriction may also be seen. Falls (typically en bloc), probably due to truncal rigidity, were common. Of note, almost all the earlier clinical features, not suggestive of SCA, were present in our patient. Only recently has attention been drawn to a possible association between SCA3 and SPS.[4] Like our case, imaging and SSEP were compatible with SCA, EMG consistent with SPS, and serum antibodies to GAD and amphiphysin were negative.

To our knowledge, this is the first reported case of SCA1 presenting simultaneously with features of SPS. The reason of coexistence remains obscure, because of differing aetiopathogenesis. Against this being a chance association is that both conditions are rare, arose and progressed in tandem and no immune basis for SPS was identified. We believe it worthwhile to consider testing for SCA in antibody-negative SPS patients with suggestive family history or radiological evidence of prominent cerebellar involvement.

LEGEND TO THE VIDEO

Patient video from 2006 showing ataxia, startle, falling en bloc, robotic gait and muscle rigidity (after clinical diagnosis).

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Rasagiline-Induced Spontaneous Ejaculation

Rasagiline is a selective irreversible MAO-B inhibitor used to treat parkinsonian motor symptoms with putative neuroprotective effects. It is well tolerated with gastrointestinal side effects being the most commonly reported. We report the first case of spontaneous ejaculation secondary to rasagiline taken in combination with levodopa therapy.

A 65-year-old man with a history of spina bifida without bladder, bowel, or sexual dysfunction who was diagnosed with Parkinson disease 4 years earlier, presented with a 3-month history of spontaneous ejaculation. He had been on rasagiline monotherapy at 2 mg daily for 1 year before levodopa was added. One month after initiating levodopa, he had his first episode of spontaneous ejaculation, which occurred in clusters every 10 minutes for 30 minutes, with episodes occurring every 2–7 days. These ejaculations occurred without erection and without being engaged in any self-stimulating or pleasurable situation. In between, he had normal sexual function and no other autonomic abnormality.

His neurological examination demonstrated left-sided rigidity and bradykinesia without resting tremor for a UPDRS III score of 13. He had mildly weak ankle dorsiflexion and decreased vibratory/proprioception at the toes bilaterally. Reflexes were decreased throughout and absent at the ankles with plantar flexor responses. He did not have orthostatic hypotension.

Spontaneous ejaculation continued even after reducing rasagiline to 1 mg, but stopped after drug discontinuation. Because he noted worsening parkinsonism, selegiline 10 mg daily was added to levodopa for 4 months, during which time he had no episodes of spontaneous ejaculation. Selegiline was then discontinued and he was rechallenged with rasagiline 2 mg daily. Within 1 month, spontaneous ejaculation recurred. He remains on rasagiline by choice and continues to experience intermittent spontaneous ejaculation. Ejaculations associated with normal sexual activity were reported to be more explosive with shorter recovery in between ejaculations.

Apart from hypersexuality, the prevalence and range of sexual dysfunction in PD is not well defined. However, there are numerous reports of sexual dysfunction following dopaminergic treatment, specifically, dopamine agonists such as apomorphine and ropinirole.[1,2] To date, only spontaneous erection has been reported as a side effect.

The role of dopamine in erection was noted after early drug trials of apomorphine for treating alcoholism.[3] Apomorphine is a potent D1 and D2 receptor agonist and thought to induce penile erection by central D2 stimulation. It has been studied and even marketed as treatment for human erectile dysfunction.[3] Two other DA, bromocriptine and ropinirole, have been reported to improve erectile function.[4]

Spontaneous ejaculation has not been reported as a consequence of dopaminergic therapy, although animal studies have shown that dopamine facilitates ejaculation. The mechanism in which ejaculation occurs without erection is unclear, but one possibility is that different dopamine receptor subtypes may be involved. The spinal cord ejaculation center in the S1–3 level integrates peripheral and central signals, but is also under supraspinal influence by the brainstem, hypothalamus, and medial preoptic area.[5] Stimulation of D2 receptors in the rat medial preoptic area by the D2/D3 agonist, quinelorane, has been shown to facilitate ejaculation. Piribedil, a D2 and D3 receptor agonist with preference for D3, significantly increases rat ejaculation with less effect on erection.[6] In contrast, bromocriptine, a D2 $>$ D3 agonist, potentiates erection only without affecting ejaculation.[6] Apomorphine, a D1 and D2 agonist, also does not affect ejaculation. Further supporting the role of D3 receptors in modulating ejaculation and its refractory period, a selective D3 receptor antagonist injected into the medial preoptic area abolished ejaculation without affecting erection.[7]

In our patient, abnormal ejaculation did not occur until the addition of levodopa, but once precipitated, he continued to experience spontaneous ejaculation until discontinuing rasagiline. Levodopa monotherapy or addition of selegiline did not produce the side effect. It is possible that rasagiline preferentially increases central dopamine at either the brainstem or the medial preoptic area to augment signals to the spinal cord ejaculation center. Alternatively, rasagiline could have previously undefined effect on D3 receptors. Our patient may be unique in his experience because of his underlying spina bifida, suggesting spinal cord or peripheral level involvement for this adverse effect of rasagiline. Neurologists should address sexual dysfunction in the routine care of PD patients and with increasing use of rasagiline in the treatment of PD, further examples of this unusual complication may become evident.

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Severe Muscular Fasciculations as an Uncommon Side-Effect due to Microdefect of an Extension Wire in Deep Brain Stimulation

Video 

Deep brain stimulation is increasingly used for the effective treatment of neurological and psychiatric disorders.[1,2] Complications related to the stimulation device ranged from 5.3 to 27%.[3,4] In long-term observations, most common hardware complications are due to discomfort of extension wires (6.7%),[5] lead fracture (1.7–15%),[3,5] migration of electrodes (2.3–2.8%),[4,5] skin erosion, and local infections (4.4–10.6%).[3,6] Another study following 319 patients up to 10 years found the total hardware-related complication rate of 1.7% per electrode-year.[6] Incidents with disruption of insulation of the extensions however are rare.

We describe a 42-year-old female patient with familial essential tremor (ET), presenting with a marked action tremor and a moderate resting tremor of both hands. Because of intentional tremor, she was severely impaired. The tremor was alcohol sensitive, and pharmacological treatment with propranolol, primidon, pramipexol, topiramat, and clozapine remained unsatisfactory. Therefore at the age of 37, stereotactic deep brain stimulation (DBS) of the ventrolateral thalamus bilaterally was performed and the pulse stimulator (Kinetra, Medtronic, Minneapolis, MN) was implanted in the left subclavicular region over the M. pectoralis. With DBS, the tremor was significantly suppressed and the patient regained a normal social life. After 30 months, the pulse generator was low on energy and therefore replaced by the same model.

