

Letters to the Editor Related to New Topics

Plasma Phenylalanine Level in Dopa-Responsive Dystonia

DYT5 is a condition characterized by levodopa (L-dopa) responsive dystonia (DRD) that shows childhood onset and marked diurnal fluctuation. Patients with DYT5 have heterozygous mutations in the GCH1 gene, which codes for GTP cyclohydrolase I (GTPCH), a rate-limiting enzyme in tetrahydrobiopterin (BH₄) synthesis.¹ BH₄ is a cofactor for aromatic amino acid hydroxylases including tyrosine hydroxylase (TH), phenylalanine hydroxylase (PAH), and tryptophan hydroxylase.² In patients with DYT5, production of dopamine is suppressed due to the decrease of BH₄ because TH is a rate-limiting enzyme in dopamine synthesis. The lack of BH₄ may also affect the activity of PAH, and patients with complete GTPCH deficiency show hyperphenylalaninemia. However, hyperphenylalaninemia has not been reported in patients with DYT5.³ Therefore, we examined blood phenylalanine levels in patients with DYT5 compared with controls to determine whether the decrease of BH₄ in DYT5 affects PAH activity.

Blood samples for analysis of amino acids were obtained from seven patients with DRD⁴ and heterozygous mutations of GCH1, 24 patients with dopa nonresponsive dystonia (non-DRD), and 12 controls. The samples were collected in a tube containing EDTA, and plasma was obtained for analysis of phenylalanine and tyrosine levels using an auto-amino acid analyzer (HS-3000; Hitachi, Tokyo, Japan). All data are expressed as means \pm SD. The data were analyzed by analysis of variance (ANOVA) with multiple comparison using the Bonferroni method. A significant difference was defined as a *P* value < 0.05.

The phenylalanine and tyrosine levels in the plasma of patients with DYT5, patients with non-DRD, and controls are shown in Figure 1. The phenylalanine levels in the DYT5 (81.1 \pm 26.6 μ mol/L), non-DRD (60.5 \pm 14.5 μ mol/L), and control (58.7 \pm 9.1 μ mol/L) groups were all within the normal range. However, the phenylalanine level in patients with DYT5 was significantly higher than those in the other groups (*P* = 0.027 by ANOVA). Multiple comparison also indicated that the level of plasma phenylalanine in patients with DYT5 was significantly higher than those in patients with non-DRD (*P* = 0.043) and in controls (*P* = 0.040). There was no significant difference in the plasma phenylalanine levels between

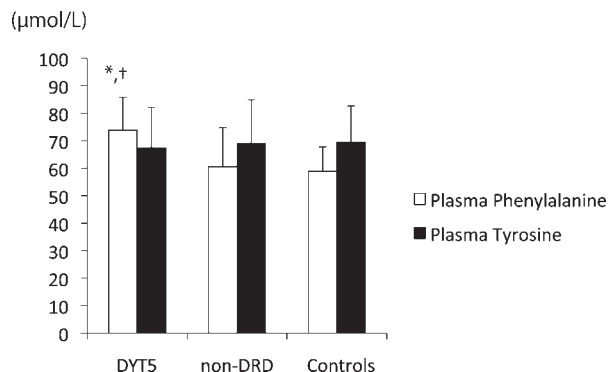


FIG. 1. Plasma phenylalanine and tyrosine levels. The plasma phenylalanine levels (open boxes) and tyrosine levels (closed boxes) are shown for patients with DYT5, patients with non-DRD, and controls. Error bars indicate standard deviations. **P* < 0.05 (DYT5 vs. non-DRD). †*P* < 0.05 (DYT5 vs. controls).

patients with non-DRD and controls. There were no significant differences in plasma tyrosine levels among all the groups.

BH₄ deficiency causes hyperphenylalaninemia and a decrease of dopamine production, because it suppresses the activity of PAH and TH. Patients with a homozygous mutation in the GCH1 gene are reported to show hyperphenylalaninemia, in addition to DRD. Patients with DYT5 having only a heterozygous mutation in GCH1 also show symptoms of DRD, but do not have hyperphenylalaninemia. Our results indicated that blood phenylalanine levels in patients with DYT5 are within the normal range, but are higher than those in controls, which suggests that the activity of PAH is partially affected by the decrease in BH₄ in DYT5.

GTPCH is regulated by BH₄ itself and phenylalanine via GTPCH feedback regulatory protein (GFRP).⁵ An increase of phenylalanine induces GFRP to upregulate GTPCH activity, whereas an increase of BH₄ downregulates GTPCH activity via GFRP. Hyland et al. has reported prolonged hyperphenylalaninemia after oral phenylalanine loading in patients with DRD,⁶ which suggests that decreased BH₄ production due to mutations in GTPCH restrict the catalysis of excessive phenylalanine by PAH. However, a defect in GFRP or in the interaction between GTPCH and GFRP would cause the same results. Our results indicate that the phenylalanine level in patients with DYT5 differs from those in controls without phenylalanine loading, which suggests that a partial defect of GTPCH affects the activity of PAH.

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Hybrid Cars May Interfere with Implanted Deep Brain Stimulators

Clinicians and patients are always concerned about potential interference between external electromagnetic fields and implantable pacemaker devices. In a recent *New York Times* article, concern was raised about emitted “magnetic fields” from hybrid cars and association with various diseases such as childhood leukemia.¹ We report a case of a patient with deep brain stimulator placement for Parkinson’s disease who developed unusual symptoms possibly related to stimulator malfunction while riding in a hybrid car.

A 73-year-old man with history of tremor-dominant Parkinson’s disease (PD) underwent bilateral subthalamic nucleus deep brain stimulator (STN DBS) placement. One month later, initial stimulator programming was performed,

and he complained of symptoms of severe nausea, dizziness, and palpitations while driving the 4- to 5-hour journey home in a 2008 hybrid Toyota Prius car. The patient’s wife had to stop the car multiple times as he felt so ill. Prior to initial programming, the patient was able to drive and ride in the Prius without any problems. After stimulator activation, the patient complained of reproducible symptoms of nausea, dizziness, lightheadedness, and cardiac palpitations when sitting in the front passenger seat. He noticed that the symptoms worsened when both the gasoline engine and electric motor were running or when the car battery was charging. The symptoms spontaneously resolved when he exited the car and never occurred when he was in his truck, which is a nonhybrid vehicle. The symptoms also improved when he manually turned off his stimulator while inside the Prius or when he moved to the back seat. These symptoms did not occur at any other time. On interrogation of his stimulator 4 weeks after initial DBS programming, seven activations were noted with only two that were accounted by the patient turning the pulse generator off and on manually. The internal pulse generators (IPGs), however, had been on 99% of the time.

The patient experienced the worst symptoms when sitting in the front seat of the Prius and when the car battery was being charged, suggesting that the electromagnetic field emitted might be interfering with his neurostimulator settings. There were multiple unaccounted activations on interrogation of the stimulator, although the IPGs were on 99% of the time. He did not get symptoms in a nonhybrid car or in the Prius when his IPG was off. We have observed similar symptoms when the voltage of an STN neurostimulator was increased rapidly. We hypothesize that the device was turning off and on rapidly, with voltage surges, thus causing the patient’s symptoms. This is the first documented case of a hybrid vehicle, potentially interfering with the IPG settings in a subject with PD and STN DBS. There has been controversy over the effect of electromagnetic fields generated by hybrid vehicles on cardiac pacemakers and implantable defibrillators. Patients with cardiac pacemakers have complained of similar symptoms as the ones which our patient experienced when inside a hybrid car or near its smart key device (internet message boards).² In the Prius owner’s manual, Toyota warns that people with implanted pacemakers or cardiac defibrillators should keep away from the vehicle smart entry and start system antennas.³ Currently, the manual does not comment specifically about DBS. We recommend that such patients should not drive a Prius or other hybrid vehicle until more research and data are available for theirs and others safety. Whether they are safe as passengers remains to be proven. Further investigation should include measurement of all electromagnetic fields and frequencies generated in hybrid and electric cars, including the Toyota Prius, and evaluating for deep brain stimulator device interference or malfunction.

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Deep Brain Stimulation in Acute Management of Status Dystonicus

Video 

Status dystonicus (SD) is a rare life-threatening complication of primary or secondary dystonia manifesting by rapid worsening into a clinical picture of extreme, generalized, continuous and painful contractions requiring urgent hospitalization.¹ SD can lead to rhabdomyolysis and ultimately severe exhaustion and metabolic failure. Treatment is always difficult.^{2,3}

We present a case of severe SD in a 12-year-old boy with primary generalized dystonia (non-DYT1) that was successfully treated with bilateral deep brain stimulation (DBS) of the internal globus pallidus (GPi).

The patient's complaints began at the age of 8 years with writer's cramp of his right hand. Over the next 3 years, he gradually developed dystonia of the left leg and cervical dystonia. At the age of 11, truncal and cervical dystonia predominated resulting in the total disability of the boy. In November 2007, within a single week and without any provoking factor, the clinical picture rapidly progressed to SD with manifestations of generalized mobile dystonia of the trunk, neck, and the limbs with only partial relief during sleep. The patient's Burke Fahn Marsden dystonia score (BFMDS) raised to 41.

