Movement Disorders
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Letter to the Editor Related to New Topics

Facial Reflex Hyperexcitability in Geniospasm Suggests a Brainstem Origin

Geniospasm (OMIM 190100) is characterized by spontaneous repetitive involuntary contraction of mentalis muscles resulting in quivering or trembling of the chin that is intensified by stress or anxiety. The movements are first noticed in infancy or childhood and usually abate by late adulthood.[1] Although geniospasm is a benign disorder the movements cause embarrassment and significant social anxiety.[1,2]

The nosology of the movements of geniospasm has been variously described as myokymia, tremor, and myoclonus but their origin remains unclear.[1–3] This report examines mentalis activity and facial nerve excitability in a patient with geniospasm.

A 42-year-old man from a four generation Australian family with six affected members with geniospasm was studied. He had been aware of semicontinuous chin quivering since childhood. Neurological examination revealed bilateral continuous, semirhythmic chin quivering. There was no facial weakness. Drugs and left lower peripheral facial nerve surgery had no effect on the movements. Botulinum toxin (Botox, Allergan) injections (30 units in each mentalis muscle) every 8 to 10 months abolished the movements.

Muscle activity was recorded from bilateral mentalis and orbicularis oculi (OO) muscles using needle and surface electrodes on a multichannel electromyography (EMG) system (Nicolet Viking III, Madison, WI). The supraorbital nerves (SON) were stimulated in the supraorbital groove at three to five times the sensory threshold and responses recorded from surface electrodes over both OO and mentalis muscles. Response latency was measured by visual inspection. Responses to facial nerve stimulation at the tragus were recorded in ipsilateral mentalis muscles.

The mentalis muscle activity responsible for geniospasm comprised brief motor unit action potentials of normal morphology, 10 to 12 milliseconds duration and amplitude 50 to 100 μV, discharging arrhythmically at five to eight per second. Both sides were involved. There were no high frequency discharges or grouped discharges of myokymia. Voluntary contraction produced normal recruitment pattern that interrupted geniospasm. Stimulation of the facial nerves at the tragus evoked mentalis responses of normal morphology and latency (without late responses).

Stimulation of the SON evoked a series of reflex responses in the facial muscles. Normal appearing blink reflexes (R1 and R2) were recorded from bilateral OO (not shown). Responses corresponding to R1, R2, and R3 were recorded from both mentalis (Fig. 1). Needle EMG confirmed the responses corresponding to the R2 and R3 were bilateral but

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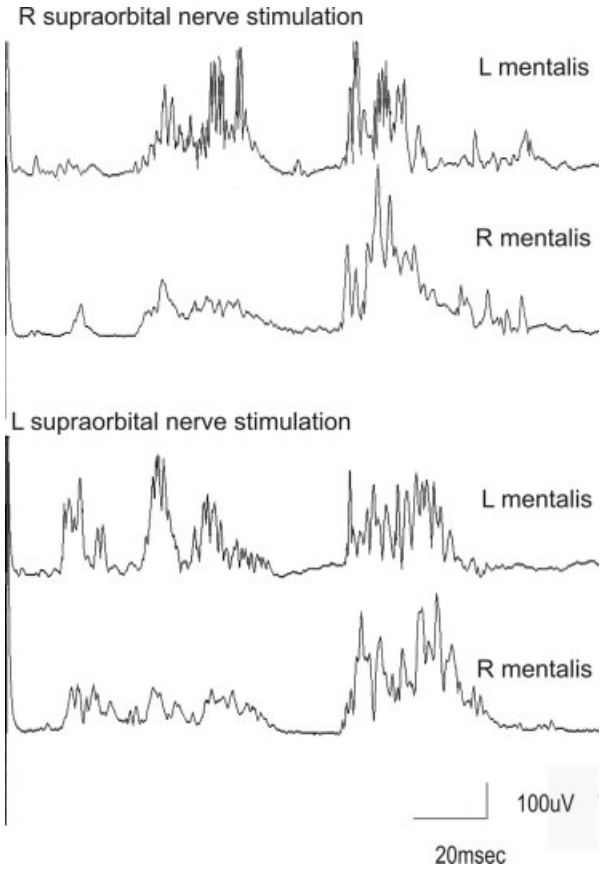

FIG. 1. Rectified surface EMG recordings from the mentalis muscles following stimulation of the supraorbital nerves (SON) (each trace represents the average of 10 trials). Unilateral SON stimulation evoked mentalis responses at latency 14 milliseconds corresponding to the R1 response of the blink reflex and bilateral responses at 42 milliseconds (corresponding to the R2 response of the blink reflex) and 90 milliseconds (corresponding to the R3 response of the blink reflex). The extent of facial muscle activity suggests facial nuclear hyperexcitability.