Few days after the replacement, the patient complained about tingling sensations in the left subclavicular region under the pulse generator and pain radiating from the sternum to the left shoulder. At that time, there were no visible or palpable correlates for the sensations described by the patient. Over the following weeks, the patient reported an increase of paresthesias, intermittent twitching movements adjacent to the pulse generator, and a dull pain in the left shoulder. Subsequent clinical reexamination revealed fasciculations of varying frequency over the left pectoral muscle (see video). These symptoms were aggravated by gentle pressure on the lateral side of the generator device. At that time, the tremor was well suppressed by the stimulation. Impedance and current of the system were unremarkable even during changes of position of the head or pulse generator (left: 622 Ω, right: 592 Ω, bilaterally: 122 μA at therapeutic electrode contacts). An X-ray of the chest confirmed the regular position of the stimulator and extension wires. Variations of the stimulation contacts on either side or changing to monopolar stimulation led to partial reappearence of the tremor but did not influence the fasciculations. However, the fasciculations were consistently stopped by turning off the electrode of the left hemisphere. Under the assumption of a current leakage in the vicinity of the pulse generator a surgical exploration was performed. Intraoperatively, the extension wires were disconnected from the neurostimulator for invasive testing of impedance and current status of the system (Intraoperative test clamps, Medtronic, Minneapolis). The intraoperative functional status of the extension wires and the electrodes was inconspicuous. Macroscopically, there was no visible defect of the extension wires. Using a surgical microscope (Zeiss, Oberkochen, Germany) the extension wires next to the neurostimulator were inspected. This inspection disclosed a minimal discontinuity of the isolation of the left extension wire. The isolation was restored using a Silicon glue (Silastic Medical Adhesive Silicone Type A, Dow Corning Corp. Midland, MI) as well as an additional sealing cap (Medtronic). Immediately after the intervention and during the 3-month postoperative follow-up the patient observed no more fasciculations or shoulder pain and the tremor is still well suppressed.

Local symptoms, for example, dysaesthesia or change in muscle tonus, can be provoked with DBS in the central or peripheral nervous system. Side-effects due to aberrant brain stimulation can be caused by an inappropriate stimulation area or as a result of lead fracture.[7] In the periphery, leaking current may cause side effects either by disruption of the isolation of an extention or misplacement of the puls generator, e.g., reverse implantation with the back side containing a small unisolated area for monopolar use, toward the skin. In the case described, an effect in the CNS was excluded as change in stimulation amplitude and location did not cease side effects. Reverse implantation as cause was unlikely as side effects occurred during bipolar use and was excluded by X-ray imaging. Therefore, disruption of isolation seemed the most likely

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cause, which could be confirmed intraoperatively. It is important to consider microscopic inspection of the extension wires, as minimal lesions of the isolation may escape primary inspection. It is surprising though, that impedance and battery status were not affected. Thus, we conclude that very small discontinuities of isolation must be considered in patients with DBS reporting uncommon side effects, such as dysaesthesia or muscle fasciculations, even if the symptoms are intermittent and impedance as well as battery status is normal.

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Gluten Sensitivity Presenting as Myoclonic Epilepsy with Cerebellar Syndrome

Gluten sensitivity (GS) is a common autoimmune disorder that may present with a variety of neurological syndromes.[1–3] GS may present as myoclonic epilepsy, which is characterized by myoclonus and cerebellar dysfunction.[2]

A 46-year-old woman presented with an unprovoked generalized tonic-clonic (GTC) seizure and was started on phenytoin. A year later, she developed severe toe myoclonus that progressed over weeks to involve the legs impairing gait and stance. Myoclonus worsened in antigravity position and on walking, leading to falls. Therapeutic trials with sodium valproate, clonazepam, primidone, and topiramate failed to improve myoclonus. Four years after the disease onset, the patient developed a slowly progressive cerebellar syndrome with scanning speech, limb and gait ataxia. The patient had a 7-year history of treated hypothyroidism. She denied gastrointestinal symptoms or a family history of epilepsy or movement disorders.

Neurologic examination disclosed action myoclonus in the tongue and both legs that markedly worsened on attempt to stand or walk. There was mild bilateral arm dysmetria. Neurologic and general physical exams were otherwise unremarkable.

Thyroid stimulating hormone was elevated at 85 mcU/mL (normal values 0.8–4.5 mcU/mL), with normal T3 and free T4 levels. Antiperoxidase and antithyroglobulin antibodies were positive at high titers (>3,000 mUI/mL). A comprehensive autoimmune and paraneoplastic panel was negative. Cerebrospinal fluid exam was normal. Nerve conduction studies demonstrated C-reflex in upper and lower extremities with a latency of about 60 milliseconds, indicating central myoclonus. A sleep and awake EEG showed occasional generalized polyspike-wave complexes. A muscle biopsy was normal. Brain and whole spine MRI were normal.

The patient received a diagnosis of Hashimoto's encephalopathy and was initially treated with high-dose intravenous steroids and intravenous immunoglobulin, without neurologic improvement. Antiendomysium antibodies were positive at a titer of 1:640, and an upper gastrointestinal endoscopy showed a lymphocytic epithelial infiltrate, with a fivefold increase in intraepithelial lymphocytes compared with column cells, suggestive of a chronic duodenitis. The diagnosis of celiac disease was established. The patient has been on a gluten-free diet and on an antiepileptic drug polytherapy regimen for the last 4 years, without neurologic improvement.

GS is a common disease. Prevalence is as high as 1% in United States and Europe.[4] Disease mechanisms include

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combined genetic, environmental, and immunologic factors. The protean clinical and neurologic manifestations of GS, in the absence of gastrointestinal manifestations,[5] may mislead the clinician from the correct diagnosis.

This patient presented generalized tonic-clonic seizures, followed by severe myoclonus that greatly limited daily-living abilities. Uncompensated hypothyroidism and high titers of antithyroid antibodies suggested a diagnosis of Hashimoto's encephalopathy. Lack of a therapeutic response to corticosteroids and intravenous human immunoglobulin argues against this diagnosis.[6] Absence of ragged red fibers on muscle biopsy argues against the diagnosis of a mitochondrial disease. Very high titers of antiendomysium antibodies associated with the duodenal biopsy findings support the diagnosis of celiac disease. However, despite the gluten-free diet, no improvement has been noted in this patient.

Myoclonic ataxia and epilepsy have been previously reported in association with GS. Bhatia et al.[2] reported 4 patients with progressive myoclonic ataxia and seizures associated with celiac disease. A gluten-free diet and immunosuppressive treatment did not prevent deterioration in these cases, as was the case in our patient. Hanagasi et al.[7] reported a 31-year-old man with celiac disease, gait disorder, and stimulus-induced myoclonus. Association of myoclonic ataxia and GS is not uncommon. Cerebellar atrophy with loss of Purkinje cells can also be seen in this setting.[8] Our patient developed cerebellar atrophy in the course of the disease.

Diagnosis delay and missing a hypothetical therapeutic window may have contributed to a poor therapeutic response in this case.[8] Alternatively, neurologic manifestations of GS may be poorly responsive to a gluten-free diet.[8] Although a gluten-free diet usually halts gastrointestinal disease progression, improving small bowel absorption, it may have a variable effect on GS-associated neurologic disease, ranging from disease resolution or stabilization to no appreciable therapeutic effect.[9]

High prevalence of GS may lead to erroneous interpretation of neurologic manifestations as secondary to GS.[9] We do not believe this was the case in our patient, who underwent a thorough diagnostic work-up.

