Movement Disorders
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Letters to The Editor Related to New Topics

Tremor and White Matter Lesions in Klinefelter Syndrome

Video 

A 56-year-old man, welder, was presented with a 42-year medical history of postural and action tremor of both hands. The tremor had worsened in the previous 3 years, making it impossible for him to execute more precise work in his job. He does not have any biological children. In his family, both his paternal uncle and two of his sisters had minor postural tremor (observed in the two sisters).

On neurological examination, he showed 5–6 Hz upper limb rest tremor, with left side predominance, and an 11 Hz postural tremor of the four limbs, predominantly kinetic and intentional on the left. The remainder of the examination was unremarkable, namely no bradykinesia, rigidity, or gait problems were present (see supporting information video). Although he presented some atypias, a diagnosis of essential tremor was made and treatment with primidone was started without significant improvement.

On the second visit to the hospital, his spouse mentioned that he was experiencing some cognitive decline (loss of initiative, memory problems, and difficulty in solving problems) and also that he had had learning difficulties in his childhood. The brain MRI identified multiple white matter T2/Flair hyperintensities in both hemispheres, confluent in the subcortical frontal areas, one small T2/FLAIR hyperintensitie in the right putamen and another on the left thalamus. None of these lesions had signs of hemorrhage at T2*, and there were no lesions on the cerebellum Figure 1. Further etiological investigation—hepatic and thyroid function, copper metabolism, immunological study, CSF and VDRL serology—did not reveal abnormalities. Neurocognitive evaluation showed below average results in multiple areas, particularly executive functions and language.

Given the presence of both tremor and cognitive decline, Fragile X-associated tremor/ataxia syndrome was considered and a genetic test was performed. The FMR1 gene CGG repeats were normal, but two alleles were found. A chromosomal analysis was performed, and it confirmed the XXY karyotype; thus revealing the diagnosis of Klinefelter syndrome.

With this new information, a more directed interview and examination were conducted. The patient had the characteristic elongated facial phenotype and was tall and thin. He did not have the sexual characteristics of this syndrome, except for small-volume testes. Endocrine studies demonstrated hypergonadotropic hypogonadism (normal testosterone with high levels of LH and FSH).

Our case shows significant similarities to another case already reported,[1] but is distinct in terms of imaging. It intends to underline the importance of considering Klinefelter syndrome diagnosis in the presence of tremor and cognitive decline. Tremor has been, in fact, reported as more prevalent in those patients than in the general population.[2] This case is quite unique in terms of imaging, because of the white matter lesions are not a recognized characteristic of this syndrome, although they have already been described for the more severe variants (XXXXY).[3] As this patient presented with lesions affecting primarily subcortical white-matter, we consider that this could theoretically explain the cognitive decline. The pathophysiological basis for the tremor is more difficult to establish. A hypothesis is that damage to corticothalamic fibers could account for it, because of the existence of cortical and subcortical oscillators taking part in tremor generation has been proposed.[4] The damage to the nucleus of the basal ganglia and left thalamus documented in the MRI is also possibly contributory. Nevertheless, we recognize the existence of reports where tremor is present in Klinefelter syndrome patients without MRI evidence of lesion.

Legend to the Video

The patient shows upper limb rest tremor, with left side predominance, and postural tremor, predominantly kinetic and intentional, with the remainder of the examination normal.

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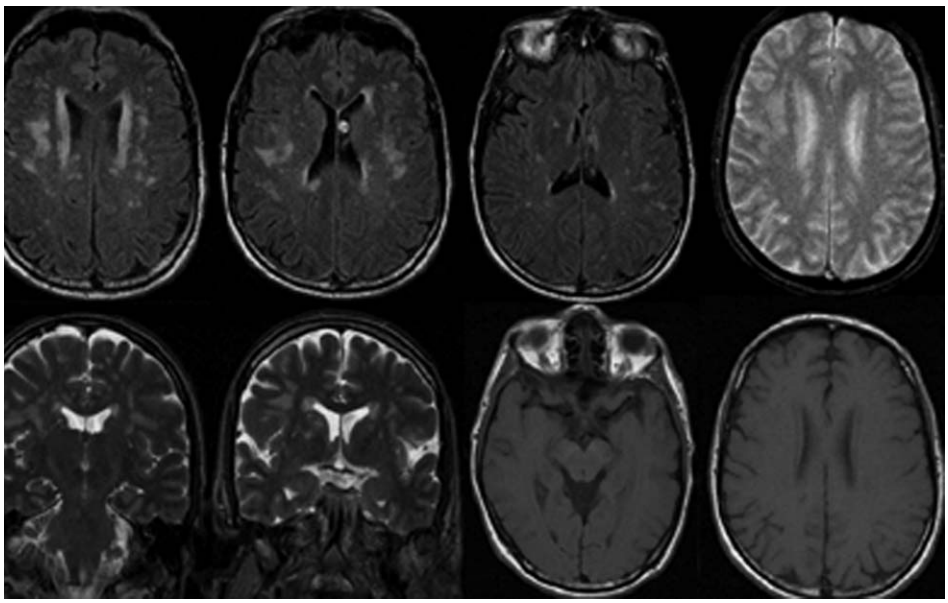

FIG. 1. T2WI and FLAIR Brain MR show multiple white matter hyperintensities in both hemispheres, some of them confluent, specially at the periventricular white matter; small hyperintensities in the right putamen. T2* GRE image does not show sign of old hemorrhage or calcium. T1WI are unremarkable.