R1 responses were more variable and largely unilateral (the anatomy of mentalis allowed surface EMG recording to pick up activity from both sides of the muscle). Spread of R2 responses beyond OO muscles is described in normal subjects with high stimulus intensities and in patients with synkinesis because of aberrant facial nerve regeneration.[4,5] It is suggested in geniospasm spread of R2 and R3 responses to mentalis indicates facial nuclear hyperexcitability.

The characteristics of geniospasm in this patient were similar to those described previously,[1–3] including spread of

facial reflex responses to the mentalis. The observations that (1) the movements resulted from spontaneous arrhythmic discharges of normal motor units in both mentalis muscles, (2) the lack of peripheral facial nerve hyperexcitability or denervation, and (3) the presence of bilateral facial nuclear hyperexcitability demonstrated by spread of facial reflexes to the mentalis muscles and a third (R3) facial reflex response, indicate a central origin of geniospasm.

The highly selective involvement of mentalis in geniospasm remains to be explained. The mentalis muscles contribute to emotional facial expressions, especially as lower lip evertors while crying and expressing doubt. There is however, only limited ability to contract voluntarily the mentalis in isolation (personal observation). In the macaque, the motor neurone column subserving mentalis lies separate from the remainder of the facial nucleus apart for some overlap with lower lip neurons.[6] The rostro-caudal extent of the mentalis subnucleus is greater, and its neurones larger than the other facial subnuclei. The musculotopic organization of the facial nucleus is mirrored in the macaque motor cortex, where movements subserved by mentalis have relatively discrete representation.[7] Together these anatomical features permit selective activation of mentalis subnuclei by descending tracts or interneuronal projections. Dissociated responses of mentalis to afferent stimuli, as in the palmomental reflex, are indirect evidence for a similar facial musculotopic organisation in humans. The "privileged" status of mentalis may reflect its phylogenetic importance in facial or nonverbal signalling, particularly as lip eversion shows increasing elaboration along the primate evolutionary pathway.[8]

In conclusion, the bilateral mentalis activity and hyperexcitability of mentalis subnuclei suggests that geniospasm is likely to originate from loss of inhibition or hyperexcitability of central projections to the facial nuclei.

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Reduced *N*-Acetylaspartate in the Basal Ganglia of a Patient with Anti-NMDA Receptor Encephalitis

Paraneoplastic encephalitis with ovarian teratoma has been associated with antibodies to NR1/NR2 heteromers of the *N*-methyl-D-aspartate receptor (NMDA). Such "anti-NMDA receptor encephalitis"[1] can cause psychiatric symptoms, seizures, autonomic dysfunction, involuntary movements (IVMs), and hypoventilation.[1] Orolingual dyskinesias, chewing movements, jaw dystonia, and choreoathetoid, myoclonic, or athetoid limb movements can also occur.[1–4] These IVMs are unrelated to EEG findings and are usually refractory to antiepileptics.[2,3] Moreover, many patients with anti-NMDA receptor encephalitis show no abnormalities on cranial MRI.[1–3] Therefore, refractory IVMs in anti-NMDA receptor encephalitis remain a major, yet poorly understood problem. We studied whether these IVMs are associated with neuronal damage in the basal ganglia or thalamus since they were previously found to be nonepileptic.[2] The *N*-acetylaspartate (NAA)/creatine (Cr) ratio on MR spectroscopy is a marker of neuronal damage. We examined this ratio in a patient with anti-NMDA receptor encephalitis who had prolonged IVMs.

A 29-year-old healthy woman developed psychiatric symptoms, central hypoventilation, seizures, IVMs, and autonomic instability. Long-lasting IVMs included masticatory-like orolingual dyskinesias, athetoid movements in the upper limbs, and dystonic posturing of the neck. The patient received intravenous infusions of midazolam and antiepileptic medication during IVMs and seizures; neither treatment was effective. Conventional 1.5 tesla brain MRI was normal, and the EEG showed no paroxysmal discharges. A mature ovarian teratoma was diagnosed. Immunotherapy and tumor resection resulted in complete recovery (Case 1, see [3] for details). Six years after the clinical onset of disease, a 3.0-tesla brain MRI showed no abnormalities.