The diagnosis of GS should be considered in the differential diagnosis of myoclonic ataxia and progressive cerebellar dysfunction of unknown etiology.

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Cervical Dystonia Associated with Spinocerebellar Ataxia Type 2 Successfully Treated with Levodopa: A Case Report

Recent reports indicate that extrapyramidal features including parkinsonism and dystonia are common in patients with spinocerebellar ataxia type 2 (SCA2), and cervical dystonia may be a clinical symptom in a subset of SCA2 patients.[1,2] Although cervical dystonia manifests as a functional disability in daily activities of patients, few reports have described its treatment.

A 51-year-old man with a family history of SCA2 experienced instability of stance from the age of 44. At age 46, he was admitted to our hospital because of a slowly progressive gait disturbance. Neurological examinations showed truncal and limb ataxia, oculomotor limitation with slow saccadic eye movement, scanning speech, decreased tendon reflexes, and frontal lobe signs. Brain MRI showed pontine and cerebellar atrophy. Genetic testing proved that the SCA2 genotype had a 42 CAG repeat in the expanded allele.

At age of 50, he developed involuntary neck movement and was readmitted to our hospital. No neuroleptics had been administered in the previous history. He had left-head rotation and experienced continuous head tremor of 4 Hz. Muscle tonus of his right sternocleidomastoid muscle was high. In addition, reciprocal contraction of the bilateral sternocleidomastoid muscle was observed. His head tremor improved when he put his hand on the right side of his neck and laid in the lateral right position, suggesting improvement in muscle spasms and head posture by application of a sensory stimulus (sensory trick). Surface electromyography (EMG) revealed an involuntary spontaneous muscle activation pattern and reciprocal contraction of the bilateral sternocleidomastoid muscles at rest (Fig. 1a). Surface EMG also confirmed that continuous contraction of the right sternocleidomastoid muscle improved by lying in the right lateral position (Fig. 1b). We considered his involuntary head movements as dystonia. His cervical tremor and head rotation markedly improved after levodopa administration (400 mg/day). Further improvement was obtained by additional administration of trihexyphenidyl hydrochloride (3 mg/day). Surface EMG confirmed diminished muscle contraction of the bilateral sternocleidomastoid muscles (Fig. 1c).

In this study, we reported a SCA2 patient who developed head rotation and continuous dystonic head tremor 6 years

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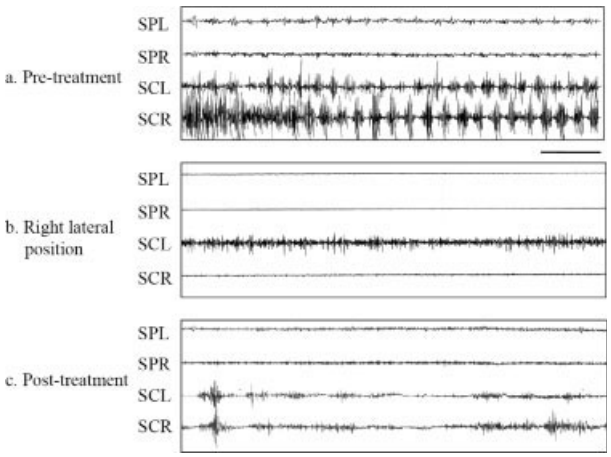

FIG. 1. Surface electromyography in the patient. (**a**) Surface electromyography showing involuntary spontaneous muscle activation pattern and reciprocal contraction of bilateral sternocleidomastoid muscles at rest. (**b**) Contraction of the right sternocleidomastoid muscle was improved by the right lateral position. (**c**) Oral administration of levodopa and trihexyphenidyl hydrochloride also improved muscle contraction of the bilateral sternocleidomastoid muscles. SPL: left splenii muscle, SPR: right splenii muscle, SCL: left sternocleidomastoid muscle, SCR: right sternocleidomastoid muscle. Scale bar, 1 s.

after the onset of the disease. Cervical dystonia was diagnosed on the basis of the presence of sensory trick, and findings on the surface EMG revealed reciprocal contraction of 4 Hz in the bilateral sternocleidomastoid muscles at rest.

Recent studies have reported that cervical dystonia is not necessarily a rare symptom of SCA2 patients, and that dystonic head tremor may be a clinical symptom of the disease. Boesch et al.[3] reported that cervical dystonia was found in 11 of 18 patients (61%) with SCA2 in which isolated lateroflexion was observed in 7 patients and combined lateroflexion and head rotation in three. Similar to the present patient, dystonic head tremor was observed in 1 patient. Zárubová and Růzicka[4] also reported an SCA2 patient with dystonic head tremor as well as complicated retrocollis at age 41 after the onset of cerebellar ataxia in her early thirties. It was suggested that degeneration of the substantia nigra and dysfunction of the basal ganglia circuitry or pontocerebellar pathway might be associated with the development of extrapyramidal symptoms in SCA2 patients.[3]

Treatment of cervical dystonia is not well established, although there was a report of a patient whose disabling retrocollis and head tremor improved by injections of botulinum toxin A into each of both splenii muscles that was followed by partial improvement of the cervical dystonia.[4] In this report, repeated administrations of botulinum toxin A resulted in marked reduction of retrocollis. In the present study, we investigated the effect of levodopa and trihexyphenidyl hydrochloride on cervical dystonia. We speculated that neuronal loss in the substantia nigra[5] may be responsible for cervical dystonia in SCA2, resulting in a reduction in intranigral dopamine concentrations. This in turn causes a relative imbalance between the dopaminergic and cholinergic neurological pathways, and anticholinergic drugs can correct this imbalance in less advanced forms of SCA2 by reducing the degree of neurotransmission mediated by neostriatal acetylcholine. Therefore, we conclude that levodopa is a potential treatment for cervical dystonia in patients with SCA2. However, it is possible that levodopa will not have an effect when D2 receptor downregulation or depletion is already apparent, as reported in SCA2 patients.[6] Hence, further studies should be performed to examine the effect of oral administration of levodopa and trihexyphenidyl hydrochloride on cervical dystonia in SCA2.

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STN Versus PPN-DBS for Alleviating Freezing of Gait: Toward a Frequency Modulation Approach?

