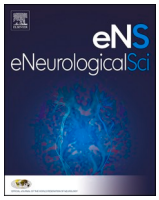
eNeurologicalSci 30 (2023) 100443

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci



Case report

Paroxysmal painful tonic spasms in neuromyelitis optica spectrum disorder

Shoena Lucas [a], Patrice H. Lalive [a,b], Agustina M. Lascano [a,b,*]

[a] Faculty of Medicine, University of Geneva, Geneva, Switzerland
[b] Division of Neurology, Department of Clinical Neuroscience, Geneva University Hospitals, Geneva, Switzerland

ARTICLE INFO

Keywords:
Central nervous system
Magnetic resonance imaging
Multiple sclerosis
Spinal movement disorder
Tonic seizures
Longitudinal extensive transverse myelitis
Area postrema syndrome
Case report
NMOSD
AQP4
autoimmune

ABSTRACT

Background: Recently, an association between painful tonic spasms (PTS) and Neuromyelitis Optica Spectrum Disorder (NMOSD) was established.
Objective: To describe the clinical characteristics of PTS in NMOSD based on a video recording and to provide a literature review on the topic.
Methods: We report a case of a 38 years-old woman with a diagnosis of NMOSD and positive aquaporin-4 IgG antibody status who developed PTS five weeks after an episode of longitudinal extensive transverse myelitis (LETM).
Results: Repetitive, brief, and painful episodes of muscle contraction were observed on the patient's left hand, spreading to the left arm, and then extending to the four limbs. While pregabalin and topiramate had no influence on these episodes, the patient responded to carbamazepine (CBZ), without symptom recurrence after one year.
Conclusions: PTS in association with LETM can be considered typical for NMOSD. Although the exact mechanism is unknown, ephaptic transmission after spinal cord damage and excitatory soluble factors released during acute inflammation responses are sought to be involved. Symptomatic treatment with CBZ achieved remission of spams in our case.

1. Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare relapsing inflammatory disorder affecting the central nervous system (CNS). Suggestive NMOSD-related symptoms include acute onset bilateral and severe visual loss, complete forms of acute myelitis, area postrema syndrome with uncontrollable hiccups or nausea and vomiting [1]. Interestingly, a set of brief and stereotyped neurological symptoms can appear at short a temporal distance of the first relapse. Paroxysmal symptoms were previously described in CNS autoimmune disorders mimicking epileptic fits or transient ischemic events [2,3]. However, limited literature exists on the association of paroxysmal phenomena and NMOSD. We discuss the association of PTS in NMOSD, provide a video recording of its characteristics and, finally, tackle treatment approach by means of an illustrative case.

2. Methods

Clinical and ancillary tests description were personally retrieved by the author, who examined the patient. This report is conducted in compliance to Swiss Federal Act on Research involving Human Beings that wave ethic approval for case report of less than five patients. Patient's consent to publication was obtained.

3. Results

A 38 years-old female patient was admitted to the division of Neurology at the University Hospitals of Geneva due to acute onset of tetraparesis with left hemibody predominance and walking impairment. Additional symptoms included saddle hypoesthesia associated with fecal and urinary incontinence and dysesthesia/allodynia of the left hemiface and left upper limb. Three months earlier, she developed intractable hiccups, nausea, and vomiting. An initial diagnosis of *H. pylori* gastritis was suspected and treated with antibiotics and proton pump inhibitor.

At admission, neurologic exam showed tetraparesis scored according to the Medical Research Council's strength assessment as follows: left elbow flexion 3/5, left fingers abduction 1/5, and left fingers flexion 2/5, others muscle groups of the upper and lower limbs were scored at 4/5.

* Corresponding author at: Division of Neurology, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland.
E-mail address: Agustina.Lascano@hcuge.ch (A.M. Lascano).

https://doi.org/10.1016/j.ensci.2023.100443
Received 27 November 2022; Received in revised form 23 December 2022; Accepted 8 January 2023
Available online 13 January 2023

She presented with left upper limb hypoesthesia, four limb ataxia and increased deep tendon reflexes. Plantar reflexes were in extension. The rest of the neurologic examination was normal.

Brain magnetic resonance imaging (MRI) revealed increased signal on T2-weighted sequences of the left antero-lateral bulb and the area postrema (Fig. 1 A-B) with gadolinium enhancement on T1-weighted sequences (Fig. 1 C). Spinal cord MRI showed gadolinium enhancement at C1-T1 level (Fig. 1 D-E). Lumbar puncture displayed 21 M/L leucocytes with lympho-monocytic predominance, 0.68 g/L of proteins, and no oligoclonal bands. Intravenous methylprednisolone was initiated at 1 g q.d. for five days, followed by 1 mg/kg/day of prednisone which was tapered down for 2.5 months associated with seven plasmapheresis sessions on alternate days for 14 days.