Immunocytochemical studies were performed as previously described.[1] In brief, HEK 293 cells were transfected with NR1 and NR2 plasmids to express NR1/NR2 heteromers. Cells expressing these heteromers reacted strongly with frozen samples of the patient's CSF.[4]

MR spectroscopy was performed when the patient had IVMs (early stage) and after resolution of IVMs (late stage). In the early stage, the NAA/Cr ratio in the voxel was 0.98 in the right basal ganglion, 0.87 in the left basal ganglion, 1.39 in the right thalamus, and 0.88 in the left

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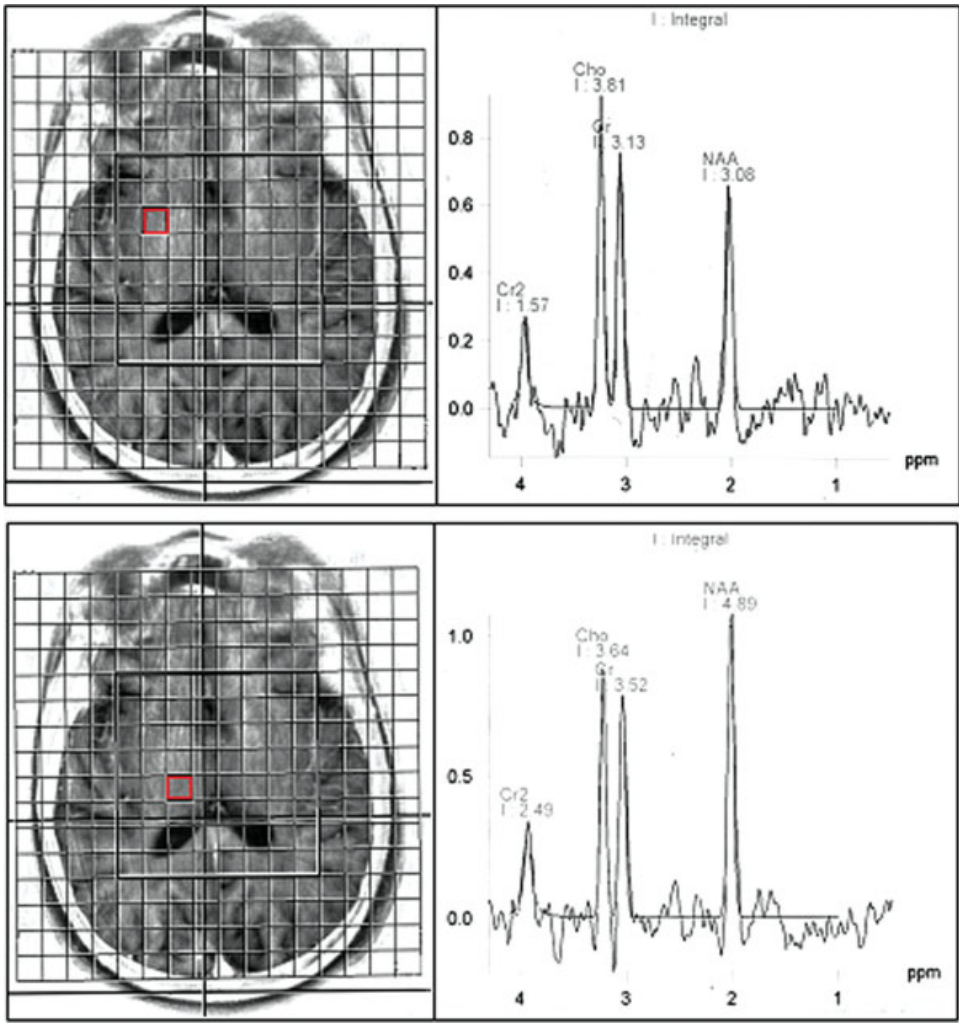