Video 

Stefani et al. reported a synergistic, clinical improvement in gait during simultaneous subthalamic nucleus (STN) and pedunculopontine nucleus (PPN) deep brain stimulation (DBS) in six patients with Parkinson's disease (PD), whereas PPN-DBS alone seemed to have mild effects.[1] Gait disorders have to be managed as a function of disease progression, gait characteristics and levodopa (L-dopa) sensitivity. Indeed, in

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TABLE *Median (±SD) values of kinematic parameters (blindly analyzed three times for each condition) in the four patients in the "off L-dopa" condition (after 3 hours of withdrawal of the usual L-dopa treatment)*

	180 Hz STN	180 Hz STN + 25 Hz PPN	25 Hz PPN	60 Hz STN	60 Hz STN + 25 Hz PPN
Stride length (m)	0.8 (0.35)	0.9 (0.36)	0.75 (0.32)	0.9 (0.38)	1 (0.29)
Velocity (m/s)	0.7 (0.31)	0.89 (0.31)	0.7 (0.29)	0.8 (0.34)	1 (0.12)
Cadence (stride/min)	126 (5)	126 (5)	126 (13)	125 (11)	128 (8.5)
Stance time (%)	67 (3)	66 (3)	67 (2.47)	66 (3)	65.5 (2)
Swing time (%)	32 (4)	33 (4)	32 (2.6)	33 (3)	33.5 (3)
Double-support time (%)	16 (3)	15.5 (3)	16 (2)	15 (1.53)	14.5 (1.7)
UPDRS III score (of 108)	24	22	28	22	20
Akinesia subscore (of 32)	12	12	14	11	10
UPDRS III gait subscore (item 30) for patient 2	2	2	3	2	2
Number of FOG episodes for patient 2	3	3	6	2	2

The baseline DBS parameters were 2.6 V, 90 μs and 185 Hz for STN (monopolar contact #1 on both sides) and 2 V, 60 μs, and 25 Hz for the PPN (monopolar contact #0 for both sides). For the 60 Hz STN DBS condition, the voltage was 4.5 V (monopolar contact #1 on both sides, 90 μs). The PPN DBS parameters were not modified. The last two rows (rows 9 and 10) summarize the gait evaluation (UPDRS gait subscores and number of FOG episodes) for the patient recorded on video.

late-stage disease, freezing of gait (FOG) and postural instability become prominent and partially resist L-dopa and STN stimulation at the usual high frequencies (i.e., 130–180 Hz). The value of low-frequency stimulation of the mesencephalic locomotor area [the PPN in general and the nucleus tegmenti pedunculopontine (the caudal representation of the PPN complex) the perifascicular nucleus and the cuneiform nucleus in particular] remains subject to debate in terms of efficacy/safety/side effects and the exact nature of the target.[2–4] The recent report by Mazzone provides neurosurgical details and clarifies the surgical approach performed onto the pontine tegmentus of these patients.[4] Furthermore, we recently demonstrated the clinical effect of novel STN-DBS voltage/frequency combinations on FOG and suggested that a more normal gait control pattern could be restored by using lower frequencies (especially 60 Hz) in patients with advanced PD presenting severe FOG.[5]

To establish whether STN stimulation at a lower frequency adds further benefit to low-frequency PPN stimulation, we took advantage of the previously studied doubly implanted patients[1] and compared the respective effects of STN-DBS [monopolar stimulation at low (60 Hz) and high (180 Hz) frequencies] and PPN-DBS (monopolar stimulation, 25 Hz optimal frequency) on gait kinematic parameters and FOG.

Four patients were available for recording. Three had remained stable since the previous study and had partially dopa-responsive gait disorders with short, infrequent FOG episodes.[1] Despite application of optimal L-dopa doses and standard DBS parameters (STN: 180 Hz; PPN: 25 Hz), the fourth patient had worsened and suffered from frequent, severe FOG episodes throughout the day. Gait analysis was performed three times for each condition with an optoelectronic system (the SMART system from BTS, Padua, Italy) by measuring the three-dimensional coordinates of retroreflective markers.[6] The following kinetic variables were blindly analyzed: gait velocity, cadence, and the mean stride length and stride phase percentages (stance, swing, and double support) for the left and right sides. To avoid circadian fluctuations, we performed all the recordings in a single session in the morning. For the patients' comfort, we recorded during their usual L-dopa treatment conditions (On L-dopa) and after 3 hours of L-dopa treatment withdrawal (Off L-dopa), notably because the fourth patient was unable to walk after a night's withdrawal of L-dopa and DBS. The order of the DBS combinations was randomly chosen and the results were blindly assessed.

We observed better results for stride length with 60 Hz STN-DBS alone [mean ± standard deviation stride length in the off L-dopa condition: 0.9 m (±0.3)] than with 25 Hz PPN-DBS alone [stride length: 0.75 m (±0.3)] or 180 Hz STN-DBS alone [stride length: 0.85 m (±0.3)] in all four patients in the presence and absence of L-dopa. In the fourth patient (with severe gait disorders and FOG), we observed a higher, synergistic effect for 60 Hz STN-DBS + PPN-DBS than for 180 Hz STN-DBS + PPN-DBS or PPN-DBS alone, both on L-dopa and after 3 hours of L-dopa withdrawal (Table 1). Five hours without L-dopa prevented this patient from initiating gait and walking unaided. He was able to do so when we blindly turned on 60 Hz STN-DBS alone (see Video, Segment 1) but remained unable to walk unaided during 25 Hz PPN-DBS alone (see Video, Segment 2) or 180 Hz STN-DBS alone.

From a clinical standpoint, we noted that the benefit of 60 Hz STN-DBS was obvious (1) in all four patients when we compared 60 Hz STN-DBS alone with PPN-DBS alone and (2) only in the patient with very severe FOG when we compared the synergistic improvement of gait during 60 Hz STN-DBS and PPN-DBS with 180 Hz STN-DBS and PPN-DBS. The fact that very few patients with PD currently have dual stimulation prevents more extensive and statistical comparisons. Our results suggest that for treating severe gait akinesia and FOG appearing after several years of STN-DBS, one should first try a low-frequency STN-DBS strategy before considering mesencephalic locomotor area (PPN) stimulation, especially in view of the inherent risks of surgery and the difficulty in targeting a degenerate, complex structure.

LEGENDS TO THE VIDEO

This 71-year-old patient developed PD 10 years ago. He started to display gait hypokinesia and FOG episodes 2 years after initiation of STN-DBS. In "Off-stim" conditions and after 5 hours of L-dopa withdrawal, the patient was unable to

walk (UPDRS motor score: 54 of 108). During 60 Hz STN alone/off-drug condition, he was able to walk unaided in open space without initiation akinesia and with only two FOG episodes during a half-turn (Segment 1: UPDRS III, item 30: 2 of 4). During the PPN-DBS alone/off-drug condition, the patient was unable to walk unaided because of severe gait initiation failure and severe half-turn FOG (Segment 2: UPDRS III, item 30: 3 of 4).

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Catamenial and Oral Contraceptive-Induced Exacerbation of Chorea in Chorea-Acanthocytosis: Case Report

Autosomal recessive chorea-acanthocytosis (ChAc) is a neurodegenerative disorder with diverse neuropsychiatric presentations including behavioral, cognitive, and movement manifestations, the latter typically chorea and oroligual dyskinesias.[1]

Several endocrine and hormonal disturbances, especially those linked to estrogen, can influence the occurrence and severity of movement disorders including Parkinsonism, chorea, dystonia, tics, and myoclonus.[2,3] We report for the first time the exacerbation of chorea in ChAc during treatment with an oral contraceptive (OC).

