

Association Between Paroxysmal Tonic Spasms and Neuromyelitis Optica

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Objective: To determine the frequency of the association between tonic spasms and neuromyelitis optica (NMO) at our center.

Design: An institutional review board–approved retrospective study of clinical, serological, and radiographic characteristics of patients with NMO.

Setting: Multiple sclerosis center.

Patients: Patients with NMO treated at our center between 1990 and 2008.

Main Outcome Measure: Records were examined for documentation of tonic spasms.

Results: Of 110 patients with *International Classification of Diseases* code 341, 57 patients met diagnostic cri-

teria for NMO. Of these, 8 patients (14%) had documented typical tonic spasms (median age at onset, 39.5 years; range, 13.8–54.2 years). Of those patients, 4 were African American, 3 were Hispanic, and 1 was white. Only 1 was male. The NMO-IgG antibody was found in 1 of 6 patients tested. Tonic spasms appeared after a mean of 24.6 months (range, 0–91 months). In 2 of 57 patients meeting NMO criteria, tonic spasms accompanied their initial episodes. Seven of 8 patients who had tonic spasms responded to treatment with carbamazepine within 1 week.

Conclusion: Tonic spasms are associated with NMO more commonly than with multiple sclerosis and may be a presenting sign in both diseases.

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MATHEWS¹ USED THE term *tonic seizures* in 1958 to describe brief recurrent stereotyped tonic spasms (dystonia) involving 1 or more limbs in patients with multiple sclerosis (MS). These tonic seizures occurred without accompanying loss of consciousness and lasted only seconds to minutes. Mathews attributed the first recognition of such tonic spasms to Guillain et al in 1928.² Mathews observed tonic seizures or spasms in 4% of patients with MS. Now more commonly referred to as tonic spasms, they occur in 3.8% to 17% of patients with MS.³ Importantly, tonic spasms may be the initial presentation of MS.⁴ Although rarely associated with disorders other than MS, there are a few reports of its association with neuromyelitis optica (NMO).^{2,5,6}

Recognition of tonic spasms in patients with NMO in our clinic prompted us to investigate the phenomenon in our patient population.

Eight of 57 patients at our clinic who met diagnostic criteria for NMO⁷ were documented to have also experienced char-

acteristic manifestations of tonic spasms. The records of their illness were critically reviewed for clinical and laboratory evidence supporting the diagnoses of NMO and tonic spasms.

REPORT OF CASES

CASE 1

A 52-year-old African American woman developed transverse myelitis and then lost sensation in her left hand. During the following month, she developed recurrent painful extensor (tonic) spasms in her left arm and both legs. Subsequently, the spasms extended to her trunk and all extremities. Treatment with carbamazepine, 300 mg, daily resulted in complete resolution of symptoms within 1 week. During the next 10 years and despite treatment with azathioprine and prednisone on alternate days inducing suboptimal lymphopenia, her clinical course was complicated by multiple relapses of optic neuritis (ON).

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CASE 2

A 14-year-old Hispanic girl was referred to our center following her third relapse of bilateral visual loss accompanied by the onset of quadriplegia. After 21 months, she developed recurrent brief tonic spasms in her left upper extremity. The spasms consisted of transient recurrent episodes of limb posturing with tonic flexion of the left elbow and wrist with adduction of the left shoulder and extension of the fingers at the metacarpophalangeal and proximal interphalangeal joints. Spasms abated within 1 week of initiation of treatment with carbamazepine, 300 mg, daily. She is blind but ambulatory and has been stable for the past 30 years while taking azathioprine and prednisone, which induced significant and consistent lymphopenia.

CASE 3

A white woman was diagnosed with NMO at age 42 years after acute onset of right-sided hemiparesis followed by multiple relapses of paraparesis associated with recurring longitudinally extensive cervical and thoracic cord lesions. Results from laboratory tests were positive for serum NMO-IgG antibody. Ten months after disease onset, involuntary stiffening of her right upper extremity occurred 4 to 5 times daily and lasted 3 to 4 minutes. During these episodes, she had tonic extension, adduction, and internal rotation of the right arm with flexion of the fingers and wrist. Treatment with carbamazepine, 300 mg, daily resulted in a prompt cessation of these events. Despite treatment with azathioprine and prednisone, she experienced numerous mild episodes of right arm weakness and ON until her management was optimized.

CASE 4

A 58-year-old Haitian American woman with recurrent episodes of painful hemibody tonic extensor spasms was admitted to the hospital at our center. She had rigid extension of her right leg and internal rotation of the right arm at the shoulder with extension of her elbow, wrist, and fingers. She progressed to a complete quadriplegia and then severe bilateral visual loss, after several stepwise episodes of transverse myelitis and ON. No serum NMO-IgG antibody was found. She was treated with intravenous methylprednisolone and then rituximab, resulting in slow recovery of visual loss but residual spasticity of her lower extremities. Carbamazepine ameliorated her dystonia but complete cessation of paroxysms did not occur until after 3 months of treatment.