Serology was negative for active/recent infection. Blood tests for autoimmune diseases showed positive anti-AQP4 IgG, anti-SSA/Ro, anti-SSB/La, rheumatoid factors IgM and IgA, and antinuclear (ANA) autoantibodies. Immunological workup was completed with an MRI sialography showing signs of chronic sialadenitis and Sjögren's syndrome was diagnosed due to xerosis, polyarthralgia and positive antibody testing.

Given typical clinical characteristic (i.e., area postrema syndrome and longitudinal extensive transverse myelitis or LETM), AQP-4 IgG positive status and neuroimagery findings, the diagnosis of NMOSD was made and rituximab treatment was started at 1 g i.v. and repeated two weeks later and then, every six months.

Five weeks after LETM onset, the patient presented with painful tonic spasms that started in left hand, rapidly spread to the left arm, and finally involving the four limbs, lasting less than a minute, at a frequency of 9–14 times a day (see Video 1). Pain intensity was assessed at 9–10/10 on the Visual Analog Scale and Quality of Life Scale of American Chronic Pain Association was rated at 5/10. Intense emotions and rapid and sudden movements triggered the spasms. Antispastic medication was initiated with baclofen 20 mg t.i.d. and pregabalin 150 mg b.i.d, followed by tolperisone 150 mg b.i.d. Due to limited symptom control, carbamazepine (CBZ) 100 mg q.d. was initiated, the dose of baclofene was decreased and tolperisone was discontinued, resulting in prompt and complete remission. CBZ was discontinued four months after onset due to lympho-neutropenia and was switched to topiramate 75 mg b.i.d. showing reappearance of PTS. For that reason, CBZ was reintroduced at 100 mg q.d. and topiramate was slowly discontinued showing complete remission. Treatment was pursued for a ten-month period and stopped by the patient. Three years after CBZ discontinuation, there is no recurrence of PTS and both clinical and radiological workup is stable.

4. Discussion

Paroxysmal movement disorders in autoimmune neurological disorders were first described in the late 50's by Matthews and were previously referred to as "tonic seizures". It was described as a transient neurological symptoms of rapid onset, brief duration and increased frequency [2]. Other terms are used to describe the same movement disorder, including paroxysmal dystonia [4], tonic spasm [5] or paroxysmal painful tonic spasm (PTS) [6].

Unravelling the mechanism of PTS remains a challenge. Ekbom et al. reported two multiple sclerosis (MS) patients with spinal cord lesions presenting with sensory-motor seizures [7]. During the attacks, patients