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References

1. Harlow TL, Rodnitzky RL, Gonzalez-Alegre P. From essential tremor to Klinefelter through Fragile X, an unexpected journey. Mov Disord 2008;23:1328–1329.
2. Harlow TL, Gonzalez-Alegre P. High prevalence of reported tremor in Klinefelter syndrome. Parkinsonism and related disorders (2008), doi: 10.1016/j.parkreldis.20008.08.009
3. Hoffman TL, Vossough A, Ficicioglu C, Visootsak J. Brain Magnetic resonance imaging findings in 49, XXXXY Syndrome. Pediatr Neurol 2008;38:450–453.
4. Raethjen J, Deuschl G. Tremor. Curr Opin Neurol 2009;22:400–405.

Clozapine for Medication-Related Pathological Gambling in Parkinson Disease

Pathological gambling (PG) is an impulse control disorder characterized by persistent and recurrent maladaptive gambling behavior.[1] PG has been reported in 3–8% of Parkinson's disease (PD) patients as an adverse effect of dopamine agonists (DA) treatment, possibly as a result of overstimulation of mesolimbic dopamine receptors, mainly D_2/D_3, in predisposed individuals.[2] Reduction or discontinuation of DA therapy or switch to a different DA are the most successful approaches in the treatment of PG in PD.[2–4] However, persisting gambling has been reported despite DA discontinuation and even after antidepressant treatment.[2–4] Anecdotal reports with dopamine D_2/D_3 blocking drugs, such as the atypical antipsychotics risperidone,[5] olanzapine,[3] or quetiapine,[3,4,6] are conflicting. Recent findings show that partial dopamine D_2/D_3 receptor agonists, such as aripiprazole, may be effective, probably more than D_2/D_3 antagonists, in treating impulsive/compulsive and addictive behaviors via regulation of reward pathway circuitries.[7,8] Emerging evidence indicates that N-desmethylclozapine, the major active plasma metabolite of the atypical antipsychotic clozapine, which has been safely used in the treatment of Levodopa-induced psychosis in PD,[9] has a potent partial agonist activity on dopamine D_2/D_3 receptors.[10]

We report 3 PD patients who developed PG, diagnosed according DSM-IV-TR[1] criteria, after treatment with DA. PG

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persisted despite the complete discontinuation of DA and SSRI treatment but remitted in two of three patients after adjunctive treatment with clozapine.

The case was a 62-year old woman diagnosed with PD at 58 years of age and treated with Selegiline (10 mg/day). She reported episodic gambling from age 49–53 and a major depressive episode with comorbid alcohol abuse at age of 54 that remitted in about 6 months. At age 61, pramipexole (2.1 mg/day) was added to selegiline to treat worsening of PD symptoms. Within 5 months, she developed uncontrollable urges to gamble (scratch cards and national lottery), losing almost all of her retirement pension every month. Pramipexole was tapered-off, and she was treated with sertraline (50 mg/day) for 4 months with persistence of PG along with worsening of motor disability. The addition of clozapine to 37.5 mg/day resulted in a marked improvement of PG in about 1 month. Then, L-dopa (450 mg/day) was added with improvement of PD without worsening of PG at follow-up after 12 months.

The case was a 42 year-old man diagnosed with PD at 40 years of age. He had a past history of alcohol abuse and major depressive disorder (MDD) and was in remission at the time of PD diagnosis. He was treated with pramipexole (4.5 mg/day) for 2 years. PG occurred 3 months after starting cabergoline (4 mg/day) for PD worsening. Horse racing, football betting, and slot machines were the preferred sources of gambling. In a few months, his losses totaled about 100.000 euros. PG persisted 2 months after discontinuation of DA therapy. He was treated with sertraline (100 mg/day) and alprazolam (0.75 mg/day) for 2 months, without any significant improvement. Clozapine was titrated to 50 mg/day with remission of PG during 6 months of follow-up.

The case was a 40 year-old man diagnosed with PD at 39 years of age and treated with pramipexole titrated to 3.8 mg/day. He had a past history of alcohol abuse and MDD in remission at the time of PD diagnosis. PG started 2 months after pramipexole dosage was increased to 7.5 mg/day to control mild motor fluctuations. He began gambling every day (mainly football betting, slot machines, and national lottery) losing a large sum of money. Pramipexole was tapered-off within 2 months, and he was subsequently treated with venlafaxine (150 mg/day), and alprazolam (1.5 mg/day), without any significant improvement over 4 months. Clozapine was added to 75 mg/day with no improvement of PG in the next 2 months.

Our data support the previously reported association between PG and DA therapy in PD patients.[2–4] Interestingly, all cases had a life-time history of MDD and/or alcohol abuse. Suggesting that predisposition for mood and addiction disorders may be a risk factor for the development of PG in PD patients taking DA,[2] and impairs remission after DA discontinuation. To our knowledge, only one study reported improvement in compulsive behaviors in a PD patient treated with DA with unspecified doses of clozapine.[4] This is the first report on the effectiveness of clozapine treatment of persistent PG following discontinuation of DA therapy. These observations require further investigation in larger samples. The use of clozapine requires stringent monitoring because of potential risk of agranulocytosis.[9]