CASE 5

A 45-year-old African American woman was admitted to the hospital after an acute onset of quadriplegia, respiratory distress, and severe unremitting pain in her trunk and extremities. She had a history of multiple episodes of paraparesis and ON in both eyes, which was managed with the use of oral steroids prescribed by her primary care physician. She had a slow recovery (after 48 months) following prolonged in-hospital treatment with

intravenous methylprednisolone and weekly intravenous methotrexate followed by long-term administration of oral prednisone on alternate days and weekly intravenous methotrexate. With this therapy, she gradually became ambulatory with a walker and then with a cane. Recurrent right upper extremity spasms began after 66 months and were characterized by tonic flexion of the right elbow and wrist as well as extension of the fingers at metacarpophalangeal and proximal interphalangeal joints. No serum NMO-IgG antibody was found. Magnetic resonance imaging of the cervical spine revealed marked fluid-attenuated inversion recovery signal abnormalities extending from the cervical medullary junction to T6. The tonic spasms responded to carbamazepine treatment within 5 days.

CASE 6

A diagnosis of NMO was made in a 44-year-old African American woman with multiple relapses of paraparesis and ON. Eight months after the diagnosis, she had recurrent tonic spasms in her left lower limb. These episodes were characterized by rigid tonic extension of the limb lasting 10 minutes. She had no serum NMO-IgG antibody. After initiation of therapy with carbamazepine, she had no recurrence of this abnormal posturing.

CASE 7

A 30-year-old Hispanic man experienced recurrent episodes of left lower extremity spasms precipitated by walking, sometimes resulting in falling. These were followed by the onset of recurrent episodes of lower extremity weakness, responding incompletely to the administration of parenteral steroid treatment. Ongoing difficulty with walking supervened. Examination during the spasms revealed tonic extension of the left leg at the knee and planterflexion of the ankle and toes. This paroxysmal tonic posturing of the lower extremity lasted a few minutes. They responded immediately to treatment with carbamazepine. Magnetic resonance imaging fluid-attenuated inversion recovery sequence of the cervical spine showed C3 through C7 and T3 through T4 increased T2 signal. Results from a serum NMO-IgG antibody test were negative. He was treated with intravenous methylprednisolone and subsequently with long-term azathioprine and prednisone. He developed an acute left ON following withdrawal of azathioprine therapy.

CASE 8

A 48-year-old woman had pain and numbness in both arms and her trunk. She was found to have longitudinally extensive cervical and thoracic cord lesions typical of neuromyelitis. No serum NMO-IgG antibody was found. Long-term treatment with azathioprine and prednisone, which did not achieve the desired lymphopenia in this patient, was associated with recurrent relapses of limb weakness and bilateral visual loss. Approximately 91 months after onset, she began to experience recurrent tonic spasms involving all extremities and her trunk.

Table. Features of 8 Patients With NMO With Paroxymal Dystonia

Patient No./Ethnicity/Sex/ NMO Age at Onset, y	Presenting Symptom of NMO	MRI Cord Segments	ON	Limb Involved (Dystonia)	Time of Onset of Dystonia, mo	Therapy Used	Response to Therapy, d
1/AA/F/52	Numbness of LUE	8	ON OU	LUE, LLE	1	Carbamazepine	7
2/H/F/14	ON	17	ON OU	LUE	21	Carbamazepine	7
3/W/F/42	Right-sided hemiparesis	4	ON OS	RUE	10	Carbamazepine	< 1 wk
4/AA/F/58	Hemilateral tonic spasms	13	ON OU	RUE, RLE	0	Carbamazepine	3
5/AA/F/45	Quadriplegia, ON	14	ON OU	RUE	66	Carbamazepine	5
6/AA/F/44	Cervical pain	12	ON	LLE	8	Carbamazepine	3
7/H/M/30	Dystonia, falls due to spasms	11	ON	LLE	0	Carbamazepine	4
8/H/F/48	TM, LE pain	3	ON	4 Extremities	91	Carbamazepine	2

Abbreviations: AA, African American; H, Hispanic; LE, lower extremities; LLE, left lower extremity; LUE, left upper extremity; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; ON, optic neuritis; OS, left; OU, bilateral; RLE, right lower extremity; RUE, right upper extremity; TM, transverse myelitis; W, white.

These paroxysms responded promptly to carbamazepine treatment.