The patient was subsequently treated with biperiden, baclofen, tetrabenazine, clonazepam, and diazepam with no clinical benefit. Finally, to relieve exhausting and painful dystonic contractions accompanied with profuse sweating, myoglobinuria, and later anuria, the patient was intubated and therapeutic coma was introduced using propofol, midazolam, atracurium, sufentanil, and tramadol. However, truncal dystonia reappeared whenever the relaxation and/or sedation were reduced.

Two weeks after the beginning of SD, the patient had quadripolar electrodes (3389, Medtronic, Minneapolis, MN) implanted to the posteroventrolateral portion of the GPi bilaterally. Although the DBS was started immediately after implantation, there was no observable change in the condition over the next 3 weeks.

One month after surgery, the truncal contractions became less intense and the dystonic episodes were less frequent. Artificial ventilation was maintained for 45 days and controlled analgesia for 70 days. During the second month after surgery, the episodes of truncal dystonia gradually disappeared. At the time of discharge from hospital, the boy manifested only mild dystonia on his right hand. His BFMDS had dropped from 41 to 5. Oral medication was limited only to biperiden. During the next 6 months, focal right hand dystonia diminished gradually (BFMDS = 1). He was able to return to school and continue with the same class. His school record, always above average, remained unaltered. At present, 15 months after the surgery, his right hand dystonia is only slightly worse (BFMDS = 3).

There is no generally accepted procedure for the management of the SD. Temporary suppression is only feasible by using general anaesthesia.^{1,4} Prior to that, anticholinergics, typical neuroleptics, tetrabenazine,³ or intrathecal baclofen^{5,6} are usually recommended. Benzodiazepines can help just as much as precipitate the development of SD.¹ Surgery is usually considered as the last option for SD. There were seven published cases of stereotactic lesions (three pallidotomies,^{4–6} three thalamotomies,^{1,7} one pallidothalamotomy⁸) and five cases of bilateral GPi DBS.^{2,4,9,10} These were cases of primary or secondary dystonia of various aetiology, with the SD mostly manifested in childhood. However, most of them had surgery performed only after the SD diminished or disappeared. Exceptions comprised acute pallidothalamotomy⁸ in one case and acute GPi DBS implantation in three patients¹⁰ performed 2–6 months after the onset of SD. All of these patients showed significant postoperative clinical improvement in one day to 3 months' time.^{8,10}

In our patient, the amplitude was gradually increased to 1.5 V on the left and 1.3 V on the right (450 μ s, 130 Hz, unipolar setup with active contacts 0 and 1 bilaterally). These parameters differed from those in previous SD cases in which an amplitude of 3.5–4.2 V, a pulse duration of 90–120 μ s and a frequency 130–185 Hz were used.^{2,10} In addition, our patient underwent surgery only 2 weeks after the onset of SD, i.e., much earlier than in previous reports. Our decision was prompted by the patient's serious condition and by the lack of response to oral treatment. Although the first signs of clinical improvement did not appear until a month after the GPi DBS started, maximum improvement finally reached 98%. This is a stronger effect than in any of the reported cases (0–20%).¹⁰ Keeping in mind the general predictors^{11,12} of clinical outcome of GPi DBS in dystonic patients, we can only speculate that this extremely successful outcome may be related to the different stimulation parameters or the early implantation so shortly after the onset of SD.

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

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LEGENDS TO THE VIDEO

Segment 1. One year before SD: dystonia of the right hand and shoulder when writing.

Segment 2. Three months before SD: cervical and truncal dystonia with jerky movements when standing and walking.

Segment 3. Second day in SD: The patient suffers from painful involuntary contractions of his back and neck muscles.

Segment 4. Seven weeks after implantation: dystonia of both hands, mild truncal and shoulder dystonia; first steps after withdrawal of analgesedation.

Segment 5. One year after implantation: marked improvement, only mild dystonia of the right hand.

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Reversible Encephalopathy and Axonal Neuropathy in Parkinson's Disease During Duodopa Therapy

Patients with Parkinson's disease (PD) assuming high dose of levodopa (L-dopa) might be exposed to the risk of neurological syndromes.¹⁻³ We report a PD patient who developed a severe encephalopathy and axonal neuropathy during Duodopa (D) therapy.

A 74-year-old woman with a 15-year history of PD was admitted to our department because of the subacute onset of a confusional state and tetraparesis.

Five months before, due to the presence of severe motor fluctuations, oral dopaminergic treatment (1200 mg/day L-dopa equivalents plus entacapone) was replaced by 76 mg/hr of daily D infusion with a significant clinical improvement.

One month before the admission the patient began to complain of bilateral pins-and-needles paresthesia and numbness in both her feet sole and, to a lesser extent, in her hands. The nerve conduction study was consistent with mild axonal sensorimotor polyneuropathy.

Two weeks before admission, after an accidental fall, the patient underwent surgery under general anaesthesia for the reduction of her left arthroprothesis dislocation. Surgery and postoperative course were without complications, and the patient was discharged home. However, on the 14th postoperative day she developed increasing weakness in both lower and upper extremities and became disoriented and increasingly confused. She was referred to our department.

On neurological examination the patient showed decreased consciousness level. If aroused vigorously she was confused and disoriented. Motor examination revealed a severe flaccid tetraparesis. Intermittent multifocal nonepileptic myoclonus was observed. General examination findings were unremarkable. An extensive diagnostic work-up (Table 1) did not support a possible immunologic, paraneoplastic, infective nor inflammatory origin of the patient's encephalopathy and peripheral polyneuropathy. Serum VB12 level was 224 pg/mL (range 200–900), serum homocysteine (Hcy) was 59 µmol/L (normal values <15), serum methylmalonic acid (MMA) was 0.22 µmol/L (normal values <0.15) with a urinary level of 20 µg/mL (normal values <5).

The day after admission, D infusion was withdrawn and replaced with a reduced dose of oral L-dopa plus entacapone. The patient rapidly improved. Within 48 hours we observed an almost complete mental status recovery. On 3rd day of D suspension, after the laboratory evidence of VB12 deficiency, supplementation was started.

Two weeks later, serum VB12 and homocysteine, serum and urinary MMA levels were normal. The strength of her upper and lower limbs was clearly improved. Three months later she was able to walk with a cane.

Cobalamine deficiency can cause neurological symptoms with the combination of axonal neuropathy and encephalopathy with behavioural changes, psychosis and cognitive

decline.⁴ Low normal values of serum VB12 and high levels of serum Hcy and MMA and urinary MMA, as observed in our patient, are typical laboratory findings of a VB12 deficiency.⁵ In a cobalamine deficient patient the exposure to nitrous oxide with inhalational general anaesthesia may lead to the abrupt and often delayed onset of severe neurological manifestations.⁶

Post-surgery confusional states are not rare in PD patients and tend to resolve after some days. However in our case, postoperative course was without complications and mental status abnormalities appeared only 2 weeks after.

Clinical and laboratory findings indicate a relationship between our patient's symptoms, VB12 deficiency and chronic administration of L-dopa high doses. Recently Toth et al.² have reported an increased incidence of peripheral neuropathy consequent to cobalamine abnormalities in PD patients on L-dopa therapy, suggesting an association between neuropathy and L-dopa exposure.

Even if VB12 abnormalities seem to play a major role in the development of our patient's symptoms, we cannot exclude alternative hypothesis. The time course of our patient's symptoms and the rapid recovery of her mental status after D withdrawal and before VB12 supplementation, support the possibility of a direct neurotoxicity of high-dose chronic L-dopa treatment.³

TABLE 1. Diagnostic workup

	On admission	2 Wk after D withdrawal
Routine blood laboratory ^a	Normal	Normal
Serum protein and immunofixation electrophoresis	Normal	Normal
Thyroid function tests	Normal	Normal
Antinuclear and antinerve Ab ^b	Not detectable	Not detectable
HIV	Negative	Negative
CSF (standard ^c and PCRs ^d)	Normal	Normal
MTHFR gene	Heterozygosity for the polymorphism C677T	–
Endoscopy ^e	Normal	–
Brain and spine MRI	Normal	Normal
Total body CT and PET scan	Normal	–
EEG	Diffuse slowing mostly in theta-delta range	Normal
Nerve conduction study ^f	Severe axonal neuropathy	–

^a(Blood count, glucose level, electrolytes, eritrocites sedimentation rate, liver and renal function, folate levels: Normal).

^bAntinuclear and antinerve antibodies (anti-Hu, anti-Yo, anti-R, anti-GQ1b, anti-GM1).

^cNormal level of protein, no cells; oligoclonal bands not detectable in three different determinations (on admission and after 2 and 4 weeks).

^dFor HSV, EBV, and CMV DNA: Negative.

^ePEJ correctly placed, normal surrounding bowel; no signs of gastropathy.

^fAbsence of sural, superficial peroneal, and radial SAPs and common peroneal and tibial CMAPs. Ulnar CMAPs were markedly reduced (0.4–0.5 mV).