FIG. 1. MR spectroscopy at the stage of IVM in a patient with anti-NMDA receptor encephalitis. MR spectroscopic data were obtained at 1.5 tesla by chemical shift imaging with a spin echo single-sequence (TR/TE = 1,500/135). Water suppression was accomplished by three chemical shift selective radio-frequency pulses preceding the section-selective RF pulses. Two-dimensional spectra were obtained using 16 × 16 phase-encoding steps (FOV = 160 × 160, VOI = 80 × 80, slice thickness = 15 mm, voxel size = 10 × 10 × 15, number of signal averages = 4, acquisition time 7.8 min). MR spectroscopy revealed that the *N*-acetylaspartate (NAA)/creatine (Cr) ratio was reduced in the voxel (red box) containing mainly the basal ganglia (0.98) (upper panel) and thalamus (1.39) (lower panel).

thalamus (Fig. 1). After resolution of the IVMs, the NAA/Cr ratios increased in the voxel containing mainly the basal ganglia (right, 1.76; left, 1.28) and thalamus (right, 1.91; left, 2.33). Control NAA/Cr ratios in five healthy subjects (mean age 29 years, range 27–32 years, 2 men and 3 women [mean ± 2SD]) were 1.51 ± 0.15 in the right basal ganglion, 1.53 ± 0.27 in the left basal ganglion, 1.73 ± 0.19 in the right thalamus, and 1.84 ± 0.28 in the left thalamus. NAA/Cr ratios in the subcortical frontal lobes were 0.83 on the right and 1.04 on the left. Control NAA/Cr ratios of the subcortical frontal lobes were 1.41 ± 0.31 on the right and 1.41 ± 0.12 on the left.

This study showed that NAA levels were reduced in the basal ganglia and thalamus during the course of IVMs, despite normal EEG and brain MRI in a patient with anti-NMDA receptor encephalitis. The basal ganglia are related to IVMs such as dyskinesias or dystonia. In dystonia associated with altered neuronal activity in thalamocortical circuits, NAA levels are decreased in the basal ganglia.[5] Thalamic lesions can cause choreoathetoid movements.[6] Therefore, the reduced NAA in the basal ganglia and thalamus of our patient suggests that the IVMs were extrapyramidal in origin. Other regions (e.g., frontal lobe) in our patient also showed decreased NAA/Cr ratios, suggesting that diffuse brain dysfunction, rather than focal neuronal dysfunction may have affected the NAA/Cr ratios in the basal ganglia and thalamus. Perfusion MRI showed hyperperfusion in the whole brain, including the basal ganglia and thalamus.[3]

The mechanism for the reduced NAA/Cr ratios is uncertain. Epileptogenic zones can spread leading to reduced

NAA on MR spectroscopy.[7] Sedation and antiepileptic medication could also have affected the NAA reduction.[8] Although these factors can affect NAA, the reduction in NAA/Cr ratios might also have involved NMDA receptor antibodies. Because clinical symptoms are reversible and usually associated with decreased antibody titers, antibodies might alter the turnover of receptors in the cell membrane. Microglial proliferation as demonstrated by pathological studies[1] might be reversible in patients with neurological improvement. We speculate that the combined effects of the factors described earlier may reversibly alter the NAA/Cr ratio.

We postulate that neuronal dysfunction caused by the associated NMDA receptor antibodies disturbed the equilibrium of circuits in the basal ganglia and thalamus, leading to IVMs. These findings were reversible and correlated with the excellent clinical outcome of the patient with anti-NMDA receptor encephalitis.

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Various Movement Disorders in a Patient with Sjögren Syndrome

Video 

Most movement disorders are usually caused by central nervous system (CNS) lesions. Occasionally, peripheral nerve lesion may cause abnormal movements. There are several hypotheses explaining the pathogenesis of movement disorders caused by peripheral neuropathy or nerve injuries. Observation of various movement disorders in a patient with Sjögren syndrome may further support the hypothetic mechanisms.

A 74-year-old woman developed unsteady gait, paresthesia of four limbs and trunk gradually for 2 months. Before these symptoms, she had to drink much more water than before because of dry mouth. On admission, neurological examination revealed mild paraparesis, asymmetrically decreased deep tendon reflexes, glove-stocking distribution of sensory deficits, absent joint position sense, and impaired vibration sensation of lower extremities. She could not stand because of severe sensory ataxia. Pseudochoreoathetosis of bilateral hands and dystonic tremor of bilateral legs with right-side predominance were observed. Sometimes there were jerks at lower limbs, which were not stimulus-sensitive. There was neither rigidity nor bradykinesia. Her family did not have any history of movement disorders and she denied any antidopaminergic, antiemetic, or sympathomimetic drug use history.