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References

1. DSM-IV-TR. Diagnostic and statistical manual of mental disorders, Fourth ed, Text Revision. Washigton, D.C. American Psychiatric Association, 2000.
2. Voon V, Fox SH. Medication-related impulse control and repetitive behaviours in Parkinson disease. Arch Neurol 2007;64:1089–1096.
3. Bostwick JM, Hecksel KA, Stevens SR, Bower JH, Ahlskog JE. Frequency of new-onset pathologic compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson disease. Mayo Clin Proc 2009;84:310–316.
4. Kurlan R. Disabling repetitive behaviours in Parkinson's disease. Mov Disord 2004;19:433–437.
5. Seedat S, Kesler S, Niehaus Dj, Stein DJ. Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents. Depress Anxiety 2000;11:185–186.
6. Sevincok L, Akoglu A, Akyol A. Quetiapine in a case with Parkinson's disease and pathological gambling. J Clin Psychopharmacol 2007;27:107–108.
7. Beresford TP, Clapp L, Martin B, Wiberg JL, Alfers J, Beresford HF. Aripiprazole in schizophrenia with cocaine dependence a pilot study. J Clin Psychopharmacology 2005;25,363–366.
8. Connor KM, Payne VM, Gadde KM, Zhang W, Davidson JRT. The use o aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients. J Clin Psychiatry 2005;66: 49–51.
9. Thomas AA, Friedman JH. Current use of clozapine in Parkinson disease and related disorders. Clin Neuropharmacol 2010;33:14–16.
10. Intrinsic efficacy of antipsychotics at human D_2, D_3, and D_4 dopamine receptors: identification of the clozapine metabolite N-Desmethylclozapine as a D_2/D_3 partial agonist. JPET 2005;315: 1278–1287.

Dentatorubral Pallidoluysian Atrophy Presenting with Urinary Retention

Dentatorubral pallidoluysian atrophy (DRPLA) is a rare, autosomal dominant neurodegenerative disorder characterized clinically by progressive dementia, ataxia, chorea, myoclonic epilepsy, and psychiatric disturbance and pathologically by combined degeneration of the dentatorubral and pallidoluysian systems.[1] DRPLA is most common in Japan[1]; but also reported in Caucasian populations.[2] Bladder autonomic involvement has not been known in DRPLA. However, we recently had a case of a man with DRPLA who presented with urinary retention. We performed an urodynamic study to explore the mechanism of urinary retention in that case.

A 54-year-old man was referred to us from a local neurology hospital to assess bladder dysfunction. He had a family history of generalized chorea and dementia: his mother developed chorea at age 40, and his daughter developed mental deterioration and ataxia at age 10 (bladder dysfunction not mentioned). He and his mother underwent gene analysis that revealed abnormal CAG expansion in *CTG-B27* gene (repeat lengths not reported). At age 20, the male patient noticed slight limb ataxia and ataxic gait. At age 45, he was diagnosed with DRPLA by gene analysis; soon after that, he gradually developed ataxic speech and mild, generalized chorea. He was started on taltirelin hydrate (thyrotropin-releasing hormone analogue) for cerebellar ataxia.[3] After administration of the agent, his ataxia improved only mildly. At age 49, he began to use a handrail on walking down the stairway. At age 50, he began to fall easily. He became slightly agitative and had dysphagia. At age 52, he suddenly had pyelonephritis due to urinary retention. After that, he had repeated episodes of transient urinary retention. At age 53, he became incontinent of urine. He became unable to stand without assistance and started to use a wheelchair.

On referral, he was alert but had cognitive impairment: the Mini-Mental State Examination scores of 15 (0–30, normal $>$ 24), the Alzheimer's Disease Assessment Scale-cognitive subscale scores of 38 (0–70, normal $<$ 10), and the Frontal Assessment Battery scores of 4 (0–18, normal $>$ 16.5). Neurological examination revealed generalized chorea and cerebellar ataxia in extraocular movement, speech, limb, and gait. Obvious pyramidal or extrapyramidal signs were not recognized. He had no Babinski sign. Magnetic resonance imaging (MRI) showed, on T2-weighted MRI images in the axial plane, pontocerebellar atrophy and high signal intensity in the cerebral white matter (Fig. 1). No orthostatic hypotension was observed. He had constipation. He had sleep apnea with the apnea–hypopnea index of 30.5 during night time (normal $<$ 10).

To investigate the pathomechanism of prominent urinary incontinence with episodes of retention, an urodynamic study was performed according to the International Continence Society standards. After voluntary urination, he had a postvoid residual volume of 150 mL. Uroflowmetry was not obtained. During the bladder filling phase, water cystometry showed a normal volume at the first sensation of 165 mL (100 mL$<$normal$<$300 mL) and at the bladder capacity of 283 mL (200 mL$<$normal$<$600 mL), but also showed marked detrusor overactivity. During the voiding phase, the patient could not contract his bladder voluntarily, indicating an underactive detrusor, whereas involuntary detrusor overactivity appeared with poor urinary flow. The sphincter electromyography (EMG) sound was unchanged, indicating detrusor-sphincter dyssynergia. Analysis of motor unit potentials in the external anal sphincter EMG was not performed. Ultrasound measurement of the prostate gland showed no prostatic hypertrophy (11.3 mL, normal $<$ 20 mL). He was taught to perform clean, intermittent catheterization once a day and was started on 8 mg/day silodosin, an alpha-adrenergic antagonist. However, he still had postvoid residual volume of 50–400 mL and occasional episodes of urinary retention for the following 2 years. He was started on 0.4 mg/day haloperidol, which ameliorated his chorea moderately.