The patient is a 38-year-old woman with no medical history until 18 years of age when the occurrence of secondary generalized seizures brought her to neurologic evaluation. Investigations with EEG tracing, brain CT and MRI scans were unremarkable. She was started on phenytoin 100 mg bid, soon switched to phenobarbital 100 mg qd because of hirsutism. She remained stable until the age of 33 when she experienced the onset of mild upper extremities chorea. One year later, overt chorea became evident, including orolingual dyskinesias with lip and tongue biting. At this point obsessive-compulsive behavior, depression and motor tics (eye blinking and lip smacking) were noticed. She was the first of four siblings, parents had remote consanguinity (forth cousins). One of her two sisters had obsessive-compulsive disorder, and her brother had epilepsy. Peripheral red-blood cell analysis revealed acanthocytes; serum transaminase levels were mildly elevated [GOT 42 U/L (5–36), GPT 60 U/L (5–52)]. Serum creatine kinase was 700 U/l (1-75) and aldolase was 9.5 U/l (<6). ESR, C-reactive protein level, rheumatoid factor assay, antiphospholipid antibodies, ANA test, and antistreptolysin O were negative or absent. Electromyography with nerve conduction studies of the upper and lower limbs were normal. Western blot analysis of erythrocyte membrane preparations using antichor1 antiserum was performed at the Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK, as previously described,[4] revealing markedly reduced levels of chorein in the proband and her brother. She was started on quetiapine 50 mg bid, paroxetin 20 mg qd, clonazepan 2 mg qd, and tetrabenazine 25 mg tid with satisfactory response of both movement and behavioral disorders. After 6 months, during a routine gynecologic evaluation, she complained of exacerbation of chorea during 3 to 4 days that preceded her menses. This catamenial worsening was noted in the four latest

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cycles. Continuous oral desogestrel 75 μg/day was started. During the initial days on this medication, she experienced an abrupt and dramatic worsening of involuntary movements, which became generalized, significantly more severe, interfering with daily activities and feeding. Hormonal treatment was withdrawn after 1 week and abnormal movements gradually returned to baseline. During follow-up, slow and insidious progression of symptoms occurred, partially controlled with changes in drug regimen.

Since the first description of the association of OCs and chorea by Fernando,[5] clinical data have grown considerably, usually in the form of case reports illustrating this phenomenon from diverse standpoints. One of the earliest reports describe five cases of chorea related to OCs, one with probable basal ganglia vasculopathy leading to acute hemichorea, and four cases in women with a history of Sydenham's chorea (SC).[3] Riddoch et al.[6] reported six additional cases, one with a history of SC. Finally, menopause and hormone replacement therapy have also been implicated in the occurrence of chorea, reinforcing the association between female hormones and this movement disorder.[3,6,7]

Although most of such cases have been hypothesized to be related to reactivation of SC, this antecedent is not found in some patients. Other immunological bases have been mentioned in the literature such as SLE, antiphospholipid or antibasal ganglia antibodies syndromes.[2,7]

This is the first case of a patient with ChAc presenting with catamenial worsening of chorea and its' even more dramatic exacerbation after starting an OC. Of importance, the case presented here had no history of SC. These observations differ from the cases described earlier mainly because the movement disorder, present for almost 2 years, was exacerbated, not triggered by the hormonal treatment. This also implies that additional mechanisms, other than a purely immunological, may have played roles in this case. Catamenial exacerbation of chorea may be explained by the reduction of endogenous progesterone levels. Recent studies have shown that progesterone and its metabolites have GABA(A)/NMDA modulatory effects on an animal model of tardive dyskinesia.[8] Although progesterone and allopregnanolone seem to have mainly an inhibitory net effect through positive GABA and negative NMDA modulation, pregnenolone has the opposite net effect. These variable effects of different progestogens may also explain the apparently paradoxical worsening of chorea when desogestrel (a synthetic progesterone analog) was initiated. Another example is a previous case of generalized chorea after treatment with medroxyprogesterone acetate.[9] Finally, induction of quetiapine or tetrabenazine metabolism, leading to a reduction in the dopamine D_1/D_2 blockage or an increase in synaptic dopamine, could explain the exacerbation of chorea. However, so far no known interaction between these two drugs and desogestrel has been described, although all three are substrates of the cytochrome P450 3A4.[10]

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Bilateral Thalamic Glioma Presenting with Parkinsonism

Video 

Thalamic tumors account for ~1–1.5% of all brain neoplasms[1,2]; primary bilateral thalamic glioma is even rarer. The exact epidemiology of these tumors is not fully clarified and the range of age of onset is quite variable.[1,2] Main symptoms are memory loss, apathy, emotional lability with sparing of sensory and motor systems.[3] A misdiagnosis with neurodegenerative disorders such as fronto-temporal dementia has been reported.[4]

Brain tumors are rare cause of secondary parkinsonism, and so far glioma, meningioma, lymphoma, and gliomatosis cerebri involving the brainstem or basal ganglia have been described. The usual presentation of parkinsonism associated with tumor is a rigid-akinetic syndrome not responsive to dopaminergic treatment. Parkinsonism has also been associated with tumors that do not involve basal ganglia, even if the coexistence of a degenerative and neoplastic disease could not be excluded. To our knowledge, bilateral thalamic glioma manifesting with parkinsonism has never been reported.

A 66-year-old man complained 1-year history of resting tremor involving the right hand, mild global bradykinesia, and gait imbalance. After the execution of a brain CT scan without contrast that resulted unremarkable, levodopa (300 mg/day) and pramipexole (1.05 mg/day) were started with no benefit. After 3 months, he developed visual hallucinations (improved after pramipexole withdrawn), apathy and a clear-cut motor worsening with postural instability, gait festination, and dysphagia. At our first observation mild camptocormia, bilateral loss of arm swing while walking, start hesitation, loss of postural reflection, marked hypofonia, and micrographia as well as resting tremor at right arm and mild rigidity in the four limbs were reported. Tremor, not a typical pill-rolling, was resting tremor characterized by right hand pronation-supination with a low-intermediate frequency, however, no electrophysiologic recording was performed. Autonomic, visual and sensory systems were normal while cognitive status was impaired (MMSE 16.9/30, ideo-motor slowness, decreased speech output, perseverative behavior, and executive dysfunction were present as well). The nigro-striatal pathway was preserved as assessed by FP-CIT SPECT imaging. Brain MR examination revealed a lesion involving both thalami. The lesion was isointense on T1W and hyperintense on T2W images, with signs of bleeding in the right thalamus. No significant contrast enhancement was detectable. Proton MR spectroscopy detected a reduction of NAA with increased MI, without a significant increase of Cho/Cr ratio (Fig. 1A,B). MR characteristics were consistent with bilateral thalamic low-grade glioma and a lesion biopsy of the right thalamus was performed.