The sensory nerve conduction study did not show any response after stimulating the bilateral median, ulnar, and sural nerves. The motor nerve conduction study revealed mildly reduced compound motor action potentials of right median nerve and both deep peroneal nerves. The F wave was normal. The surface electromyographies of right anterior tibialis and quadriceps femoris demonstrated rhythmic muscle activities (Fig. 1).

CSF study revealed mild elevated protein (60.8 mg/dl) without pleocytosis. The serology failed to disclose paraproteinemia, vitamin B12 deficiency, and syphilis. The Schirmer's test was pathologic (2 mm OD, 0 mm OS). Salivary scintigraphy, with Tc-99m, revealed impaired uptake and excretory functions of bilateral parotid glands. The anti-Ro/SS-A antibodies was 150 U/ml (normal <10 U/ml), and the anti-La/SS-B antibodies was negative. The clinical symptoms and laboratory findings were compatible with the diagnostic criteria of Sjögren syndrome.

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

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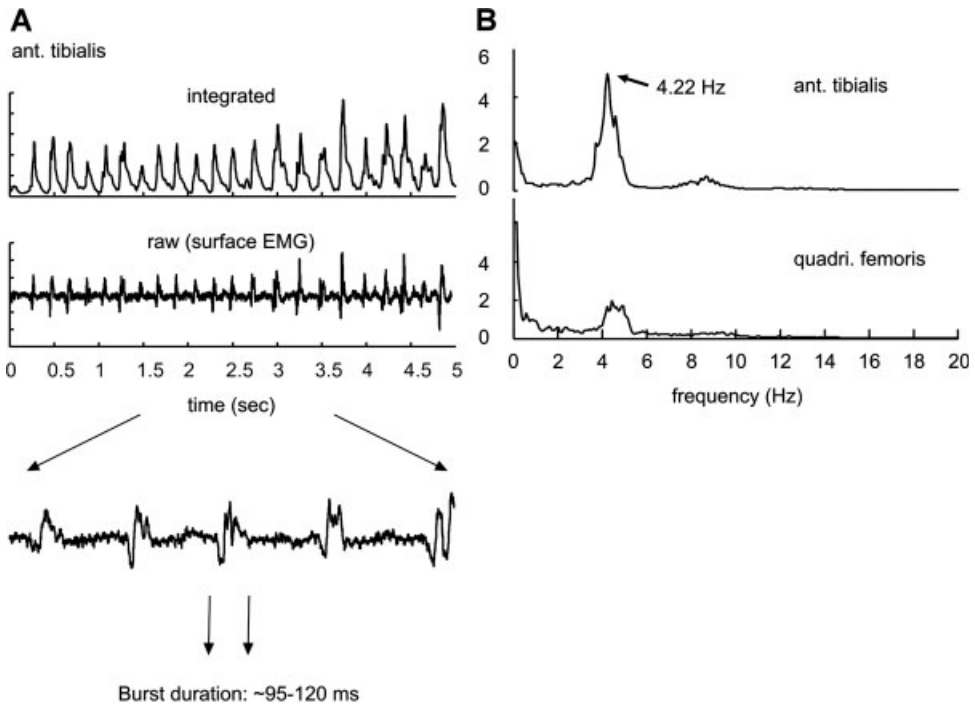

FIG. 1. Surface electromyographies: the band past filter was between 3 and 3,000 Hz. The time constant of integrated activity was 100 ms. (**A**) Right anterior tibialis demonstrated rhythmic muscle activities. The burst duration ranged from 95 ms to 120 ms. (**B**) The frequency was peak at 4.22 Hz.

The magnetic resonance images of the brain and spinal cord were unremarkable.