To the best of our knowledge, this is the first case of prominent urinary incontinence with episodes of retention being present in DRPLA. Urodynamic study revealed a combination of detrusor overactivity during filling and underactive detrusor during voiding,[4] with detrusor-sphincter dyssynergia, findings that have also been reported in multiple system atrophy. The underlying mechanisms are probably the result of involvement of the dentatorubral and pallidoluysian systems (explaining the detrusor overactivity) and the posterior and lateral funicles and Clarke's nucleus[5] (explaining the detrusor-sphincter dyssinergia and the underactive detrusor). However, to clarify this issue, further uroneurological examination in multiple cases is necessary. In conclusion, we report a case of DRPLA presenting with prominent urinary incontinence with episodes of retention. DRPLA should be listed in the differential diagnosis of neurogenic urinary retention.

Author Roles: J. Yuasa performed the urodynamic tests. R. Sakakibara, S. Isaka, M. Kishi, E. Ogawa, T. Uchiyama, and T. Yamanishi were involved in design and review of the manuscript.

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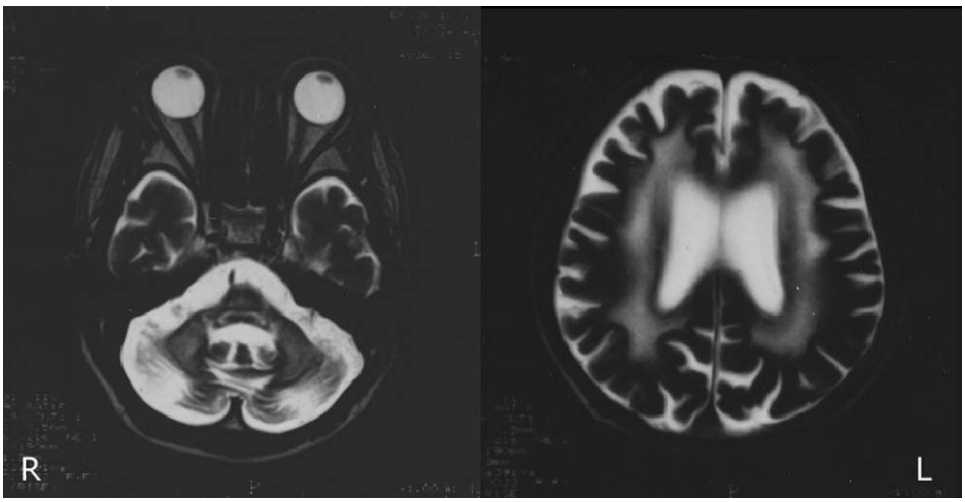

FIG. 1. MRI images of the case. T2-weighted MRI images in the axial plane showed pontocerebellar atrophy and high signal intensity in the cerebral white matter.

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References

1. Oyanagi S. Hereditary dentatorubral-pallidoluysian atrophy. Neuropathology 2000;20 Suppl:S42–S46.
2. Le Ber I, Camuzat A, Castelnovo G, et al. Prevalence of dentatorubral-pallidoluysian atrophy in a large series of white patients with cerebellar ataxia. Arch Neurol 2003;60:1097–1099.
3. Shibusawa N, Hashimoto K, Yamada M. Thyrotropin-releasing hormone (TRH) in the cerebellum. Cerebellum 2008;7:84–95.
4. Yamamoto T, Sakakibara R, Uchiyama T, et al. Neurological diseases that cause detrusor hyperactivity with impaired contractile function. Neurourol Urodyn 2006;25:356–360.
5. Takeda S, Takahashi H, Ikuta F. Dentatorubropallidoluysian atrophy (DRPLA): comparative pathological study on clinical groups classified into juvenile, early adult and late adult types. No To Shinkei 1992;44:111–116.

Dyspnea as First Sign of Autonomic Failure in Postmortem Confirmed Multiple System Atrophy

Respiratory disturbances including inspiratory sighs, sleep apnea, and laryngeal stridor are considered to be "red flags" for the diagnosis of multiple system atrophy (MSA) versus Parkinson's disease (PD).[1] Obstructive sleep apnea and exertional dyspnea may be the presenting symptom of MSA[2]. Moreover, daytime hypoxemia with an increased alveolar-arterial oxygen gradient has been described in patients with "probable" MSA.[3]

Some MSA patients may misleadingly appear as PD for many years.[4] In these patients, dopaminergic treatment remains effective for a long time, signs of autonomic failure may be missing in early stages and some patients even receive subthalamic nucleus (STN) deep brain stimulation (DBS).[5]

We here describe a MSA patient with misdiagnosed PD who showed unexplained and persisting dyspnea as the first sign of autonomic failure.

A 55-year-old woman presented left-sided L-dopa responsive parkinsonism with typical resting tremor leading to the diagnosis of PD. Dyskinesia appeared within 2 years of dopaminergic treatment. The patient was then explored for unexplained and persisting resting dyspnea 7 years after symptom onset. She did not present inspiratory sighs, and a polysomnography that was done 3 years after disease onset did not disclose sleep apnea or nocturnal stridor at that time. ECG, transthoracic echocardiography (ejection fraction = 77%, pulmonary artery systolic pressure = 30 mm Hg) and chest X-ray were unremarkable. Respiratory function tests were normal except for a mild reduction in forced expiratory flow. Blood gas analysis disclosed mild hypoxemia (69 mm Hg, for age adjusted lower limit = 77 mm Hg) with an increased alveolar-arterial oxygen gradient (29.5 mm Hg, for age adjusted upper limit: 19.3 mm Hg), normocapnia (41 mm Hg, normal: 35–45 mm Hg), normal HCO_3^- levels (27.6 mmol/L, normal = 22–28 mmol/L) and normal oxygen saturation (96.3%, normal: >94%). Hemoglobin and hematotocrit were within the physiological range. A thoracic computed tomography was performed several years later without any sign of lung artery obstruction, while the patient was still complaining of dyspnea. She eventually received deep brain stimulation (DBS) of the STN 8 years after disease onset. At the time of surgery, she had a preserved L-dopa response (59% reduction of UPDRS III scores), severely disabling dyskinesia up to 25% of waking day time, without significant cognitive impairment. During the first 16 months of DBS she gained 16 kg of weight. Urinary incontinence developed during the