Histological examination showed glial cells, monomorph, with ovalar hypercromatic nuclei, increased cellularity (Fig. 1C), positive reactive for glio-fibrillary acid protein. Moderate mitotic index was observed (K_i67 30%), no microhemorrage, necrosis or vascular proliferation were evident. The diagnosis was glial neoplasia, WHO grade II.

Chemotherapy with temozolamide is ongoing, but the clinical conditions have progressively worsened, and at the last examination he could not walk without assistance.

Previous reports have described extrapyramidal signs in association with brain tumors even without basal ganglia involvement, that usually did not disappear after tumor exeresis, thus suggesting a possible association with degenerative parkinsonism.[5] However, in our patient, the result of FP-CIT SPECT allowed us to rule out a degenerative dysfunction of nigro-striatal pathway.

The role of thalamus in cognitive function is well known and dementia due to thalamic lesions usually includes impairment of language, executive functions, and behavior disturbances such as depression, apathy, indifference, poor motivation, and memory loss which could be referred to the interruption of the thalamic projections to cingulate cortex.

The relationship between parkinsonism and thalamic lesions is less evident. Thalamus, and particularly ventro-posterior-lateral nucleus, is an important relais in striato-cortical loop. The involvement of thalamic projections to the premotor cortex could explain motor hesitation in our patient. Resting and mostly unilateral tremor is less easy to explain, whereas hypofonia has been described as an aspect of language impairment in thalamic ischemic lesions.

Clinical presentation of bilateral thalamic tumor is often insidious and pyramidal as well as sensory symptoms are evident only in late stages. Previous evidences suggest to consider thalamic glioma in the differential diagnosis of dementia; the present report underlines the possibility that bilateral thalamic tumor might present with parkinsonism.

LEGENDS TO THE VIDEO

On examination, this 66-year-old man exhibited a bilateral loss of arm swing, mainly on the right side, while walking, a significant loss of postural reflection, resting tremor at right arm, characterized by hand pronation-supination, and mild axial rigidity and in the four limbs with moderate bradykinesia.

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Authors Roles: Daniela Frosini: Research project: Conception, organization, execution; Manuscript: Writing of the first draft, review and critique; Roberto Ceravolo: Research project: Conception, organization, execution; Manuscript: Writing of the first draft, review and critique; Carlo Rossi: Research project: Conception, organization, execution; Ilaria Pesaresi: Research project: Organization, execution; Mirco Cosottini: Research project: Organization, execution; Manuscript: review and critique; Ubaldo Bonuccelli: Research project: Conception; Manuscript: review and critique.

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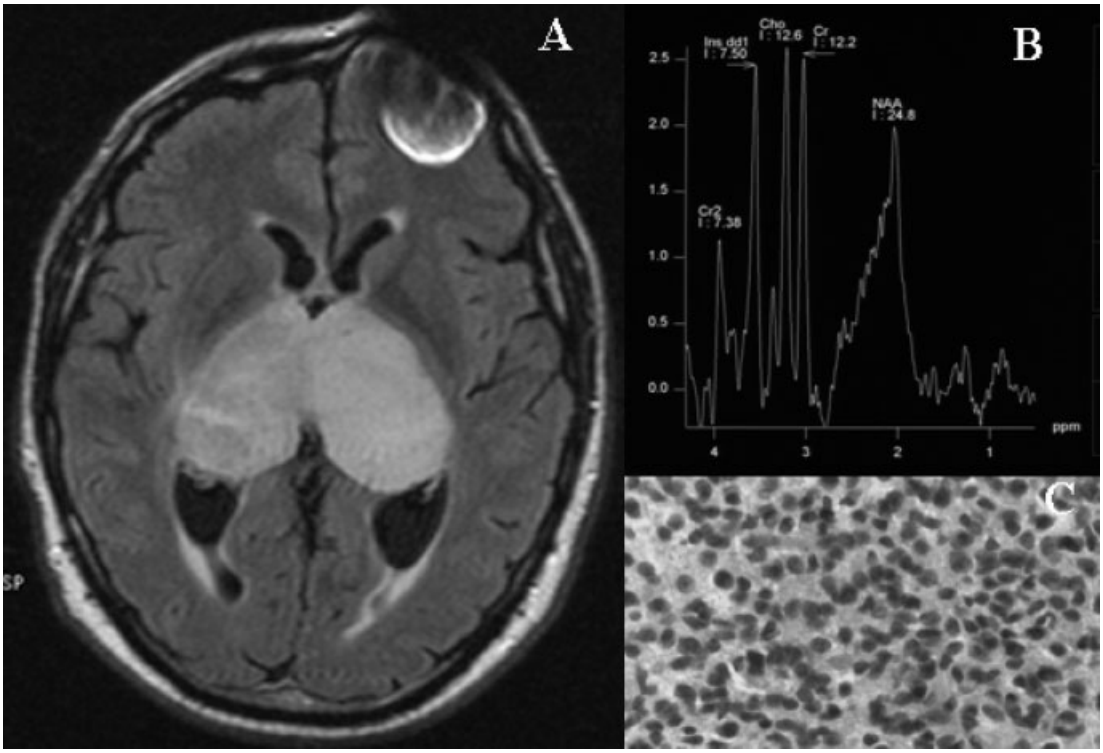

FIG. 1. (**A**) FLAIR imaging showing bilateral enlarged, high signal intensity thalami; (**B**) MR spectroscopy; and (**C**) Hematoxylin–eosin colored lesion tissue.

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Deep Brain Stimulation for Parkinson's Disease when HIV Coexists

The incidence of movement disorders in human immunodeficiency virus (HIV) infected patients is low,[1] around 1%, and of these, about 50% have Parkinsonism related to the HIV.[2] With improved medical therapy for HIV and its complications, such patients are surviving longer, and in line with the aging general population, are prone to developing other degenerative disorders. Deep brain stimulation (DBS) is recognized as an effective treatment for medically refractory Parkinson's disease.[3] Surgeons have had to adapt to deal with the challenging spectrum of HIV and its diseases. Risk of infection when implanting prostheses is one such concern. Complications of implantation of DBS electrodes into the brain can have significant morbidity.[4] We describe a case of deep brain stimulation of the subthalamic nucleus in a patient with Parkinson's disease who also had HIV infection.

A 47-year-old right-handed Caucasian man was initially diagnosed with HIV at the age of 20 after presenting with lymphadenopathy. He was started on antiretroviral treatment in 1986, and he never had HIV-related complications. At the

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age of 40, he first noticed symptoms of Parkinson's disease. As his rigidity and bradykinesia worsened, he was started on multiple typical medical therapies, including Ropinirole, Carbidopa, Levodopa, and Entacapone.

Over years and despite these, he suffered significant on/off fluctuations and severe global dyskinesias. After investigation and multidisciplinary medical, cognitive, psychiatric, and surgical consideration, he was offered deep brain stimulation for his motor symptoms. Preoperative CD4 count was 650 cells/cu mm and viral load was undetectable. There were no neurological symptoms or signs relating to HIV. His HIV medications were Nevirapine 200 mg twice daily and a Emtricitabine/Tenofovir combination (Truvada) one tablet once daily, which he continues to date.

