Pearls & Oysters: Tonic eye deviation in stiff-person syndrome

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PEARLS

1. Stiff-person syndrome (SPS) is an autoimmune disease characterized by muscle rigidity, episodic muscle spasms, as well as continuous cocontraction of agonist and antagonist muscles.
2. Although a criterion for diagnosis of SPS, anti-glutamic acid decarboxylase (anti-GAD) antibodies can be negative in up to 40% of patients. In absence of antibodies, characteristic EMG findings of continuous motor unit activity and decrease in this activity with diazepam are helpful in diagnosis.

OY-STERS

1. Abnormalities of eye movements are rarely encountered in SPS and their exact frequency is unknown.
2. Spasticity in SPS improves following treatment of the underlying condition and with immunomodulation. However, the response of eye movement abnormalities to treatment remains enigmatic.

CASE REPORT A 50-year-old man presented to our hospital with gradually progressive difficulty in walking of 3-month duration (video on the *Neurology*® Web site at Neurology.org). He also complained of tightness in the lower limbs, back, and abdomen. He could not bend forward because of stiffness of back and trunk. There were painful spasms in his legs that worsened at night. Two weeks after onset of his illness, he noticed persistent deviation of both eyeballs to the left along with difficulty in moving his eyes to the right. There was no ocular pain, ptosis, or double vision. Clinical examination revealed tonic deviation of eyes to the left with restriction of extraocular movements to the right side (figure, A). He had grade 3 spasticity in both the legs with brisk deep tendon reflexes in all 4 limbs. There was exaggerated lordosis of cervicothoracic as well as lumbar spine (figure, C) along with tautness of abdominal and paraspinal muscles (cervical, thoracic, as well as lumbar). The remainder of the neurologic

examination (cognitive functions, speech, motor power, sensory examination, and coordination) was normal. Based on clinical features, a possibility of SPS was considered. Although tonic eye deviation can also occur in progressive encephalomyelitis with rigidity and myoclonus, this diagnosis seemed unlikely in the absence of myoclonus, encephalopathy, and sphincter dysfunction. Complete blood counts, serum vitamin B₁₂, thyroid and liver function tests, urea, electrolytes, glucose, and serum protein electrophoresis were normal. Antinuclear and anti-neutrophil cytoplasmic antibodies were negative. CSF analysis was normal: cells 5/mm³, glucose 72 mg/dL, protein 39 mg/dL, and no oligoclonal bands. Gadolinium-enhanced MRI of brain and spinal cord was normal. Anti-GAD, anti-amphiphysin, and anti-acetylcholine receptor antibodies were negative. CT of the thorax revealed an anterior mediastinal mass (figure, D), which was FDG (fluorodeoxyglucose) avid on PET-CT (figure, E). CT-guided fine-needle aspiration cytology of the mass revealed thymoma type B3. Electrophysiologic testing including sensory and motor nerve conduction studies as well as repetitive nerve stimulation were normal. Needle EMG revealed continuous motor unit activity in quadriceps, hamstring, lumbar, and thoracic paraspinal and as well as in abdominal muscles. Motor unit potentials were normal in duration and amplitude, and there was no evidence of any denervation. The motor unit activity decreased following administration of diazepam, which was highly suggestive of a diagnosis of SPS. Thus, despite absence of anti-GAD antibodies, a diagnosis of paraneoplastic SPS was made. The patient underwent thymectomy and received IV immunoglobulin 400 mg/kg/d for 5 days. Because there was a favorable response with it, a second IV immunoglobulin pulse (400 mg/kg/d for 5 days) was administered 6 weeks later after which he had a remarkable amelioration of his stiffness and improvement in ocular movements (figure, B). At 6-month follow-up, he was doing well and was independent in all his activities of daily living.

Supplemental data
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(A) Extraocular movement abnormalities at presentation. The primary position of the eyes is shown in the center (e); note tonic eye deviation to the left side. Parts a–d and f–i show the position of eyeballs on attempting gaze in different directions as shown by arrows. The patient was asked to look upward and to right (a), upward (b), upward and to left (c), to right (d), to left (f), downward and to right (g), downward (h), and downward and to left (i). (B) Eye movements after treatment. Note remarkable improvement in movements of eyeballs. (C) Exaggerated cervical, thoracic, as well as lumbar lordosis. (D) A well-defined lobulated homogeneous soft tissue mass in anterior mediastinum (blue arrow). The mass was FDG (fluorodeoxyglucose) avid on PET-CT (blue arrow) as shown in panel E.

DISCUSSION Anti-GAD antibodies have a major pathogenic role in SPS. GAD is the key enzyme that converts glutamate into γ -aminobutyric acid (GABA). It exists in 2 isoforms, GAD65 and GAD67, which function together to regulate levels of GABA. While GAD67 is responsible for maintaining a basal level of GABA, GAD65 is activated when additional GABA is required, such as during periods of stress. By binding to specific transmembrane receptors in both pre- and postsynaptic neurons, GABA triggers opening of chloride channels causing inward movement of chloride into the cell resulting in membrane hyperpolarization. Thus, it acts as a major inhibitory neurotransmitter of brain and spinal cord. In SPS, autoantibodies are directed primarily against GAD65 resulting in reduced production of GABA.¹ Deficiency of GABA leads to disinhibition of GABA-dependent spinal and suprasegmental inhibitory networks ensuing excessive motor neuron firing and the resultant clinical symptomatology. Other antibodies that may be associated with SPS include antibodies against GABA_A receptor-associated

protein and anti-amphiphysin antibodies. GABA_A receptor-associated protein is involved in normal trafficking and assembly of GABA_A receptors. Antibodies against this protein result in defective signal transmission by interfering with normal assembly of GABA_A receptors. Anti-amphiphysin antibodies inhibit the functioning of protein amphiphysin, which is highly expressed in neurons with intensive synaptic activity. Although the exact mechanism of stiffness in anti-amphiphysin antibody-related SPS is still unclear, several hypotheses have been presented. It is likely that dysfunction of this protein hinders vesicular endocytosis thereby resulting in defective recycling of GABA_A receptors. Alternatively, anti-amphiphysin antibodies may decrease efficacy of GABA by impeding the function of Na-K-Cl cotransporters.^{2,3}