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Compared to the oral treatment, high dopamine levels due to the faster D absorption and probably reduced renal excretion, may increase the risk of neurological adverse effects

Interestingly, Antonini et al.⁷ described the case of a patient who developed an acute polyneuropathy after 7 months of D treatment. The possibility of Guillain-Barré syndrome was hypothesized, but treatment with plasmapheresis did not lead to any significant improvement and D treatment was interrupted.

Our findings, as other authors previously argued,^{1–3} confirm that PD patients taking high dose of L-dopa may present central and peripheral nervous system syndromes. In this setting a cobalamin deficiency may occur and VB12 supplementation may be useful. The exposure to nitrous oxide with inhalational general anaesthesia may increase the risk of severe neurotoxicity and should be carefully considered.

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Restless Legs Syndrome as an Initial Manifestation of Metastatic Conus Medullaris Lesion

Restless legs syndrome (RLS) is a common sleep disorder characterized by an unpleasant sensation of the legs, associated with the urge to move them. The symptoms are prominent at rest, mainly during night time and relieved with leg movement.¹ Periodic limb movements in sleep (PLMS) are seen in up to 80% of patients with RLS.² RLS could be idiopathic or secondary to other disorders.² Idiopathic RLS classically presents before the age of 45 years, whereas secondary RLS occurs later in life.² Although myelopathy is one of the common causes of secondary RLS, RLS has never been reported in patients with conus medullaris syndrome (CMS). Herein, we report a 64-year-old man experienced RLS symptoms which predated the onset of metastatic CMS.

A 64-year-old right-handed man with hypertension, dyslipidemia, and tobacco abuse was evaluated for a 1-month history of "weird, uncomfortable sensations in both legs, especially at night." The sensation was characterized by tightness of the calves, worse in supine position, and occurring mainly at bedtime. The symptoms were relieved by movement or rubbing of the feet or on walking. Four weeks later, patient began to experience perianal and genital numbness associated with erectile dysfunction. Examination showed decreased pinprick and vibration in S3–S5 dermatome with normal muscle strength throughout. Deep tendon reflexes were normal, except for bilateral patellar hyperreflexia and absence of the ankle jerks. Anal wink and cremasteric reflexes were absent. The patient had difficulty with tandem and toe walking. During hospitalization, the patient developed fecal incontinence and scissoring gait.

Laboratory tests revealed no anemia, normal serum ferritin level (389 ng/mL) and normal kidney function. Lumbar spine MRI showed a 2-cm intramedullary, enhancing lesion at the conus medullaris associated with central edema of the lower thoracic cord (Fig. 1). Brain MRI depicted numerous small, round, enhancing lesions along the gray-white matter junction. Polysomnography revealed PLMS with a severity index of 46.4 events per hour. Patient was subsequently started on gabapentin with partial relief of RLS symptoms. Chest CT revealed a 1.8 × 1.9 cm² mass in the right lower lobe and hilar lymphadenopathy. Bronchoscopic biopsy showed a poorly differentiated, non-small cell carcinoma, consistent with adenocarcinoma. Administration of high-dose dexamethasone partially improved saddle anesthesia and scissoring gait but dramatically alleviated the RLS symptoms.

Patients with CMS typically develop saddle anesthesia with normal strength or only subtle leg weakness.³ Urinary or fecal incontinence tends to occur early in the course of the disease.³ Patients with CMS may experience low-back pain that worsens when supine prior to the onset of sensory deficits.³ To our knowledge, RLS-like symptoms have never been reported as an initial presentation of CMS. However,

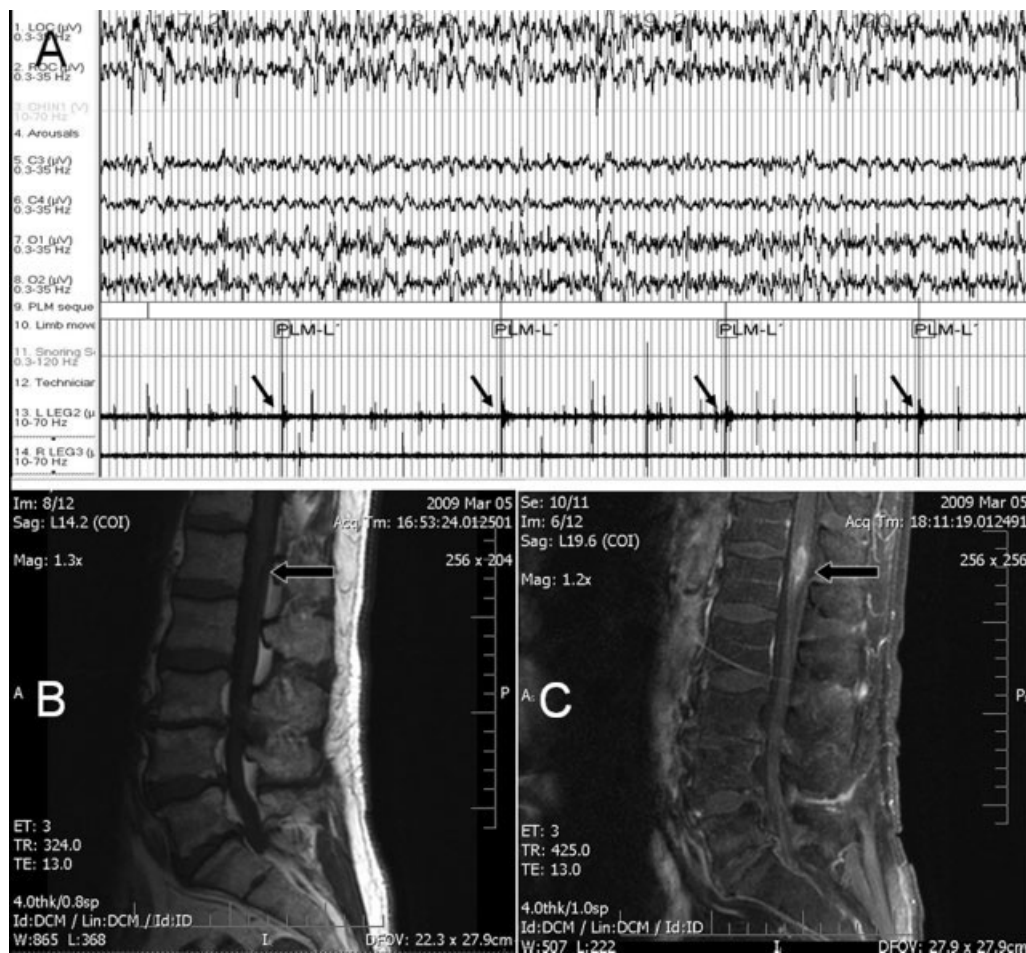


FIG. 1. Polysomnogram and lumbosacral spine MRI. **A:** Overnight polysomnography showing the EEG and the anterior tibialis surface EMG electrodes in 120-s epoch. Periodic leg movements occurring in the left leg at 20- to 40-s interval during NREM sleep (arrow). **B:** Sagittal T1-weighted MRI shows normal-appearing conus medullaris (arrow). **C:** Sagittal T1-weighted MRI with contrast reveals intramedullary enhancing lesion involving conus medullaris (arrow).

our patient first presented with symptoms typical for RLS, which fulfilled the NIH diagnostic criteria.² Our patient also met supportive criteria based on the presence of many PLMS (>15/hr).²

Extrinsic compression at the lumbosacral spine or intramedullary lesions of the conus could cause CMS.³ Differential diagnoses of intramedullary conus lesions includes neoplasms, granulomatous diseases, demyelinating diseases, and myelitis.³ In our patient, brain MRI revealed multiple enhancing nodules located at the gray-white matter junction favoring the diagnosis of metastatic lesions. Metastasis to the spinal cord is uncommon. It accounts for 0.9 to 5% of overall metastases and metastatic conus medullaris lesions are rarely reported.³ The most common metastatic malignancies to the conus medullaris are breast and, like in our patient, lung carcinoma.³

Genetic factors, iron homeostasis, and the central dopaminergic system play an important role in RLS pathophysiology.⁴ Spinal cord lesions are among one of the common causes of secondary RLS.¹ Improvement of CMS after ste-

roid administration followed by elimination of RLS symptoms in the present case hints CMS as a possible etiology of RLS. A small cluster of hypothalamic dopaminergic neurons, A11 nuclei, is the sole source of spinal dopamine. Damage to A11 nuclei or its diencephalospinal tract in animals causes hyperexcitability of the spinal cord and leads to PLM and RLS symptoms.^{1,5} Because the axons of A11 nuclei travel along the entire length of the spinal cord,⁵ the conus medullaris lesion in this patient might disrupt this dopaminergic tract and elicited the RLS symptoms.

The current case highlights the unusual presentation of RLS preceding the onset of CMS from metastatic lung cancer. Intravenous steroids alleviated the secondary RLS symptoms in our patient. Underlying causes of RLS should be explored extensively especially in patients with late-onset RLS.