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TABLE 1. *Histomorphological findings*

	Neuronal loss and gliosis	Alpha-synuclein glial inclusions	Alpha-synuclein neuronal inclusions
Putamen	+++	++	+
Cerebellum (dentate nucleus and white matter)	++	+++	0
Mesencephalon	++	++	0
Pons	++	++	++
Medulla oblongata	++	++	++

Lesions are graded from +++ (great number of typical lesions) to 0 (absence of typical lesions)

first year after surgery, while L-dopa response was still 31%. Parkinsonism rapidly deteriorated and the patient became bedridden 5 years after DBS surgery. She finally died 15 years after symptom onset and the diagnosis of MSA was confirmed postmortem (Table 1). Neuronal loss and gliosis were marked in putamen, mesencephalon, pons, medulla oblongata, dentate nucleus, and white matter of cerebellum. Abundant alpha-synuclein glial inclusions were found in these areas, as well as alpha synuclein neuronal inclusions in the putamen, pontine, and inferior olivary nuclei.

We here present a postmortem confirmed patient with MSA who was considered as having PD for many years. Because of her sustained response to L-dopa and the presence of severe motor fluctuations, STN-DBS was eventually performed 8 years after disease onset. At that time, the patient did not have "classical" features of autonomic failure in MSA, such as urinary dysfunction or orthostatic hypotension.

The autonomic system covers for many vital functions, including respiratory control. Respiratory disturbances, such as sleep apnea and laryngeal stridor are well known in MSA patients and their presence in a patient with parkinsonism are considered to be a "red flag" sign.[1] By contrast, isolated dyspnea as manifesting symptom has only been described in a few patients.[2] In recent years, several post mortem studies have confirmed the extension of the neurodegenerative process in MSA to brainstem areas that are involved in respiratory control such as rhythmogenesis and chemosensitivity.[6] Finally, neurogenic respiratory abnormalities may also be seen in lewy body dementia and the specificity of dyspnea for the diagnosis of MSA warrants further confirmation in a larger study.[7]

As the diagnostic work-up did not reveal any significant restrictive or obstructive lung disease, heart failure, pulmonary artery obstruction or increased systolic pressure, we believe that our patient's dyspnea is best explained by an impairment of central respiratory control. Respiratory function tests showed mild hypoxemia with an increased alveolar-arterial oxygen gradient, the latter suggesting a reduced efficiency of oxygen exchange between pulmonary alveoli and pulmonary capillaries. Although the origin of these abnormalities needs to be further investigated, they have already been described in patients with "probable" MSA[3] and may explain our patient's dyspnea.

In conclusion, respiratory disturbances may be the first sign of autonomic failure in MSA and should cautiously be looked for in PD patients who are scheduled for DBS.

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References

1. Kollensperger M, Geser F, Seppi K, et al. Red flags for multiple system atrophy. Mov Disord 2008;23:1093–1099.
2. Glass GA, Josephs KA, Ahlskog JE. Respiratory insufficiency as the primary presenting symptom of multiple-system atrophy. Arch Neurol 2006;63:978–981.
3. Shimohata T, Shinoda H, Nakayama H, et al. Daytime hypoxemia, sleep-disordered breathing, and laryngopharyngeal findings in multiple system atrophy. Arch Neurol 2007;64:856–861.
4. Wenning GK, Colosimo C, Geser F, Poewe W. Multiple system atrophy. Lancet Neurol 2004;3:93–103.
5. Visser-Vandewalle V, Temel Y, Colle H, van der Linden C. Bilateral high-frequency stimulation of the subthalamic nucleus in patients with multiple system atrophy–parkinsonism. Report of four cases. J Neurosurg 2003;98:882–887.
6. Benarroch EE. Brainstem respiratory control: substrates of respiratory failure of multiple system atrophy. Mov Disord 2007;22:155–161.
7. Mizukami K, Homma T, Aonuma K, Kinoshita T, Kosaka K, Asada T. Decreased ventilatory response to hypercapnia in dementia with Lewy bodies. Ann Neurol 2009;65:614–617.

Greeter's Cramp

Video 

We describe a patient who develops an unusual puckering of her lips whenever she speaks. She has a partial response to levodopa (L-dopa), highlighting the value of a trial of L-dopa especially in patients describing diurnal fluctuations, which was initially a feature in our patient.

A 46-year-old woman who works as a supermarket customer-greeter presented to us in July 2005 with a 3-month history of speech disturbance that was not context-related. She develops an unusual puckering of her lips, which only occurs on speaking. Initially, there was a brief period of normal speech in the morning. We captured this morning transition from normal to abnormal speech on video. Initially sensory tricks such as touching the corner of her mouth helped, but this later became less effective. She also started to have mild difficulties manipulating food in her mouth. The problem became severe enough to stop her working.