Rigidity in SPS usually begins insidiously in thoracolumbar paraspinal muscles and extends over time to involve proximal leg and abdominal wall muscles, resulting in a stiff, robotic gait and hyperlordosis of the

spine. The rigidity may fluctuate, increasing with physical/mental stress, cold, and intercurrent infections and decreasing with sleep. Another clinical hallmark of SPS is the presence of episodic spasms, which are sudden and sometimes painful. They are often precipitated by external stimuli and physical obstacles and may result in unprotected falls.⁴

SPS is primarily a clinical diagnosis, often instigated by a high degree of suspicion, and no specific neurologic signs or laboratory tests are available to confirm the diagnosis. The variability in clinical presentation further accentuates the problem in diagnosis, largely accounting for long delay (range: 1–18 years; mean: 6.2 years) in diagnosis. Diagnosis criteria for SPS proposed by Dalakas⁵ include the following:

1. Muscular rigidity in trunk and proximal limbs
2. Continuous cocontraction of agonist and antagonist muscles
3. Episodic muscle spasms
4. Absence of other neurologic disease causing stiffness/rigidity
5. Presence of serum anti-GAD antibodies

Patients fulfilling all these criteria are diagnosed as SPS and patients who do not meet all the criteria are labeled as atypical SPS. Response of stiffness to diazepam is considered as a diagnostic criterion by some neurologists, although it was not part of the original criteria of Dalakas.⁵

Final diagnosis of SPS is established by the following:

1. Clinical findings
2. Exclusion of pyramidal and extrapyramidal disorders, namely, neuroleptic malignant syndrome, serotonin syndrome, Isaac syndrome, chronic spinal interneuronitis, zoster or radiation myelopathy, tetanus, hyperekplexia, hereditary spastic paraparesis, leukodystrophies, primary lateral sclerosis, dystonia (generalized and focal), muscle disorders (channelopathies, myotonia, and paramyotonia), drugs (monoamine oxidase inhibitors, phenothiazines, amphetamines, and tetrahydropyridine), and progressive encephalomyelitis with rigidity and myoclonus
3. Supportive evidence from EMG that shows continuously firing motor unit potential of otherwise normal configuration without any signs of denervation
4. Elevated anti-GAD antibodies; MRI of the nervous system is usually normal^{1,6}

This patient satisfied all the clinical criteria except for negative anti-GAD antibodies. These antibodies may be absent in up to 40% of patients with SPS. Other antibodies that are found in patients with SPS include anti-amphiphysin antibodies, antibodies

against GABA_A receptor protein, and anti-gephyrin antibodies.⁷ A careful search for paraneoplastic etiology should be done in all cases of SPS. Paraneoplastic variety accounts for 5% of all cases of SPS. The most common malignancies associated with SPS include malignancies of lung, breast, colon, thymus, and lymphomas.⁶ Approximately 10 cases of thymoma associated with SPS have been described (PubMed database).

Ocular abnormalities described in SPS include (1) nystagmus in conjunction with ataxia, (2) abduction deficits in association with myasthenia and thymoma, and (3) slowed and impaired saccade initiation.^{8,9} Gaze-evoked nystagmus probably results from an abnormal eye position signal arising from brainstem. The horizontal neural integrator responsible for maintaining eyes in eccentric gaze position lies in medial vestibular nuclei and prepositus hypoglossal nucleus. In experimental animals, injection of GABA antagonists into these structures impedes the gaze-holding mechanisms.

The other structures that have an important role in control of ocular movements include dorsolateral pontine nucleus (DLPN) and nucleus of optic tract (NOT). DLPN receives corticopontocerebellar fibers subserving smooth pursuit movements, and injections of GABA antagonists in DLPN disrupt smooth pursuit movements. NOT mediates gaze-holding and smooth pursuit movements by sending signal outputs to flocculus via inferior olive. Manipulations of GABAergic neurons in NOT may give rise to nystagmus and smooth pursuit asymmetries in experimental animals. Other brain areas such as deep cerebellar nuclei and superior colliculus also have GABA-mediated effects on gaze.⁷

Tonic eye deviation in SPS is sparsely reported in the literature. This possibly results from continuous neuronal discharge in gaze-holding neurons consequent to GABA dysfunction. As detailed before, the postulated hypothesis for impaired smooth pursuit and impaired saccade initiation lies with dysfunction of DLPN and NOT, respectively. At follow-up, this patient had improvement in tonic eye deviation but slow saccades and impaired smooth pursuit persisted.

This report expands the spectrum of clinical findings in SPS to include tonic eye deviation, impaired smooth pursuit, and poor saccade initiation. It also indicates that ocular abnormalities respond to treatment in synchrony with other clinical manifestations of SPS.

AUTHOR CONTRIBUTIONS

All authors have made substantive contribution to the study and all authors endorse the data and conclusions. Sudheer Chakravarthi: data collection and drafting the manuscript. Manoj Kumar Goyal: conceptualization and revision of the manuscript. Vivek Lal: revision of the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Neurology 2015;84:e124-e127

DOI 10.1212/WNL.0000000000001512

This information is current as of April 27, 2015

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