Author Roles: Teerin Liewluck wrote the first draft of the manuscript and reviewed the literature. Michelle A. Ferreira was involved in the patient's clinical care. Yolanda Reyes-Iglesias and Alberto R. Ramos reviewed and critiqued the manuscript.

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Paraneoplastic Chorea Associated with Breast Cancer

Video 

We report on a unique case of chorea that was caused by paraneoplastic encephalopathy associated with breast cancer.

A 60-year-old woman developed acute schizoaffective psychosis with onset in January 2005. The condition was managed with a combination of neuroleptics (haloperidol, olanzapine, and risperidone) and electroconvulsive therapy. Approximately 2 weeks after the psychosis started, choreatic movements, predominantly on the left hemibody, gradually appeared. Psychiatric symptoms completely resolved by 1 month after their appearance. Thus, neuroleptics were stopped within two subsequent months. However, the movement disorder persisted for more than 2 years.

Two months after the first neuropsychiatric signs had occurred, a ductal carcinoma of the left breast was diagnosed. The patient underwent mastectomy with total exten-

eration of the lymph nodes in the left axilla, followed by one cycle of chemotherapy (5-fluorouracil, doxorubicin, and cyclophosphamide) and antihormonal treatment (anastrozole) with a beneficial effect on the cancer, and she is still in remission.

In September 2007, the patient was admitted to our movement disorder center. Clinical examination showed generalized choreatic movements with predominant involvement of the left extremities (see Video). Laboratory work-up revealed normal routine blood parameters except for an increase of the erythrocyte sedimentation rate to 22/44. Levels of thyroid hormones, oncomarkers, serum copper and ceruloplasmin, titers of rheumatoid factor, the lupus erythematosus phenomenon, antistreptolysin O, lupus anticoagulant, anticardiolipin, and anti-*Borrelia burgdorferi* antibodies were normal. Blood smear did not reveal acanthocytosis. The genetic tests for Huntington's and Wilson's disease were also negative. However, indirect immunofluorescence and ELISA for antineural antibodies (anti-Hu, anti-Ri, anti-Yo, anti-amphiphysin, anti-CRMP5/CV2, anti-Ma1, and anti-Ma2) detected serum positivity for anti-Hu and anti-Ri antibodies. A routine cerebrospinal fluid (CSF) examination for biochemical changes (proteins, glucose, and lactate) and cytology was normal. Immunocytochemical studies of the CSF including isoelectrofocusing revealed oligoclonal banding. Serum and CSF PCR, tests of antibodies (IgG, IgM) against Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, herpes simplex virus 1 and 2, and *B. burgdorferi* were negative. Brain magnetic resonance imaging (1.5 T) disclosed symmetric nucleus caudatus and putamen atrophy, bilateral atrophy of the parahippocampal gyrus and the hippocampus (Fig. 1). Electroencephalography showed mild diffuse slowing of basic activity. The patient had normal cognitive functions (MMSE score was 30). Whole-body fluorodeoxyglucose-positron emission tomography negative, as well as chest CT scan, and echocardiography.

Treatment with amantadine sulphate infusions for 5 days and pulsed intravenous methylprednisolone therapy in a total dosage of 3,000 mg (6 days \times 500 mg) had no effect on the chorea.

To date, only 30 cases of chorea associated with cancer have been reported (included cases are cited by Ref. 1 plus^{2–5}). These include chorea as a paraneoplastic complication of small cell lung carcinoma (18 cases), lung adenocarcinoma (one case), lung mass revealed by radiotomography (two cases), lymphoma (five cases), thymoma (one case), renal cell carcinoma (two cases), and testicular cancer (one case). To the best of our knowledge, no case of chorea associated with breast cancer has been reported so far.

The most frequently detected antineural antibodies associated with chorea are anti-Hu and anti CRMP5/CV2 antibodies. Anti-Hu antibodies in paraneoplastic chorea are mostly reported in association with SCLS.⁶ Interestingly, so far they have not been reported to occur with breast cancer. Anti-Ri antibodies are frequently associated with breast cancer and paraneoplastic opsoclonus-myoclonus-ataxia syndrome. But no case of their association with chorea has been reported.

The role of antineuronal antibodies in the pathogenesis of paraneoplastic disorders has not yet been sufficiently elucidated. The discovery of paraneoplastic antibodies led to the proposal of an autoimmune hypothesis, according to which there is a cross-reaction between antigens of the nervous system and “onconeural” antigens.⁷ Most paraneo-

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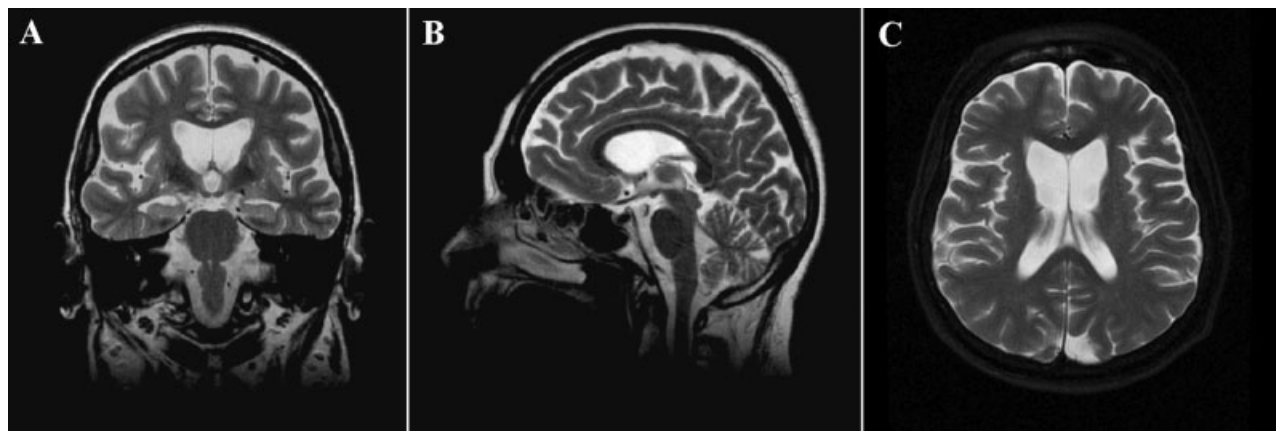


FIG. 1. T2-weighted MRI scans in coronal (A), sagittal (B), and axial (C) planes showing symmetric nucleus caudatus and putamen atrophy as well as bilateral atrophy of the parahippocampal gyrus and the hippocampus.

plastic antigens are localized in the cytoplasm (e.g., anti-Yo) or in the nucleus (e.g., anti-Hu). They are thought to induce cellular immune responses against antigens responsible for the neurological damage. Support for the autoimmune hypothesis of paraneoplastic syndromes is derived from the different effects that therapy has on individual syndromes. In paraneoplastic syndromes with antigens localized on the cell surface, immunotherapy (plasmapheresis, intravenous immunoglobulins, corticosteroids, or immunoabsorption) is generally effective; however, it is often unsuccessful in syndromes with intracellular antigens.⁷ Thus, the chorea of our patient failed to respond to corticotherapy, as the antibodies anti-Hu and anti-Ri are intracellular.

LEGEND TO THE VIDEO

Patient with generalized choreatic movements with predominant involvement of the left extremities during standing and walking.

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Unilateral Periodic Limb Movements: Is This a Pointer for Atypical Presentation of Corticobasal Degeneration Syndrome?—A Case Report

A 75-year old right-handed woman presented with a 1-year history of apathy and slowly progressive language disturbances including decrease in spontaneous speech, monotone speech, and initial loss of verbal fluency. At the time of the first examination, she was not on medication. General neurological examination was normal for age whereas neuropsychological evaluation showed a deficit in language (slow speech, loss of verbal fluency), in sustained attention and abstract capacity. The Mini Mental State Examination (MMSE) was 23/30. The brain CT scan revealed mild diffused atrophy.

Four months later, she developed postural instability with frequent falls and complained of mild sialorrhea. At that time, her MMSE score had deteriorated to 15/30, and Rivastigmine therapy she was started without any clinical improvement.

Her apathy and difficulty in performing household abilities worsened over the following months. The neurological examination performed 1 year later revealed hypomimic face and mild camptocormia, decreased upper limbs swing while walking, mild freezing, mild bradykinesia, and limited vertical upgaze. Mild lead-pipe rigidity was evident in the upper right arm.

Neuropsychological assessment showed deficits in multiple domains (memory functions, constructive praxis, verbal fluency with palilalia, and attention).

A marked diffuse anintensity of basal ganglia with mild midbrain and cortical atrophy was observed in the brain MRI. FP-CIT SPECT showed reduced striatal uptake, with clear-cut predominance on the left side, and the PET scan with fluorodeoxyglucose (FDG) showed major hypometabolism in frontal lobes, with mild predominance on the left side. As she was complaining of moderate difficulties in falling asleep and maintaining it, but without excessive daytime sleepiness, a polysomnographic recording was also performed (Fig. 1). Sleep variables (including microstructural and polygraphic analysis) were evaluated according to the conventional criteria.^{1–3} She had a marked reduction in total sleep time. Pathological PLM index was observed and most PLMS occurred on the right side regardless of the patient's position, confirming the asymmetry of periodic movements. REM sleep without atonia and REM Behavior disorder were not observed.