The subthalamic nuclei (STN) were targeted bilaterally using the MRI-based direct targeting stereotactic technique refined by test stimulation and intra-operative clinical assessment in the awake state.[5] As there were concerns over potential risks of hardware infection, the wires were not externalized in the immediate postoperative period for clinical testing (as we would do normally) and the battery was inserted subcutaneously on the same occasion as electrode implantation. Electrode position was assessed by postoperative stereotactic CT fused with the preoperative MRI. The patient was treated with 1.5 g three times daily of prophylactic cefuroxime for three days.

On the first day, postoperatively, he suffered transient mild hallucinations. The pulse generator was switched on two days later to a voltage of 1.4 without significant dyskinesias and without titration of dopaminergic doses at that stage. He was discharged home day 5 postoperatively, to continue with programming and drug adjustments on an outpatient basis.

At follow-up, 17 months later, his stimulation settings for the left electrode were: case+ contact 2−, voltage: 3.7 V, pulse width: 60 μs, frequency 130 Hz and for the right electrode: case+ contact 6−, voltage: 3.1 V, pulse width: 60 μs, frequency: 130 Hz. He reported no apparent side effects and no dyskinesias; his rigidity and mobility were significantly improved with mild improvement in his speech. His levodopa equivalent medication dosage had been decreased by 25% to Carbidopa-Levodopa (Stavelo) 100 mg six times daily and Ropinirole (extended release) 20 mg daily. His UPDRS post stimulation was 14 on-medication (preop: 39 off, 22 on).

This is a case of DBS in a patient with idiopathic Parkinson's disease who also suffered from co-incidental HIV. This combination raises important clinical issues. There is a concern that immunosuppressive diseases may increase the risk of postoperative infection in surgical patients. Further, with an implanted foreign body into the brain, the consequences of an infective complication could be grave. Previous case reports suggest good outcomes in HIV positive patients undergoing major aorto-femoral bypass surgery.[6] One recent study found that the post surgical infection rates of HIV patients undergoing orthopaedic implant surgery, including arthroplasty, were statistically similar to non HIV-infected patients when prolonged prophylactic antibiotics and systematic antiretrovirals were administered appropriately.[7] DBS surgery is indicated in medically refractory patients with Parkinson's disease. On the basis of this case, we suggest that patients with HIV disease and a normal CD4 count are not at any added risk.

Author Roles: (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique. Hettige: 3A, 3B; Samuel: 3A, 3B; Clough: 3B; Hulse: 3A, 3B; Ashkan: 3A, 3B.

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Classic Pelizaeus-Merzbacher Disease in a Girl with an Unbalanced Chromosomal Translocation and Functional Duplication of *PLP1*

Video

We report the case of a 2½-year-old girl, first child of nonconsanguineous parents. Family history is unremarkable. The pregnancy and term delivery were normal.

Hypotonia and poor head control were noted at 3 months, nystagmus and esotropia at 4 months, and head titubation at 8 months of age; dystonia developed at 1 year. She does not have seizures.

Motor development was significantly delayed with rolling at 9 months, and at 2½ years she is unable to sit. She has a palmar grasp and can transfer objects. First words were spoken at 1 year with a current vocabulary of 10 to 15 words. She is a social and interactive child.

Examination showed severe failure to thrive, with weight of 8.8 kg (2 kg below the 3rd percentile), length 78 cm (98th percentile), and head circumference 48 cm (50th percentile). She had marked head titubation, axial hypotonia, and appendicular hypertonia, particularly in her lower limbs. Dystonia was evident in all four limbs. She lacked nystagmus and eye movements were normal. Hyperreflexia, with spread and bilateral crossed adductor reflexes, was present in the lower limbs. Plantar responses were upgoing bilaterally.

Magnetic resonance imaging (MRI) at 2½ years showed profound diffuse hypomyelination involving the brainstem, internal capsules, corpus callosum, and deep and subcortical white matter of the cerebral hemispheres (Fig. 1). Magnetic resonance spectroscopy was normal and other investigations including serum lactate and very long-chain fatty acids were normal.

Routine chromosomes were normal. Microarray analysis of chromosomes showed duplication of Xq22.2, including the proteolipid protein gene (*PLP1*) gene, and duplication of 1p36.32. Fluorescence in situ hybridization confirmed the insertion of an extra copy of Xq22.2 into 1p36 and duplication of 1p36.32. The diagnosis of Pelizaeus-Merzbacher disease (PMD), due to an extra copy of the *PLP1* gene, contained in the duplicated segment of the X chromosome, was carried out.

PMD is an X-linked dysmyelinating disorder of the central nervous system, characterized by nystagmus, hypotonia, and developmental delay, with subsequent progressive spasticity. It is divided into connatal and classic forms. Connatal PMD, the most severe, presents shortly after birth with nystagmus, hypotonia, seizures, and stridor. Classic PMD, the commonest form, presents in the first few months, with nystagmus, hypotonia, and motor delay. Head titubation, limb spasticity, ataxia, and extrapyramidal features develop within the first few years, whereas the nystagmus becomes less evident and may disappear.[1,2] Cognitive abilities are impaired to a lesser degree than motor abilities. The classic MRI feature of PMD is diffuse hypomyelination.[1,2]

PMD is caused by alterations in the *PLP1* gene, located atXq22, and it is allelic to spastic paraplegia 2 (SPG2). *PLP1* duplications cause 60 to 70% of cases, usually causing classic PMD. Point mutations account for 20 to 30% of patients, causing a range of clinical phenotypes, from connatal PMD to SPG2.[1,2]

Since PMD is X-linked, typically affected persons are men. Most female carriers are asymptomatic. Symptomatic female carriers have a milder phenotype and later onset than affected men in the same family.[3] Female carriers of *PLP1* duplications are usually asymptomatic due to skewed X inactivation, with the duplicated X chromosome preferentially inactivated.[4]

Women with classic or connatal PMD are uncommon. A few case reports exist, but these predate genetic testing for this disorder. Women with *PLP1* mutations presenting in childhood have a milder clinical phenotype than classic PMD,[5,6] or other contributing abnormalities.[7]

Our patient presented with features consistent with classic PMD. Her unbalanced chromosome rearrangement results in a functional duplication of *PLP1*. A female patient with functional disomy for Xq22-q23 due to complex rearrangements of chromosomes 3 and X has been reported.[8] Despite the presence of two active copies of *PLP1*, she did not show features of PMD, suggesting other factors are at play in the pathogenesis of this disorder. For our patient, the predominant problem is PMD, and although the duplication of 1p36 is not associated with PMD, it could be contributing to the severity of her phenotype because it is associated with poor weight gain, developmental delay, and variable congenital anomalies of the heart and skull, the latter two of which she lacks.