Abnormal movements, including pseudochoreoathetosis, tremor, myoclonus, and dystonia, have been reported in patients with peripheral trauma or neuropathy for several decades. The dystonic tremor in this case is a novel feature of peripheral-induced movement disorder. The mechanisms underlying the peripheral trauma or neuropathy induced movement disorders may be heterogeneous. The basal ganglia receive and encode the sensory inputs. The processed information will guide the motor program in the cortex. If there is a defect in peripheral afferent or central response to somatosensory inputs, the sensorimotor integration may develop abnormally and result in dystonia.[1] Presence of neuronal plasticity will adapt to altered sensory inputs and the reorganization can occur in cortex, basal ganglia, and thalamus. The central reorganization may be responsible for the generation of tremor and dystonia in peripheral nerve injury.[2,3] Impairment of proprioceptive afferents may modulate the excitability of motor neurons and interneurons in spinal circuits. Hyperexcitability of the dorsal horn interneuron, which could attribute to decrease or loss function of the inhibitory spinal interneuron, was observed in segmental spinal myoclonus.[4] The defect of proprioceptive afferents also contributes to develop an abnormal oscillatory drive from the motor cortex to the spinal motor neurons and then cause pseudochoreoathetosis.[5] Antecedent dysfunction of CNS, perinatal injury, genetic predisposition, history of dopamine receptor-blocking agents exposure[3,6] probably explain why some patients are susceptible to peripheral nervous disease induced movement disorders.

We conclude that the somatosensory inputs and feedback to the CNS play an important role in the pathogenesis of peripheral nervous disease induced movement disorders. The defect may involve multiple level of CNS, including motor cortex, somatosensory cortex, basal ganglia, and spinal cord. The impaired somatosensory afferents could explain why the various movement disorders exist in a patient with subacute sensory neuronopathy caused by Sjögren syndrome.

LEGEND TO THE VIDEO

The patient had choreoathetoic movements of bilateral hands, dystonic tremor, and some myoclonic jerks of bilateral legs. The tremor pattern was different bilaterally. Dystonic posture of the both feet was intermixed occasionally. Sometimes she swung left leg forth and back involuntarily.

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Paroxysmal Dystonia Associated to Primary Sjögren's Syndrome

Sjögren syndrome (SS), the second most common autoimmune rheumatic disease, is characterized by keratoconjunctivitis sicca and xerostomia resulting from immune lymphocytes that infiltrate the lacrimal and salivary glands.[1]

Neurological complications of primary SS may affect the peripheral nervous system (PNS) or, with a lesser frequency, the central nervous system (CNS) with a frequency ranging from 1.5% to 25%.[2] PNS manifestations include cranial neuropathies, distal sensory or sensorimotor neuropathy, sensory neuronopathy, autonomic neuropathy, mononeuritis multiplex, motor neuron disease, and myopathy; whereas CNS manifestations include neuropsychiatric dysfunction, focal brain lesions, relapsing-remitting multifocal CNS disease mimicking multiple sclerosis, meningitis, and myelopathy.[3]

Movement disorders, and particularly dystonia, associated with primary SS are infrequent.[4–6] We report a patient with paroxysmal dystonia associated to primary SS.

The patient was a 57 year-old female, with previous history of high blood pressure, right nephrectomy because of chronic pyelonephritis, allergy to amynoglucosides, and surgery because of left ulnar entrapment neuropathy at the elbow. She was under treatment with hydrochlorothiazide. Her sister was diagnosed with rheumatoid arthritis. She was first evaluated in 2001 in our Movement Disorders Unit because of sudden episodes of dystonic posturing of the right arm lasting 2 min, with a frequency of 3–4 per day, not precipitated by voluntary movements. Blood count, routine biochemistry, thyroid hormone plasma levels, interictal electroencephalography, and cranial CT were normal. The patient was diagnosed with idiopathic paroxysmal dystonia. Treatments with carbamazepine (200 mg TID), gabapentin (800 mg TID), phenytoin (300 mg TID), valproic acid (500 mg TID, lamotrigine (100 mg BID, acetazolamide and topiramate (100 mg TID), were unsuccessful or had adverse effects. Dystonic episodes were controlled with clonazepam at increasing doses up to 0.5 mg TID was started.