Two years after the onset, her clinical condition had further deteriorated as she had ideomotor apraxia, marked reduction of vertical eye movements and marked hypofonia, mild right plastic rigidity, alien right limb, bradykinesia and dystonic right leg, right hyperreflexia. Brain FDG PET was repeated at this stage and showed marked hypometabolism in fronto-parietal left lobes.

On the basis of clinical and imaging data, a final diagnosis of corticobasal degeneration (CBD) was made.

The initial presentation of CBD was certainly atypical. The initial symptoms suggested a diagnosis of possible

fronto-temporal dementia, which was supported by the neuropsychological evaluation. A few months later, she developed extrapyramidal signs with MRI findings consistent with a diagnosis of a possible PSP. The FP-CIT SPECT, however, showed a markedly lateralized (left) nigro-striatal dopaminergic dysfunction, which is not typical for PSP, and the FDG PET scan showed a clear hypometabolism on the frontal lobes consistent with the first hypothesis of a frontotemporal dementia, with extrapyramidal signs.

The final clinical diagnosis of CBD was only reached at the end of 2-year follow-up based on the evolution of symptoms and the result of the second FDG PET. A definitive diagnosis cannot be made, due to the lack of neuropathological confirmation. In line with the diagnosis of CBD which is a typical asymmetrical Parkinsonism, the analysis of the polysomnographic recording revealed evident asymmetry of PLMS, with marked prevalence on the right side. It is interesting to note that the polysomnography findings had been observed a long time before a left fronto-parietal hypometabolism was detected with the FDG PET.

Sleep abnormalities in CBD have rarely been investigated with polysomnography. To the best of our knowledge, there are two case reports in which CBD has been associated with subclinical rapid eye movement (REM) sleep behavior disorder (RBD),^{4,5} whereas in other 6 patients described in literature periodic limb movements during sleep (PLMS) have been observed.^{6,7} In particular, Iriarte et al. had described the unilaterality of PLMS in a patient with CBD for the first time, as we have reported in this case.

Our findings suggest, if confirmed in larger populations, that unilateral PLMS could represent a early sign of CBD, useful as a putative supportive feature of the diagnostic process in cases of atypical presentation of CBD.

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FIG. 1. Unilateral periodic limb movements showed at patient's polysomnography.

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Incidental Lewy Body Disease Restricted to the Heart and Stellate Ganglia

α -Synuclein is a major component of Lewy bodies (LBs) and Lewy neurites (LNs), the pathological hallmark of Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Although α -synuclein accumulates both in the central and peripheral nervous systems, including the enteric and cardiac nerve plexuses,^{1,2} neuronal degeneration in PD and DLB is believed to begin within the central nervous system (CNS) and later affect peripheral autonomic neurons. Moreover, LBs occur in a significant proportion of neurologically asymptomatic individuals older than 60 years of age, which is termed incidental Lewy body disease (ILBD). Braak et al.³ devised a staging system for LB pathology, with six stages that characterize a progression from the medulla oblongata (stage 1), through the pontine tegmentum (stage 2), into the midbrain (stage 3), and then the basal prosencephalon and mesocortex (stage 4), and finally through the cerebral neocortex (stages 5–6). In subclinical PD, the LB pathology was almost exclusively in the medulla oblongata (dorsal vagal nucleus) and in the olfactory bulb. However, it is controversial where LB pathology starts and how it progresses. We report a nonparkinsonian young adult who was proved at autopsy to have LBs and LNs in only the cardiac sympathetic nerve and stellate ganglia.

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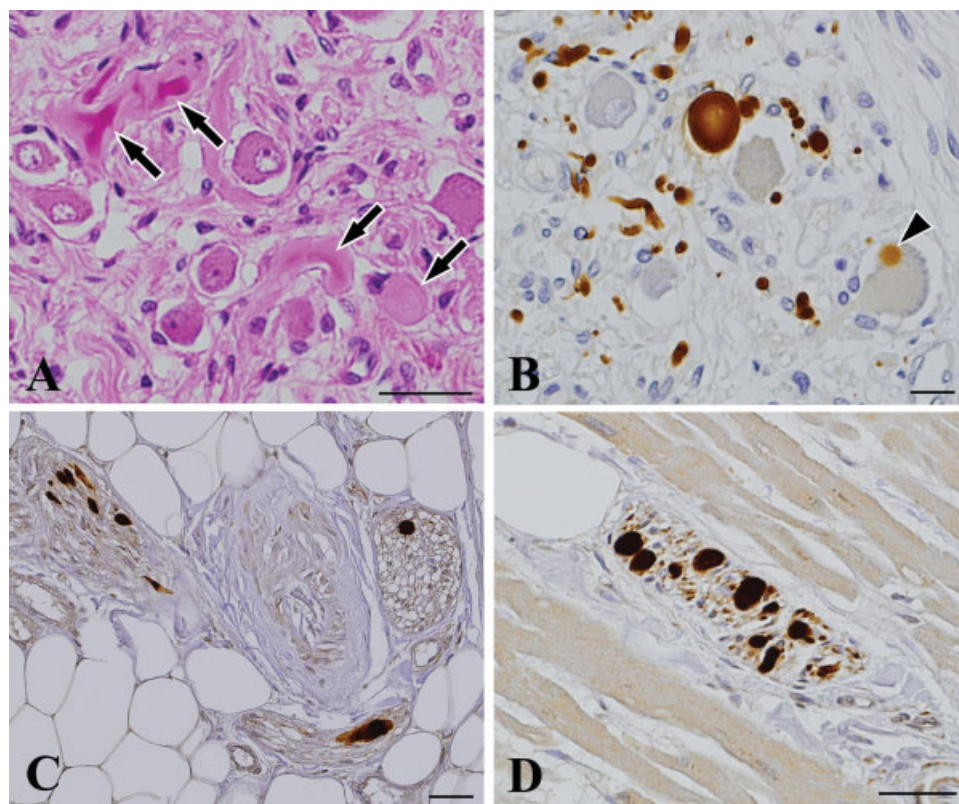


FIG. 1. A: Intraneuritic Lewy bodies (arrows) in the stellate ganglia. Hematoxylin and eosin. B: α -Synuclein-positive Lewy bodies and Lewy neurites in the stellate ganglia. Arrowhead indicates an intracytoplasmic Lewy body. C, D: α -Synuclein-positive Lewy neurites in the epicardium (C) and myocardium of the heart (D). Bars = 20 μ m.

A 35-year-old man without Parkinsonism and autonomic symptoms died of head trauma due to violence by his family member. He had no family history of PD. Postmortem examination revealed neither neuronal loss nor gliosis in the substantia nigra and locus ceruleus. Despite extensive search with α -synuclein immunohistochemistry, no LBs were found in the CNS, including the olfactory bulb and entire spinal cord. The most striking feature was the restricted occurrence of LBs and LNs in the stellate ganglia and cardiac sympathetic nerve, but not in the other visceral organs (Fig. 1). A number of intraneuritic LBs and a few intracytoplasmic LBs were found in the stellate ganglia. In addition, numerous LNs were seen in the cardiac sympathetic nerve; ~ 50 and 70% of the nerve fascicles in the epicardium and myocardium contained abnormal α -synuclein aggregates, respectively.

In ILBD cases, LBs have been reported to occur in the brain, spinal cord, sympathetic ganglia, and visceral autonomic nervous system. Braak et al.⁴ reported that α -synuclein accumulates in the enteric nerve plexuses in a patient with ILBD (Braak stage 2). However, there have been only a few cases, in whom LBs were restricted to the peripheral autonomic nervous system. Abbott et al.⁵ have shown that constipation could be one of the earliest markers of the beginning of PD processes. This is supported by the finding that LBs can occur in the enteric nervous system in elderly individuals without LBs in the CNS.¹ Recently, Fumimura et al.⁶

reported that accumulation of α -synuclein was found in the adrenal gland in 207 (26.4%) of 783 cases ranged in age from 48 to 104 years, in whom one had LBs only in the adrenal gland. These findings suggest that LBs in the visceral autonomic nervous system can occur independently of α -synuclein pathology in the CNS.

Kaufmann et al.⁷ reported two cases presenting with pure autonomic failure; one developed PD 20 years after onset of the disease and the other developed DLB 4 years later, suggesting that neurodegeneration in PD and DLB may begin outside the CNS. In our case, LB pathology was observed only in the stellate ganglia and cardiac sympathetic nerve, being more severe in the latter. Orimo et al.⁸ have shown that degeneration of the cardiac sympathetic nerve begins early in the disease process of PD, accounting for reduced cardiac uptake of *meta*-iodobenzylguanidine, a physiological analog of norepinephrine. The latter authors also demonstrated that LNs were seen in the epicardial nerve fascicles in 18 of 20 patients with ILBD (Braak stage 2 or 3).² The LB pathology observed in our case is in line with the finding that accumulation of α -synuclein in the cardiac sympathetic nerve precedes that of neuronal somata in the paravertebral sympathetic ganglia in PD.² It is possible to consider that the pathological process of PD targets the peripheral autonomic nervous system at the same time or even before lower brainstem nuclei become involved. The present case may be at the earliest stage of PD.