The rest of her history was unremarkable. She was never prescribed any neuroleptics or any other relevant medications and there was no family history of any movement disorder. General systemic and neurological examination was completely normal, except for this speech abnormality. Slit lamp examination of her eyes did not show any Kayser–Fleisher rings. She had an extensive battery of investigations, all of which were normal. This included cranial magnetic resonance imaging, functional imaging of dopamine transporters (DAT, ioflupane-I-123), chest radiograph, ceruloplasmin studies, *DYT1* gene, *GCH1* gene, thyroid function, antistreptolysin O titre, syphilis serology, and autoantibodies, including lupus and antibasal ganglia antibodies. We did not examine her cerebrospinal fluid.

We performed an apomorphine challenge (see Video). She responded to 3-mg apomorphine, and was therefore commenced on a therapeutic trial of L-dopa. The patient reports further improvements on her maximum total daily dose of 800-mg L-dopa, taken as co-careldopa 25/100 (carbidopa 25 mg/L-dopa 100 mg) two tablets four times daily. The improvement with L-dopa was demonstrated by the review of her videos and subjective improvement, whereby the patient reports improvement with her speech, eating, and drinking. She did not respond to treatment trials of cabergoline (up to 6 mg daily), nor trihexyphenidyl hydrochloride (up to 12 mg daily); both were therefore stopped. She went on to receive botulinum toxin injections to the perioral muscles, with further partial improvement.

Our patient is unusual because of the type of dystonia, and her response to L-dopa. Focal task-specific dystonias, such as writer's cramp, are well-described. Less common are task-specific oromandibular dystonias such as specific context-related use of speech (auctioneering[1] or praying[2]) or the embouchure dystonias.[3] Our patient has task-specific dystonic spasms, or puckering, of the lips that occurs whenever she speaks. A literature search did not reveal similar descriptions of this, apart from the passing mention of a patient who developed dystonic spasms of the lips on public speaking.[1]

Patients with diurnal fluctuations of dystonia usually obtain a marked response to low-dosage L-dopa or dopamine agonists.[4] Our patient's diurnal fluctuation was only prominent at the start of her symptoms and the response to L-dopa is partial. We do not think our patient has Parkinson's disease, because of the lack of parkinsonian features after a follow-up of 5 years. Additionally, our patient had a normal result of DAT scan, which is highly sensitive for the diagnosis of Parkinson's disease.[5]

Our patient also did not seem typical of the dopa-responsive dystonias (DRD): patients with classic DRD show marked improvement to low-dose L-dopa and this marked response is considered a hallmark to help establish the diagnosis. Some types of DRD with *GCH1* mutation can present with idiopathic focal dystonia and respond less markedly to L-dopa than classic DRD.[6] A dopa-responsive oromandibular dystonia was described associated with *GCH1* mutation[6] but this was not task-specific, unlike our patient. Our patient was negative for *GCH1* mutations. The genetic basis for most DRD is thought to be due to *GCH1* mutations, although mutations in other enzymes involved in dopamine synthesis have been reported, including tyrosine hydroxylase, 6-pyruvoyltetrahydropterin synthase, and sepiapterin reductase.[7] Patients with this latter group of mutations are more severely affected.[7] Our patient only had genetic testing for *GCH1* mutation by DNA sequencing of the *GCH1* gene, including the intron/exon boundaries, which did not detect any mutation. The use of apomorphine challenge to predict a response to L-dopa may be helpful,[8] as in our patient.

We describe an interesting speech-specific oromandibular dystonia, whereby there is an unusual puckering of lips whenever the patient speaks. It is partially responsive to L-dopa, highlighting the value of a trial of L-dopa in dystonias with diurnal fluctuations.[4] In view of our patient's occupation as a supermarket customer-greeter, we call it a "Greeter's Cramp."

Legends to the Video

Segment 1. Patient describing problem, illustrating the abnormal puckering of her lips when she speaks.

Segment 2. Early morning transition from normal to abnormal speech. As her problem worsened, she lost this early morning normal speech.

Segment 3. Sensory tricks used to improve her speech.

Segment 4. Response to 3 mg apomorphine after 30 min.

Segment 5. Improvement of speech demonstrated, 5 months into her therapeutic trial of L-dopa.

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Author Roles: S.H. Wong and P.J.W. McKee were involved in the patient care and wrote the article and recorded the video of the patient.

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

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References

1. Scolding NJ, Smith SM, Sturman S, Brookes GB, Lees AJ. Auctioneer's jaw: a case of occupational oromandibular hemidystonia. Mov Disord 1995;10:508–509.
2. Ilic TV, Potter M, Holler I, Deuschl G, Volkmann J. Praying-induced oromandibular dystonia. Mov Disord 2005;20: 385–386.
3. Frucht SJ, Fahn S, Greene PE, et al. The natural history of embouchure dystonia. Mov Disord 2001;16:899–906.
4. Fahn S, Marsden CD. The treatment of dystonia. In: Marsden CD, Fahn S, editors. Movement disorders 2. London: Butterworth & Co Ltd; 1987. Chapter 18, p 359–382.
5. Kägi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. J Neurol Neurosurg Psychiatry 2010;81: 5–12.
6. Steinberger D, Topka H, Fischer D, Muller U. GCH1 mutation in a patient with adult-onset oromandibular dystonia. Neurology 1999;52:877–879.
7. Bressman SB. Genetics of dystonia: an overview. Parkinsonism Relat Disord 2007;13 (Suppl 3):S347–S355.
8. Langkafel M, Heinz A, Schols L, Przuntek H. Apomorphine—test in dystonia. J Neurol Transm 1991;4:293–295.