In March 2007, the patient developed progressive paresthesia and dysesthesia of the right arm. She then reported a mild dryness in the eyes and the mouth at least 10 years before. Brain MR imaging showed multiple hyperintense lesions in the white matter and in the grey matter-white matter border, both in T-2 (Fig. 1a) and in FLAIR weighted images (Fig. 1b–d). Cervical spine MR showed mild paracentral C6–C7 and D1–D2 herniations. Serum antinuclear antibodies were positive (1:1280 with speckled pattern) but anti-DNA was negative. Rheumatoid factor (125 mg/dL), anti-Ro/SS-A and anti-La/SS-B were positive. ANCA, antithyroid, crioaglutinin, anticardiolipin, and antiphospholipid antibodies were negative. Serum concentrations of folic acid, vitamin B12, thyroid hormones, immunoglobulins, C3 and C4, plasma protein electrophoresis, and levels of antistreptolisin O antibody were within the normal range. Cerebrospinal fluid showed normal glucose and total protein levels and 0 cells/mm^3 and IgG 2.2 mg/dL. Serum electrophoresis and immunoelectrophoresis showed one oligoclonal band. Serological studies for syphilis, Brucella, Borrellia, and HIV were negative both in the serum and in the cerebrospinal fluid. All CSF cultures, and serologic studies for herpesvirus simplex types 1, 2, and 6, herpesvirus varicella-zoster, cytomegalovirus, and enteroviruses were negative. The right arm somatosensory, visual and auditory evoked response tests were normal. Schirmer test was positive in both eyes. Histological examination of a sublabial salivary gland biopsy showed a grade 3 of Greenspan et al. (moderate infiltrate or less than one aggregate of 50 or more lymphocytes, histiocytes, and plasma cells per 4 mm^2). The patient was diagnosed with primary SS. Because dystonic episodes were controlled with clonazepam, and the dryness of the eyes and mouth was mild, she was only treated with symptomatic therapy with artificial tears and mouthwashes.

Our patient developed a typical focal paroxysmal dystonia, and 7 years later sensory symptoms, in the right arm, that were possibly related with the presence of brain white matter lesions. The etiologic study led to the diagnosis of primary SS according to current classification criteria.[7]

The association between SS and dystonia is infrequent. Van den Berg et al.,[4] reported a 36-year-old man with painless fixed dystonic posture of the left hand as the first symptom of SS, which improved with cyclophosphamide and prednisone. Jabbari and Salardini[5] reported three patients previously diagnosed with SS who developed intermittent tonic/dystonic limb spasms. Moreover, Papageorgiou et al.[6] reported a patient with a comorbidity of SS and coeliac disease, who developed orofacial dystonia which resolved almost completely after a treatment with corticosteroids.

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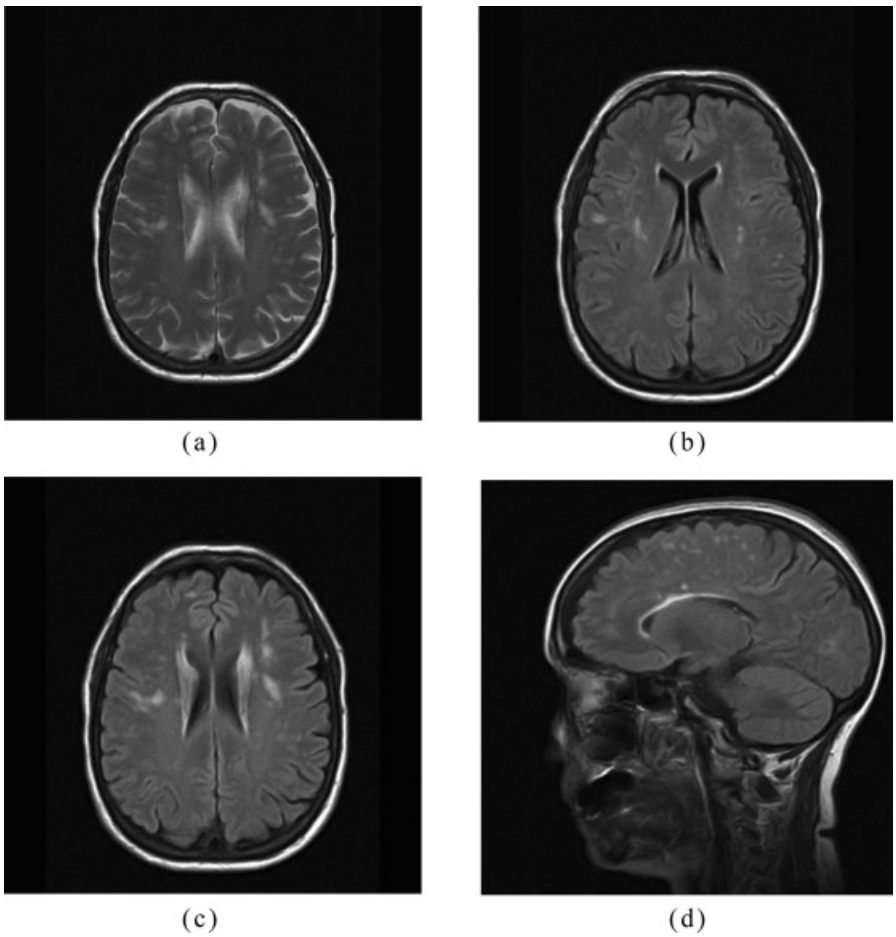