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Giant Somatosensory Evoked Potential in a Patient with Shaking TIA

Video



Patients with transient ischemic attack (TIA) may present with episodic myoclonus, athetoid movement, or dystonic posturing.¹ Patients may report that their limbs were jerking, shaking, swinging, flapping, trembling, twisting, or wavering.^{1–3} Some authors considered the involuntary movements as a form of partial motor seizure,⁴ but others denied epileptic origin and attached the term “shaking TIA.”^{2,5}

We describe a 56-year-old man who developed episodic clonic movements of the right leg and arm in association with left internal carotid artery occlusion. Median nerve somatosensory evoked potential (SEP) studies showed abnormally increased amplitude of left central cerebral potentials.

A 56-year-old man suddenly developed dizziness and a few jerking in the right leg and arm while running. He did not feel that he was losing consciousness. Over the next two weeks, he noticed four to five times of brief attacks of jerks per day. They occurred immediately after rising from the sitting or supine position, while running, or after standing for a period of longer than 30 min. He had smoked a pack of cigarette per day for the past 30 years. On neurological examinations performed between the attacks, he had no motor weakness and sensory functions tests were normal. He had no cranial nerve deficits. His cerebellar function tests were normal. Deep tendon reflexes were normoactive and symmetric. Interictal electroencephalography (EEG) studies were normal. Twenty-four-hour video-EEG monitoring captured four stereotyped brief attacks of clonic movements causing flexion and extension of the right knee and hip and abduction and adduction of the right shoulder. However, there were no epileptiform discharges. During the attacks, there was no eye ball deviation, head turning, or facial involvement. T1- and T2-weighted brain magnetic resonance (MR) imaging studies were normal. A digital subtraction angiography study showed occlusion of the left internal carotid artery and diffuse atherosclerosis of the right middle cerebral and internal carotid arteries. Brain HMPAO-single photon emission computed tomography study showed reduced perfusion in the left middle cerebral artery territory. According to the method reported elsewhere, SEPs were obtained with median nerve stimulation at the wrist.⁶ The amplitudes of N20-P25 (left/right = 11.6/4.7 μ V) and P25-N33 (left/right = 9.9/4.9 μ V) peaks at the left central area were increased abnormally (Fig. 1). Cerebral revascularization was performed with external to internal carotid artery bypass surgery. At two months' follow-up examination, frequency of the attacks was reduced to less than once a day, and there was giant SEP in the left central area.

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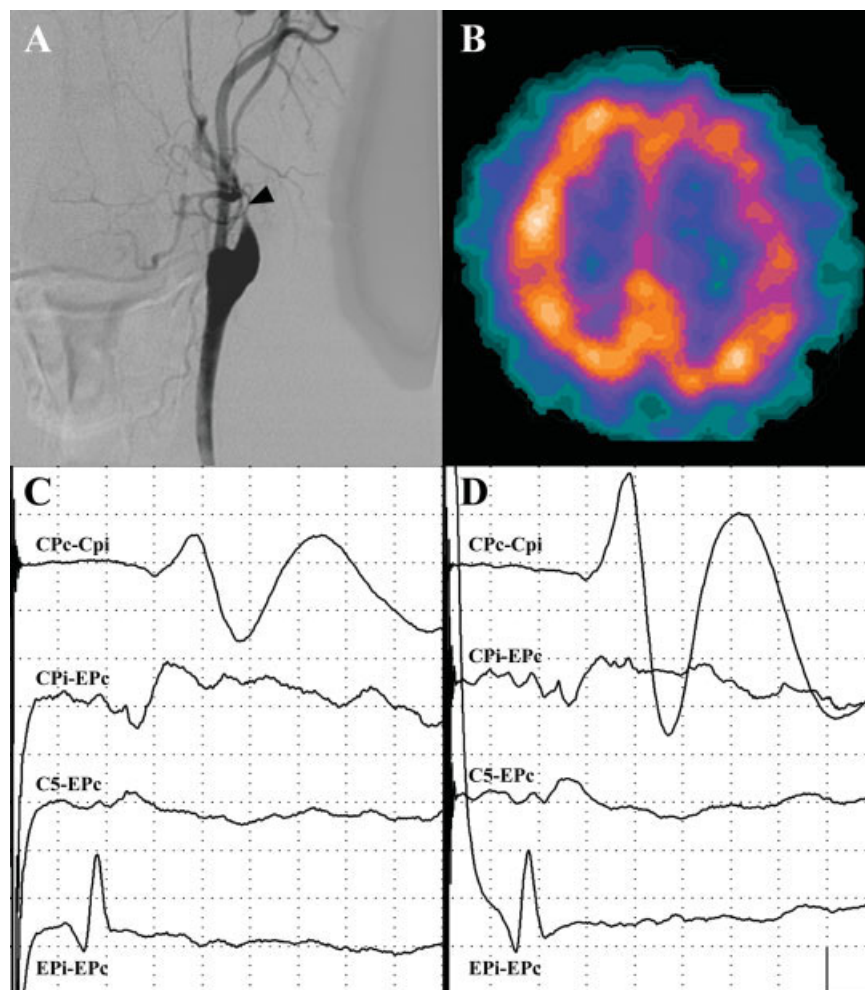


FIG. 1. Results of neuroimaging and somatosensory evoked potential studies. (A) A digital subtraction angiography of left common carotid artery shows complete obstruction of left proximal internal carotid artery (arrow head). (B) A ^{99m}Tc -single photon emission computed tomography scan study shows hypoperfusion areas in the left cerebral cortex. (C and D) Median somatosensory evoked potential (SEP) studies show giant potentials in the left central cerebral area (N20-P25 = 11.6 μV and P25-N33 = 9.9 μV). (C): left median nerve SEP, D: right median nerve SEP, vertical bar = 2 μV , horizontal bar = 5 m s).

Patients with TIA may present with involuntary movements that are precipitated by rising from supine to standing position, walking, running, or hyperextension of the neck.^{1,4} All have an occlusion or high-degree stenosis in the common or internal carotid artery, and most respond to surgical cerebral revascularization or correction of orthostatic hypotension.^{1,2,4} Therefore, reduced cerebral blood perfusion seems to be the underlying mechanism of limb shaking TIA. However, its anatomical origin and pathogenesis are uncertain.

Some authors considered the shaking TIA, characterized by a sudden onset of brief clonic involuntary movements involving the extremities on one side, as a form of partial motor seizure.⁴ Ischemic damage to the neurons may increase membrane instability, excitatory neurotransmitter release, neuronal depolarization, and electrically irritable tissue.⁷ In a patient with recurrent left leg shaking TIA, an ictal single photon emission tomography study demon-

strated localized hyperperfusion in the right mesial frontal cortex, suggestive of increased cortical neuronal activity.⁸ However, it can also be a secondary change to the leg movements.

Others denied epileptic origin of the involuntary movements on the basis of many clinical findings (e.g., no epileptiform activities on ictal EEG study; no definite tonic-clonic jerking; no typical Jacksonian march; no head-eye turning; rare evolution to generalized seizure; and no effect of anti-convulsant treatment).¹⁻³ Therefore, they suspected that shaking TIA is resulted from reduced cortico-subcortical inhibition caused by cerebral ischemia and consequent hyperactivity of subcortical neuronal structures.^{1,5}

A giant SEP, defined as a larger than 8.6 μV amplitude difference between the N20 and P25 peaks or a larger than 8.4 μV amplitude difference between the N33 and P25 peaks at the central cortical area,⁶ represents increased cortical neu-

ronal excitability. Therefore, we suspect that limb shaking TIA is associated with ischemia induced cerebral cortical neuronal hyperexcitability.

LEGENDS TO THE VIDEO

A transient ischemic attack causing shaking limbs.

A 56-yr-old man shows sudden onset of repetitive jerks causing flexion and extension of the right knee and hip and abduction and adduction of the right shoulder.

Author Roles: M.S. Lee was involved in Research: conception and design, acquisition of data, analysis and interpretation of data, Manuscript: drafting and critical revision, and others: obtaining funding, administrative, technical, or material support, and supervision. W.J. Kim was involved in Research: analysis and interpretation of data, Manuscript: drafting, others: administrative, technical, or material support. C.H. Lyoo was involved in Research: acquisition of data and analysis and interpretation of data, Manuscript: drafting, and others: obtain funding and administrative, technical, and material support. S.J. Kim was involved in Research: acquisition of data, Manuscript: drafting, and others: administrative, technical, or material support. G. Suh was involved in Research: acquisition of data, Manuscript: drafting, and others: administrative, technical, or material support.

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Eating Dystonia

Video



olated eating dystonia is a very rare condition, and may be considered as a subtype of oro-mandibular dystonia (OMD).^{1–3} Although most cases are idiopathic, neuroleptic drugs can induce OMD.⁴ We present two patients with eating dystonia: one is tardive, and the other is idiopathic in origin.