Lingual Myoclonus Secondary to Bilateral Cortical Strokes in a Probable Case of Antiphospholipid Syndrome

Video 

Lingual myoclonus is a rare disorder, often of unknown etiology. A few cases of rhythmic myoclonic movements of the tongue[1–5] have been reported with other movement disorders such as a palatal myoclonus[6] because of brainstem lesions,[3–5] whereas others have no detected structural abnormalities.[1,2] This report describes a case of nonrhythmic lingual myoclonus after bilateral cortical strokes for which the patient was vulnerable as a corollary of probable antiphospholipid syndrome.

CASE REPORT

A 26-year old Thai woman was referred to our clinic to investigate the cause of repeated strokes. The precipitating event was drooling upon awakening 2 months earlier, accompanied by slurred speech. She had a history of nephrotic syndrome and had been treated with prednisolone and cyclophosphamide for 9 years, until she was lost to follow-up 2 years before the drooling episode. A CT scan of the brain after the onset of drooling showed a hypodense lesion at the right frontoparietal area. Ten days later her symptoms subsided, but after 3 weeks she was again unable to speak normally. Subsequent CT scans of the brain showed an additional hypodense lesion at the frontal and insular areas, but on the left side. There were no lesions in the brainstem or cerebellum.

On examination, the patient was found to be alert with bilateral lower facial weakness consistent with an upper motor neuron lesion and was severely dysarthric. Examination of the tongue revealed bilateral, nonrhythmic, asymmetric, and jerky movements involving the entire tongue. There were no voluntary and reflexive movements of the tongue. In addition, she had bursts of eyelid myoclonia. There was no dysphagia, no weakness of the limbs, and no abnormal movement of the palate. Sensory, deep tendon reflexes and cerebellar examinations were entirely normal.

A MRI of the brain showed hypersignal intensity of bilateral frontotemporal and insular areas on T1, T2, and fluid-attenuated inversion recovery (FLAIR) images without fluid restriction on diffusion-weighted images (Fig. 1a–d). A MRA of the cerebral vessels revealed irregularities of left internal carotid artery and left middle cerebral artery. Electromyography (EMG) of the genioglossi showed nonrhythmic bursts of activities consistent with myoclonus, the duration of which was <50 ms (Fig. 1e). Median nerve somatosensory evoked potential (SEP) showed low N20 amplitude on both sides, correlating with bilateral cortical lesions, but there was no giant SEP. Electroencephalography and visual evoked potentials were normal. Blink reflexes and auditory brainstem evoked responses (ABERs) were normal, suggesting intact brainstem pathways.

Protein C, protein S, antithrombin III and fibrinogen levels, and anticardiolipin IgG and IgM were all normal except for a positive lupus anticoagulant test. Carotid duplex ultrasonography did not reveal atherosclerotic plaque or significant stenosis. Echocardiography showed anterior and anteroseptal wall hypokinesia, but coronary angiography did not show significant coronary artery disease. From the laboratory results and two recent strokes, antiphospholipid syndrome was suspected and the patient was treated with hydroxychloroquine and warfarin.[7]

One year after initiating treatment, the patient was able to speak more clearly, protrude and move her tongue sideways, and the severity of lingual myoclonus was decreased. No further medication was given to treat the lingual myoclonus. Eyelid myoclonia was not ameliorated by the treatment regimen and it persisted.

DISCUSSION

The patient had lingual myoclonus because of arterial thromboses that resulted in infarction of bilateral cortical areas involving the homuncular representation of the tongue (Fig. 1). The propensity for strokes was due to probable antiphospholipid syndrome.

The cortical origin of lingual myoclonus in our case was supported by EMG of the tongue revealing bursts of myoclonic discharges of <50 ms in duration. Furthermore, the