None of these patients had a history of trauma, connective tissue disorder, neuroleptic medication use, or family history of dystonia. None had brain abnormalities typical of MS and all had longitudinally extensive spinal cord lesions characteristic of NMO.

RESULTS

The median age at onset in our patients who met diagnostic criteria for NMO⁷ was 39.5 years (range, 13.8-54.2 years) (**Table**). The 1:7 male to female ratio reflects a strong predilection of NMO and tonic spasms among females. The occurrence of tonic spasms in 4 African Americans, 3 Hispanics, and 1 white person with NMO reveals a predilection for the illness in populations with African ancestry. All patients had acute myelitis and ON (4 had bilateral involvement). All had longitudinally extensive cervical and/or thoracic spinal cord involvement seen on magnetic resonance imaging. None had the brain lesions typical or suggestive of MS.

Five patients had single limbs affected with tonic spasms (3 upper extremity, 1 lower extremity, and the extent of limb involvement was unclear in 1 record). Two of our patients had simultaneous involvement of the ipsilateral arm and leg, and 1 patient had tonic spasms involving all limbs and his truncal musculature. The occurrence of tonic spasms in our NMO case series was 14% (8 of 57 patients with NMO). Although this is higher than in our population with MS, reports of its association with MS in the literature range from 3.8% to 17%.

Based on our observations, it is evident that tonic spasms may occur at any time during the course of NMO. In our limited series of patients, this manifestation of illness appeared after a mean duration of illness of 24.6 months (range, 0-91 months). Two of the 8 patients presented with tonic spasms as their initial sign of illness, with classic manifestations of NMO occurring 2 to 3 months after their onset.

COMMENT

Tonic spasms, typically consisting of recurrent brief episodes of sustained increased muscle tone with abnormal posturing in 1 or more limbs, occurred in our

patients with NMO. The spasms lasted a few seconds to minutes with a frequency varying around 2 to 15 times a day, consistent with previous descriptions.¹⁻⁷ None of the patients experienced a preictal aura, loss of consciousness, loss of sphincter control, or postictal sequele.

Management of tonic spasms is rarely problematic. Commonly used medications include carbamazepine,⁸ benzodiazepines, phenytoin, or barbiturates. Carbamazepine acts as a membrane-stabilizing drug, binding to sodium channels when the neuronal membrane is depolarized and limiting inward flux of sodium.⁸ Our patients responded well to carbamazepine with all but 1 experiencing remission of tonic spasms within 1 week of initiating treatment with the drug.

The pathogenesis of tonic spasms in patients with NMO is unclear. In the past, a number of mechanisms have been proposed. Ostermann and Westerberg⁹ theorized that in MS, the phenomenon arose from axonal irritability secondary to release of soluble inflammatory mediators¹⁰ or by a transversely spreading ephaptic activation of axons within the partially demyelinated lesion in the fiber tracts. A similar argument could be made for NMO. Soluble arachidonic acid metabolites, the leukotrienes, may play a role^{7,8}; leukotriene C has been shown to have the ability to tonically depolarize Purkinje cells.⁷ Also, irreversible depolarization has been produced in ischemic brain models.⁸ We hypothesize that leukotrienes are potentially primary factors in mediating tonic spasms in MS and NMO.

An alternative explanation based on anatomical location has been proposed. Tonic spasms have been reported in patients with lesions in the spinal cord, contralateral cerebral peduncle, internal capsule, thalamus, and subthalamus.^{4,11} Authors have hypothesized that bilateral tonic spasms can result from lesions at the pyramidal decussation of the medulla oblongata, spinal cord, or both. Two of our patients had upper cervical cord lesions.

The association of tonic spasms with MS is well documented in the literature but there are only 3 reports suggesting their association with NMO. One report by Guillemin² details the case of a young woman with NMO-like aspects of her illness with tonic spasms. Wingerchuk et al⁶ reported a tonic spasms incidence rate of 35% in patients with relapsing-remitting NMO (17 of 48 patients). Komolafe et al⁵ subsequently described a 28-

year-old Nigerian woman with NMO who presented with neck pain, paroxysmal tonic spasms, and spastic quadriplegia. The observations by Wingerchuk et al and our own finding that paroxysmal tonic spasms are more common in NMO suggest that NMO be included in the differential diagnosis of such patients. Our lower incidence of tonic spasms in NMO than in the Wingerchuk et al series may be the result of our long-term use of steroids in such patients.

Lack of familiarity with the association of tonic spasms with NMO, as with MS, can lead to diagnostic difficulty, particularly in cases when they occur as a presenting sign in the absence of other NMO manifestations. Recognition of tonic spasms is important because of its disease association and the salutary response to appropriate therapy.

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