Case 1: A 26-year-old female was admitted for the evaluation of involuntary oro-lingo-mandibular movements mainly during eating (Video Segment 1). Her complaints began 7 months after she was put on olanzapine 10 mg/day for schizophrenia. Involuntary movements were characterized by rapid and strong flexion of the neck, sometimes accompanying blepharospasm and dyskinesia of the facial muscles resembling Meige syndrome, which only became manifest during eating and swallowing. Her neurological and physical examination was normal. Her olanzapine treatment was discontinued and quetiapine 600 mg/day was initiated. Treatment with clonazepam up to 4 mg/day, biperiden HCl 6 mg/day and clozapine up to 300 mg/day were unsuccessful. She denied botulinum toxin (BoNT) treatment. Her antipsychotic treatment was withdrawn completely for 3 months then her “Unified Dystonia Rating Scale” (UDRS) score decreased by 80%. She takes valproic acid 1500 mg/day and aripiprazole 20 mg/day for a year until now.

Case 2: A 20-year-old man was admitted to our hospital with involuntary movements during eating. His neurological examination was normal. Involuntary movements involving the oro-lingo-mandibular musculature during eating were observed (Video Segment 2). He did not have any problems during speaking or drinking water. Involuntary movements were characterized by rapid and strong flexion of the neck, sometimes accompanying blepharospasm and dyskinesia of the facial muscles resembling Meige syndrome. The patient was helped to chew and swallow by touching his left hand to the chin. This geste is probably a sensory trick used for inhibiting dystonic movements. He was considered as idiopathic eating dystonia, 0.5 mg/day clonazepam treatment was initiated and was increased to 2 mg/day gradually. Clonazepam treatment was discontinued due to sedation. We injected 50 U BoNT-A (Dysport, IPSEN Biopharm Group, Wrexen, Cluyd, UK) into per lateral pterygoid muscles, and 12.5 U

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into per submentalis complex twice in a 4-month interval. A total of 125 U BoNT-A were administered in each visit in electromyography (EMG) guidance. No side effects were observed. We used UDRS to quantify the improvement after injections. The score was four pre-BoNT and it was two post-BoNT after each session.

Both patients had normal routine laboratory studies, including routine biochemical examination, serum copper, ceruloplasmin, urine copper, and thyroid function tests. Peripheral blood smears to investigate acanthocytosis revealed no abnormality. Cerebral magnetic resonance imaging studies were also normal. Tetrabenazine could not be used due to health insurance problems.

Both patients resembled Meige syndrome, but dystonic movements occur with specific activity (task-specific dystonia) which made the diagnostic distinction possible. Task-specific OMD appears less frequently. In our study, the two cases with eating dystonia can be classified as a task-specific dystonia appearing only during eating.

Although most cases of OMD are considered as idiopathic, neuroleptic drugs can induce OMD and eating dystonia.⁴ Tardive disorders are persistent syndromes of abnormal, repetitive, and stereotypic involuntary movements, which commonly affect the face or neck, and are often exacerbated by specific actions resembling task-specific dystonia. Being exposed to dopamine-receptor-blocking agents for at least 3 months is essential for diagnosing tardive dystonia. Treatment strategy for tardive dystonia can be summarized as discontinuation and the use of low but effective doses of single atypical antipsychotic drug or changing the medication.⁵ In Case 1, the discontinuation of antipsychotic medication helped to decrease the symptom up to 80%, but as her psychiatric status needed medication, we initiated aripiprazole.

Eating dystonia has been reported due to haloperidol, but to our knowledge, this is the first case of tardive eating dystonia induced by atypical neuroleptics.¹ Idiopathic eating dystonia has not been described before jaw dystonia seems similar.² No specific etiologic cause has been found in our second case. The decrease in symptom was maintained with 125 U (equivalent to 1.09 ng) BoNT treatment in each visit. Previous insufficiency reported by Lagueny et al. might be due to different muscle selection or toxin injection without EMG guidance.

Our cases are diagnosed as "eating dystonia" induced by attempts to crush food and resulting in prolonged jaw-opening spasms that severely impede chewing and swallowing. Dystonia manifested only with eating, but not with drinking or any other action (whistling, smiling, etc.).

Pathophysiologic mechanisms of eating dystonia are not well understood. It seems that the oral medication and BoNT therapies are partially effective in eating dystonia. We consider that further studies are necessary to elucidate the mechanism and therapeutic choices.

LEGENDS TO THE VIDEO

Segment 1. Case 1 with tardive eating dystonia showing severe involuntary dystonic movements affecting oro-lingo-mandibular and cervical musculature during eating. These movements completely disappeared as soon as eating stopped, and did not occur at rest, and during speaking, or drinking.

Segment 2. Case 2 with idiopathic eating dystonia. Severe involuntary dystonic movements appeared during eating.

These movements completely disappeared as soon as eating stopped, and did not occur at rest, and during speaking or drinking.

Author Roles: Yasar Kutukçu: Writing of the first draft, Case 1 clinical follow-up. Semai Bek: Writing of the first draft, Case 1 clinical follow-up. Tayfun Kasıkçı: Case 2 clinical follow-up. Gençer Genç: Case 2 clinical follow-up. Zeki Odabasi: Review and critique.

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Complex Movement Disorders in a Sporadic Boucher-Neuhäuser Syndrome: Phenotypic Manifestations Beyond the Triad

Video



The triad of spinocerebellar ataxia, hypogonadotropic hypogonadism, and chorioretinal dystrophy constitute an autosomal inherited recessive disorder known as Boucher-Neuhäuser Syndrome.^{1,2} While most literature on this condition report on endocrinological and ophthalmological findings, the association with abnormal movements beyond ataxia has not previously been described. In this article, we review a sporadic case of Boucher-Neuhäuser Syndrome who developed a spectrum of complex movement disorders in addition to ataxia.

A 45-year old Thai man was first evaluated at the age of 39 by an ophthalmologist because of progressive bilateral visual loss. Fundoscopic examination showed atrophic changes of the retinal pigment epithelium and choriocapillaris in the midperiphery of both eyes, and bone spicule-like clumps of pigment

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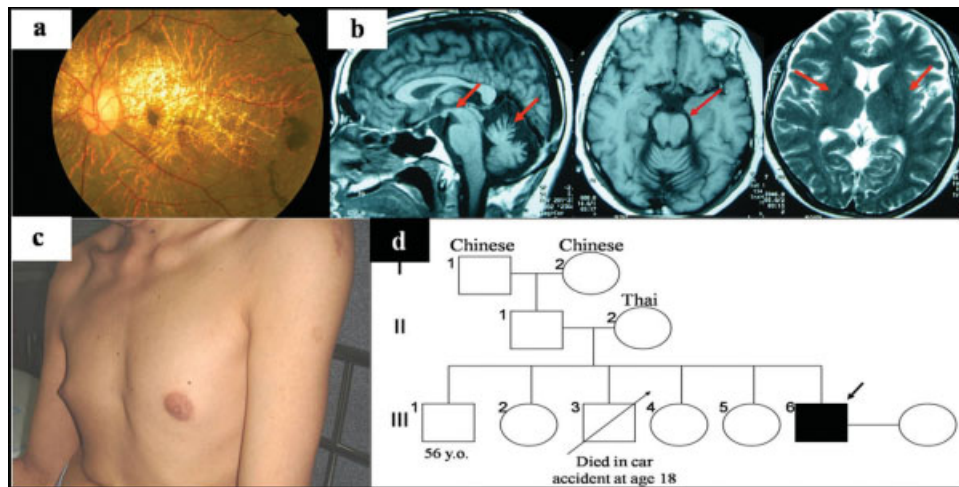


FIG. 1a: Chorioretinal dystrophy with clumps of pigment deposition; **b:** T1 weighted MR brain images revealed midbrain, cerebellar and putamen atrophy; **c:** Gynecomastia; **d:** Family pedigree. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

deposits (Fig. 1a). The findings were consistent with a diffuse, slowly progressive choroidal dystrophy involving choriocapillaries, retinal pigment epithelium, and outer retina.

The patient, at the age of 43, developed dystonia in the right foot and dystonia and chorea in the proximal arms, orobuccal, and cervical regions. Bilateral dysmetria, intention tremor, and dysdiadokokinesia were marked in both upper extremities in association with titubation and truncal ataxia. His cognitive function was normal. Nerve conduction studies revealed symmetrical sensorimotor demyelinating peripheral neuropathy with reduced conduction velocities and delayed distal latencies. MRI of the brain showed cerebellar atrophy, most pronounced at the vermis, and atrophy of both the putamen and rostral midbrain (Fig. 1b).

The patient had limited development of secondary sexual characteristics. The patient weighed 55 kg (<5th percentile for age) and his height was 170 cm (in the 50th percentile for age) and his limbs were long with an arm span of 185 cm. He had gynecomastia of 1.5 cm (Fig. 1c) and he spoke with a high-pitched voice. The patient was the youngest of six children born to healthy nonconsanguineous parents (Fig. 1d). There is no family history of neurological or movement disorders.