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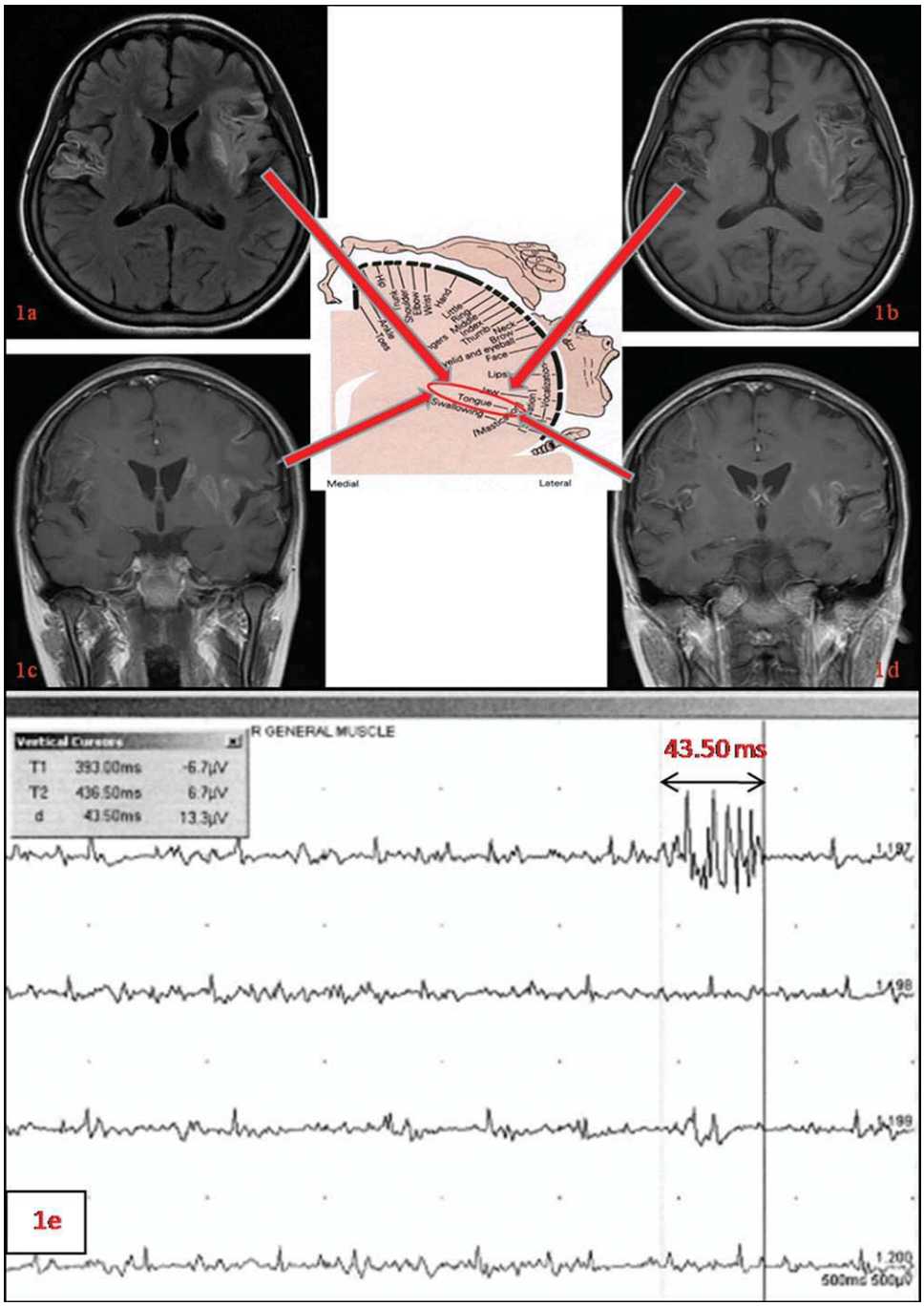

FIG. 1. (**a**–**d**) Shows MRI of the brain (a, c, d showing FLAIR and b showing T1W images). There are hyperintense lesions of bilateral fronto-temporal and insula areas and left putamen. The lesions involved bilateral tongue homunculus of the motor cortex. **e**, Shows electromyography (EMG) of the genioglossus showing bursts of myoclonic discharge of 43.50 ms in duration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

imaging evidence of bilateral cortical lesions without brainstem involvement together with normal blink reflex and ABERs supports the conclusion that the lingual myoclonus was most likely to be of cortical origin. However, lack of giant SEP in our case may be because the median nerve was stimulated to study the SEP. The absence of reflexive movement of the tongue made opercular syndrome and lingual apraxia unlikely.

A literature review of other cases supports an assessment that this was a distinct and rare presentation of lingual myo-

clonus in the patient. Previous reports described the movement of lingual myoclonus to be rhythmic and symmetrical, whereas the movement of this patient was jerky, nonrhythmic, and asymmetric with electrophysiological confirmation of cortical myoclonus.[1–3] Anatomical lesions in other studies were either in the brainstem regions or no lesions were detected.[1–3,5] As far as we are aware, lingual myoclonus due to bilateral cortical lesions has never been reported in the literature. A previous case series reported the onset of lingual myoclonus after acute and subacute viral encephalitis, but no information on imaging and electrophysiology is available in that cases.[4]

The patient described in this article presents a rare lingual movement disorder. The evidence suggests that her lingual myoclonus was caused by cortical lesions. Therefore, we conclude that in addition to brainstem lesions, abnormal tongue movements can also be the result of cortical lesions.

LEGENDS TO THE VIDEO

There are bilateral, nonrhythmic, asymmetric, jerky movements of the tongue. The patient was asked to move the tongue sideways but could not do it and moved her lips instead. Loss of nasolabial folds had disappeared at the time the VDO was taken (55 seconds). Follow-up at 6 months showed that the patient could protrude and moved her tongues. Her lingual myoclonus decreased in frequency (78 seconds in total).

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References

1. Bettoni L, Bortone E, Chiusi M, Tortorella R, Zanferrari C, Mancia D. Isolated episodic lingual myoclonus. Eur Neurol 1999;41: 118–119.
2. Gobernado JM, Galarreta M, De Blas G, Jimenez-Escrig A, Hernandez A. Isolated continuous rhythmic lingual myoclonus. Mov Disord 1992;7:367–369.
3. Kulisevsky J, Avila A, Grau-Veciana JM. Isolated lingual myoclonus associated with an Arnold-Chiari malformation. J Neurol Neurosurg Psychiatry 1994;57:660–661.
4. Sridharan R. Rhythmic involuntary lingual movements (lingual myoclonus): study of 4 cases. Indian J Pediatr 1984;51:733–737.
5. Troupin AS, Kamm RF. Lingual myoclonus. Case report and review (Abstract). Dis Nerv Syst 1974;35:378–380.
6. Mondria T, de Gier HH, Boon AJ. New device to control combined lingual and palatal myoclonus. Mov Disord 2007;22:573–576.
7. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.