FIG. 1. T-2 (**a**) and FLAIR-weighted images (**b**–**d**) in brain MRI showing hyperintense lesions in the white matter and in the grey-white matter border.

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A Case of Parkinson's Disease Worsened by Captopril: An Unexpected Adverse Effect

We describe a 67-year-old female with an 8-year history of idiopathic Parkinson's disease (PD) and a past medical history of ischemic heart disease.

She was treated with levodopa/carbidopa 1,000 mg, pergolide 1.5 mg, entacapone 800 mg, selegiline 10 mg, amatadine 200 mg. She developed motor fluctuations 5 years after disease onset. The severity of PD was graded as Hoehn and Yahr 2−3 and a diagnosis of an akinetic-rigid form of PD with peak-dose dyskinesia was made.

The average duration of "off" time was less than 10% per day.

Her UPDRS scale was scored with a motor examination score of 26 and dyskinesia score of 7. She was then provided with oral captopril 6.25 mg three times per day at the cardiovascular outpatient clinic for 2 weeks.

An increase in duration of the "off" time was noticed by the patient following the captopril intake.

According to patient's diary, her average duration of "off" time increased to more than 50% of day.

No new medication like neuroleptic and antidopaminergic agents had been taken.

Although the daily levodopa/carbidopa 1,250 mg and pergolide 2 mg were titrated during her outpatient clinic visit, she visited emergency room (ER) every 2 days within 1 week due to frequent wearing off.

Oral and sublingual captopril 25 mg were prescribed at the ER because a higher blood pressure was noted during the "off" state. No signs or symptoms indicative of a stroke were noted. Laboratory data showed no obvious abnormality.

After hospitalization, her UPDRS scale was scored with a motor examination of 43 and dyskinesia score of 3 while an increase of akinesia and "off " time duration was reported about 80% per day. Administration of apomorphine to abort her "off" phenomenon and titration of pergolide dosage to 10 mg were only partially effective. Her condition gradually improved after captopril was totally discontinued for about 3 weeks. Her peak-dose dyskinesia increased while a decrease of akinesia and "off" time was reported about 30% (motor exam score 28, dyskinesia score 7).

Her medication was titrated to levodopa/carbidopa 1,000 mg and pergolide 1.5 mg 5 weeks after discharge.

Captopril is an angiotensin converting enzyme (ACE) inhibitor, which can cross the brain-blood barrier.[1] Some reports suggest that captopril may cause clinical parkinsonism features.[2,3] Similarly, in our case, it increased akinesia and decreased peak-dose dyskinesia.

Although we cannot totally exclude the placebo or psychological effect in our patient and we did not try to reintroduce captopril to establish a casual relationship, we still observed that a random captopril use as administered at an ER visit resulted in an increase of severity and duration of akinesia.

Other ACE inhibitors like perindopril on the other hand may facilitate dopaminergic release and improve motor function in PD patients.[4]

There is experimental suggestion that captopril increases dynorphin and GABA levels through peptidase inhibition,[5] while perindopril increases extracellular dopamines levels, preproenkephalin mRNA, and D2 receptors in the striatum.[6]

Dynorphin and GABA may act on presynaptic and postsynaptic opioid receptors and further inhibit dopamine release.[7]

We thus think that captopril and perindopril may act differently at the direct and indirect motor loop of the basal ganglia causing different clinical manifestations.

Further study is needed to clarify the effect of different ACE inhibitors on PD.

We encourage clinicians to report the rare adverse effect of captopril when treating patients with Parkinson's disease.

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