An endocrinological assessment at the time of examination showed a testosterone level of 0.8 nmol/L (normal 5.9–24.7) and free androgen index of 1.19% (normal 40–90). This level of testosterone, together with luteinizing hormone (LH) of 0.8 mIU/mL (normal 1–10.5) and follicle stimulating hormone (FSH) of 0.2 mIU/mL (normal 1–8.4), was consistent with hypogonadotropic hypogonadism.

The occurrence of hypogonadism and cerebellar ataxia encompasses a heterogeneous group of disorders with phenotypic overlap and interfamilial variability.³ The Boucher-Neuhäuser Syndrome (BNS) can be clinically distinguished from the Gordon Holmes and the Woodhouse Sakati syndromes by the presence of chorioretinal dystrophy and the lack of mental retardation.^{3,4} Nevertheless, the diagnosis of BNS is still made on the basis of clinical findings and it is possible that these disorders are simply clinical variants of a single gene disorder.⁵

Although the patient's presentation met the criteria of the triad of manifestations, several unique clinical characteristics in our patient are worth further discussion.^{1,2} All previously reported cases were either siblings with unaffected parents or born to consanguineous parents, representing a specific pleiotropic single gene disorder with an autosomal recessive pattern of inheritance.⁵ This is in contrast to our patient who was the only affected individual in the family, suggesting that BNS can occur sporadically or possibly be an X-linked recessive. In addition, most previously reported cases suggested that peripheral nerves could be involved in BNS as evidenced by decreased or absent deep tendon reflexes with normal sensory examination. Our patient's nerve conduction study provided the first electrophysiological evidence of demyelinating neuropathy in BNS.

Ataxia is seldom the first presenting symptom but tends to develop after the onset of progressive visual loss and poor sexual development.^{5,6,7} Neurologic signs usually develop during adolescence or young adulthood and are slowly progressive or nonprogressive, whereas the age of onset of ophthalmic features varies from the first to the sixth decade of life with a pronounced variability in progression.⁸

In addition to ataxia, our patient also had marked cranio-cervical chorea and dystonia, consisting of oromandibular dystonia, dynamic jerky anterocollis, upper truncal dystonia and dystonia in both upper extremities. These findings further imply that the pathology in BNS is not limited to the cerebellum, pituitary, hypothalamus, and retina, but might also involve the extrapyramidal system.

What ties the classic clinical triad to the newly described clinical features remains unknown. However, it is more likely to occur because of an underlying mechanism, possibly due to a single gene disorder, than just by chance. Therefore, the application of molecular genetics to these patients can lead to important discoveries in the development and functioning of the cerebellum-basal ganglia-pituitary-retina interplay in humans.

Legends to the Video

The patient had oromandibular dystonia with frequent pursing of lips, anterocollis with dynamic neck flexion, and intermittent contraction of pectoralis major which led to flailing of the left arm. Cerebellar signs including intention tremor and dysdiadokokinesia were demonstrated. While walking with assistance, his gait was wide-based and ataxic. Axial and foot dystonia were also observed.

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Opsoclonus Myoclonus Syndrome in the Context of Salmonellosis

Video 

Opsoclonus is characterized by involuntary, multidirectional, and chaotic saccadic eye movements without intersaccadic interval. In opsoclonus myoclonus syndrome (OMS), it is frequently accompanied by myoclonic jerks of the trunk and limbs, as well as cerebellar ataxia and postural tremor. Neuroblastoma predominates in pediatric OMS,¹ while main causes in adults are paraneoplastic and parainfectious syndromes. We here describe the first OMS case in the context of enteric Salmonellosis.

A 62-year-old man without any relevant past medical history complained of sudden onset of dizziness and oscillopsia. The very next day, he presented in the emergency room where ocular flutter, severe cerebellar ataxia with limb tremor, and myoclonic jerks were noted. The third day, a febrile diarrhea appeared that persisted for 7 days.

Extensive screening for viral infection, tumor markers, autoimmune and antineuronal antibodies (anti-Hu, anti-Yo, anti-Ri) was negative, except for a transient moderate inflammatory syndrome. Stool culture revealed the presence of *Salmonella enterica enterica veneziana* (initially and 1 month after admission). Cerebrospinal fluid (CSF) analysis showed isolated intrathecal IgG synthesis. Repeat brain MRI, thoracoabdominal computed tomography, and whole body flurodeoxyglucose positron emission tomography was normal. EMG surface recordings showed short-lasting (<100 ms), irregular discharges in all limbs, consistent with myoclonic jerks. Myoclonus was amplified by mental calculation and upright position.

The patient was referred to our unit 1 month after symptom onset where the diagnosis of parainfectious OMS was suggested. At that time, ocular flutter was still present. The

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patient was unable to stand and walk without assistance because of severe cerebellar ataxia and limb tremor with superimposed myoclonus (video segment 1). The limb tremor was present in supine and upright position and also included the body with some titubation in upright position. Clinical improvement was observed 10 days after treatment with oral antibiotics (sulfamethoxazole/trimethoprim and ofloxacin) and intravenous immunoglobulin. One month later, he was able to walk without help and stool culture had become normal. One year later, he showed mild postural tremor of the right arm, as well as mild gait ataxia and some minor saccadic intrusions (video segment 2).

We describe a patient with ocular flutter, cerebellar ataxia, and myoclonus, consistent with the diagnosis of OMS. Main causes of OMS in adults are paraneoplastic and parainfectious syndromes.¹ Most common tumors are lymphoma, malignant melanoma, ovarian, small lung, renal, and breast cancer. Parainfectious OMS has been described in the context of infection with *Streptococcus*, Human Immunodeficiency Virus, West Nile Virus, Varicella Zoster Virus, *Borrelia burgdorferi*, and *Mycoplasma pneumoniae*. Moreover, OMS may be associated with multiple sclerosis, sarcoidosis, stroke, celiac disease, toxic-metabolic states such as hyperosmolar coma and may occur during pregnancy. OMS can be a side effect of treatment with amitriptyline, imipramine, lithium, phenytoin and diazepam or cocaine and toluene abuse. Poisoning with organophosphates, strychnine or thallium may also cause OMS. As in our patient, CSF analysis may reveal intrathecal IgG synthesis.² Repeat MRI was normal but may display abnormalities in pons and cerebellum.³

Although we cannot entirely exclude a pure coincidence, the presence of diarrhea with detection of *Salmonella enterica* enterica veneziana in stool culture suggests a parainfectious etiology of OMS in our patient. An acute contamination is very unlikely since neurological signs preceded his febrile diarrhea. However, the patient had several episodes of diarrhea during the year before, meaning that he could have been a chronic carrier. His febrile diarrhea may thus be considered as a repeated manifestation of Salmonellosis. *Salmonella* has been linked to neurological syndromes such as Guillain-Barré syndrome, Miller-Fisher syndrome, Bickerstaff encephalitis, meningitis, encephalopathy, cerebellar syndromes, and neuropathy.⁴ One case report has described isolated, very short-lasting ocular flutter after *Salmonella* infection.⁵

Although the exact mechanisms are unknown, OMS is believed to result from Purkinje cell dysfunction in the dorsal vermis.¹ As a consequence, neurons of the fastigial nucleus are relieved from their inhibitory control resulting in opsoclonus. This hypothesis is supported by findings from functional MRI showing an activation of the fastigial nucleus in two patients with OMS but not in healthy controls.⁶ Many neuronal autoantibodies such as anti-Ri, anti-Hu, anti-Yo, and anti-Ma2 have been linked to OMS.⁷ However, autoantibody screening is frequently negative suggesting that cell-mediated immune mechanisms may also play a role in OMS. In this regard, a treatment with rituximab, an anti-CD20 monoclonal antibody, has been efficacious in some patients.¹

Intravenous immunoglobulin and corticosteroids seem to be effective in adults with OMS.⁷ The management further

consists in the treatment of the underlying process. Our observation underlines the importance of an exhaustive work-up including stool culture to exclude Salmonellosis. Antibiotics and immunoglobulin may have attenuated the abnormal immune process in our patient and may explain the rapid clinical recovery after treatment initiation.

Legends to the Video

Segment 1. The patient was unable to stand and walk without assistance because of severe ataxia and jerky limb tremor. The tremor also included the body with some titubation in upright position. Examination of the upper limbs showed a moderate to severe postural and kinetic tremor, mainly of the right side. The kinetic tremor became more prominent when the moving limbs approached the nose, consistent with an intention tremor. Eye examination revealed an ocular flutter as indicated by the intermittent rapid back-to-back saccades in the horizontal plane.

Segment 2. One year later, moderate postural tremor of the right upper limb was noted as well as a mild gait ataxia. Eye examination showed some mild saccadic intrusions.

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Author Roles: Flabeau—data acquisition and data analysis of research project; writing of the first draft of manuscript. Meissner—conception and data analysis of research project; review and critique of manuscript; supervision of other. Foubert-Samier—data acquisition of research project; review and critique of manuscript. Guehl—data acquisition of research project; review and critique of manuscript. Desbordes—data acquisition of research project; review and critique of manuscript. Tison—conception of research project; review and critique of manuscript; supervision of other.

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