In conclusion, we describe a woman with classic PMD secondary to an unbalanced chromosome rearrangement, and functional duplication of *PLP1*. In patients with typical clini-

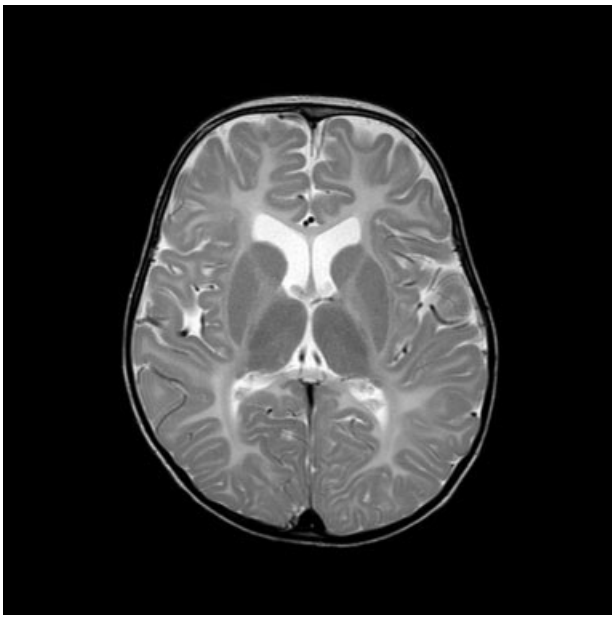

FIG. 1. T2 axial magnetic resonance imaging at age 21/2 years showing diffuse hypomyelination of the internal capsules, subcortical white matter and deep white matter.

Additional Supporting Information may be found in the online version of this article.

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cal and radiographic features of PMD, female gender should not exclude the possibility of PMD without genetic testing for *PLP1* mutations.

LEGENDS TO THE VIDEO

Patient at age 2½ years with main features of axial hypotonia, appendicular hypertonia, dystonia, and head titibuation.

Author Roles: E.M. Yiu: Manuscript: Writing of first draft, review and critique; S.A. Farrell, Manuscript: Review and critique; T. Soman, Manuscript: Writing of first draft, review and critique.

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Excellent Response to Oral Zolpidem in a Sporadic Case of the Myoclonus Dystonia Syndrome

Video 

Zolpidem is an imidazopyridine agonist with a high affinity for the benzodiazepine receptor α1 subunit site.[1] It has been reported that this drug improves motor symptoms in patients with various movement disorders including, Parkinson's disease and focal dystonias.[1] Here, we present a patient with the myoclonus dystonia syndrome, unresponsive to other medications that was successfully treated with oral zolpidem administration.

A 36-year-old woman, a middle school teacher, presented for evaluation of involuntary jerking movements of the neck for over 16 years. The frequency of these movements slowly progressed over time and increased during certain stressful situations or with increased concentration; they were interfering with social activities. The patient reported no history of head trauma, peripheral traumatic or surgical incidents, or neurological diseases. There was no exposure to neuroleptic medications. There was no family history of movement disorders.

On examination, the patient had lightning myoclonic jerks of the neck directed to the left side at rest, and movement with slight dystonia of the neck toward the same side. The frequency of myoclonic jerks and the intensity of the dystonia were reduced by touching the forehead or neck. There was no observable myoclonus or dystonia on the limbs (Video, segment 1). The evaluation including neuropsychological testing for memory and frontal lobe functions, a magnetic resonance imaging of the brain, an electroencephalogram, serum chemistries, a complete blood count, serum ceruloplasmin, thyroid function tests, and genetic testing for the DYT1 mutation in the torsion A gene and ϵ-sarcoglycan gene (SGCE), were all normal. The symptoms were not improved with oral levodopa, trihexiphenidyl, or diazepam treatment.

We evaluated the effectiveness of a priori treatment using 10 mg zolpidem tartrate. The symptoms near completely resolved within 1 hour after taking this medicine and the patient was symptom-free for 6 hours without somnolence (Video, segment 2). With dose escalation to 10 mg four times a day, the patient's symptoms improved and she could carry out the normal activities of daily living during daytime.

The myoclonus dystonia syndrome is a rare dominantly inherited disorder characterized by a variable combination of myoclonic jerks and dystonia. Although the disease is benign in most cases and could improve spontaneously, sometimes, these abnormal movements interfere with the daily activities of living.[2] Myoclonus is a most disabling finding; it appears predominantly in the neck and upper limbs and infrequently

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involves the legs. Treatment with anticholinergic drugs, clonazepam, and diazepam have been reported to relieve the myoclonus in some cases.[2] Recently, sodium oxybate has been shown to be effective in several patients with ϵ-sarcoglycan linked myoclonus dystonia.[3] In addition, deep brain stimulation with the internal globus pallidus or thalamus as targets has been reported to be safe and effective.[2]

The pathophysiology of myoclonus dystonia syndrome is largely unknown; however, involvement of the basal ganglia in the myoclonus dystonia syndrome has been suggested based on neurophysiological studies.[4] In addition, myoclonus in the myoclonus dystonia syndrome appears to be generated at the subcortical level, and possibly involves basal ganglia and brainstem circuits.[2,5]

Zolpidem is a selective agonist of the benzodiazepine subtype receptor BZ1. The location of the highest density of zolpidem binding receptors is in the output structure of the basal ganglia—the ventral globus pallidus, the substantia nigra pars reticulate, and the subthalamic nucleus.[1] Dystonia is associated with hypoactivity of the globus pallidus interna and widespread brain alterations in the $GABA_A$/benzodiazepine receptors.[6] In addition, the paradoxical responses of benzodiazepine to myoclonus are probably related to their action on the $GABA_A$ receptors.[7] Although the precise mechanism of zolpidem remains unclear, by binding to these sites zolpidem may help restore the basal ganglia output influence on the thalamus and motor cortex resulting in the improvement of motor symptoms in some movement disorders including the myoclonus-dystonia syndrome. In addition to the direct drug effects on the basal ganglia and associated structures, we cannot rule out the possibility that the anxiolytic influence or placebo effect of zolpidem may contribute to its beneficial effects on the disease.

In conclusion, this case suggests oral zolpidem may be a useful pharmacologic alternative for patients with the myoclonus dystonia syndrome that are unresponsive to other medical treatment.

Author Roles: I.-S. Park and J.-S. Kim wrote the first draft of the manuscript. J.-Y. An, Y.-I. Kim and K.-S. Lee contributed the manuscript writing process and were involved in the patient's care. Review of initial manuscript for major intellectual content and critical revision was done by J.-S. Kim. All authors read and approved the final manuscript.

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LEGENDS TO THE VIDEO

Segment 1. The patient had lightning myoclonic jerks of the neck to the left side during at rest and cervical dystonia toward the same side. The frequency of myoclonic jerks and the intensity of dystonia were reduced by touching the forehead or neck. There was no observable myoclonus and dystonia on the limbs.

Segment 2. One hour after oral zolpidem administration. The myoclonus was almost resolved.

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