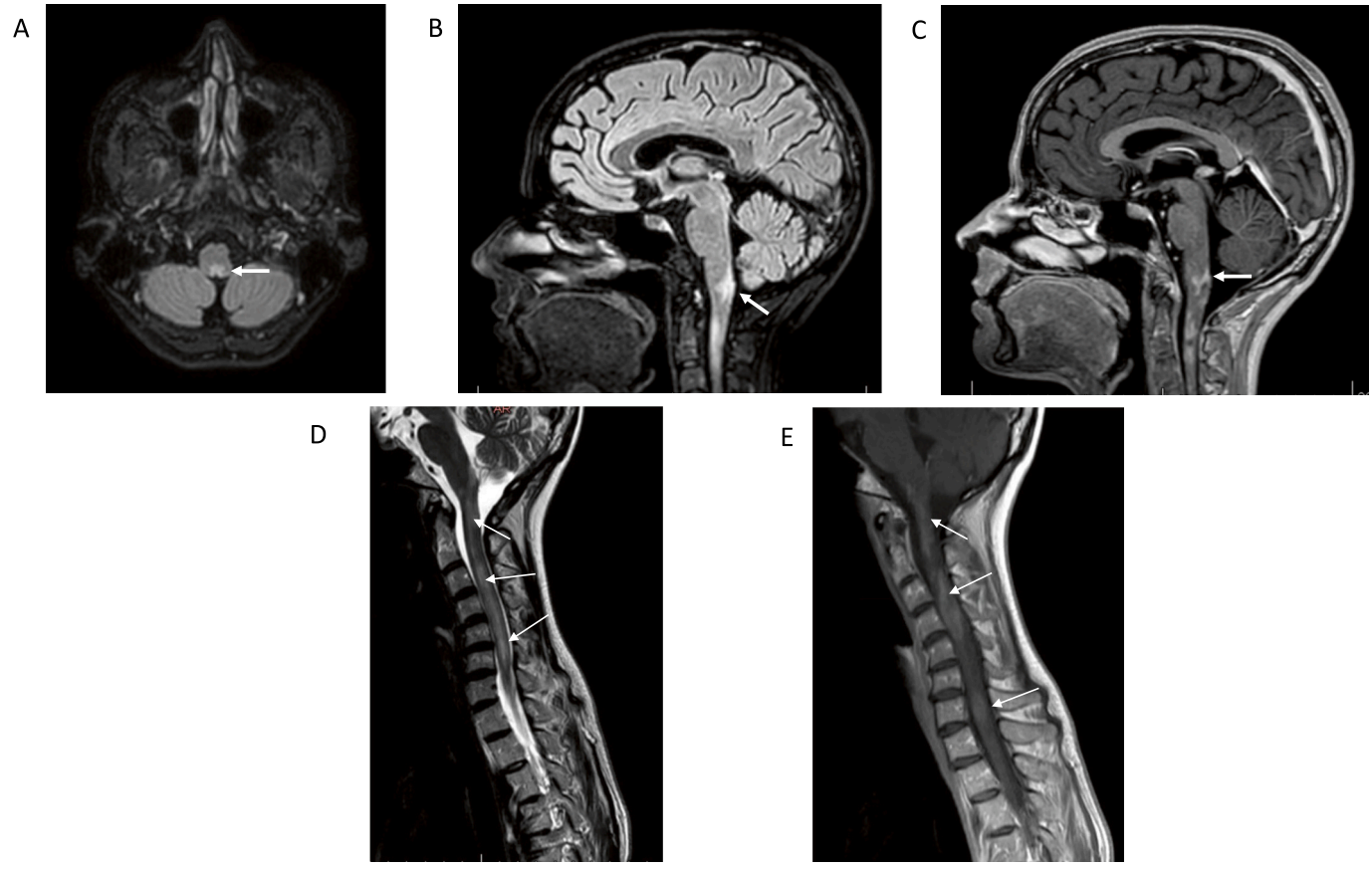


Fig. 1. Brain and spinal cord magnetic resonance imaging of a patient with neuromyelitis optica spectrum disorder and painful tonic spams.
Above: Axial (A) and sagittal (B) fluid-attenuated inversion recovery (FLAIR) brain MRI showing increased signal on T2-weighted sequences (arrow) and sagittal T1-weighted brain MRI (C) demonstrating gadolinium enhancement of the area postrema (arrow).
Below: Sagittal cervical spinal cord T2-weighted FLAIR MRI hyperintensity (D) and gadolinium enhancement (E) from C1 to T1 depicting longitudinally extensive transverse myelitis (arrow).

showed unilateral tonic spasms, accompanied with a tonic posture of the limbs, and preceded/followed by contralateral sensory disturbances. The combination of ipsilateral motor and contralateral sensitive complaints can be explained by an impairment of the lateral funiculus at the spinal cord level, which gathers fibres of the lateral corticospinal and spinothalamic tracts. Given the spatio-temporal correlation, a transversally spread activation of the damaged axons known as *ephaptic transmission* was proposed as the physiopathological mechanism underlying PTS in demyelinating disorders [3].

From a biological standpoint, it was hypothesized that the release of excitatory soluble factors during acute inflammation provoke "irritation" of demyelinated axons in MS active plaques, therefore, facilitating the spreading of the anomalous transmission [5,8]. Furthermore, a correlation between PTS and MRI lesions was described by Maimone et al., who reported a patient developing tonic spasms on the left hemibody during an MS relapse associated with a new MRI hyperintense T2-weighted lesion located on the posterior limb of the right internal capsule [8].

The occurrence of PTS in NMOSD varies from 14% to 95% [5,10]. This can be explained by the difference in the study design, due to their retrospective nature. While comparing the prevalence of PTS in NMOSD and MS groups, a recent cross-sectional study reported a higher incidence in NMOSD, up to 22 times more [4]. Kim and collaborators proposed that the association of PTS and acute myelitis allows to distinguish NMOSD from MS with a specificity of 98.7% [6]. We hypothesize that PTS is more frequent in NMOSD due to the different pathological mechanisms of demyelination and disease behaviour - i.e., astrocytopathy with secondary and severe demyelination versus demyelination as a result of oligodendrocyte destruction in MS and the presence of extensive spinal cord lesions, rarely observed in MS [11].

Potential risk factors of PTS in NMOSD show that only the presence of acute myelitis is related with a higher probability of developing PTS [6]. In our patient, PTS occurred five weeks after LETM and lasted for several months, which corresponds to the recovery phase. This suggests that partial remyelination is more likely to be the origin of spasms rather than the demyelination. No association was established with age at disease onset, sex, annualized relapse rate, presence of optic nerve damage at disease onset, expanded disability status scale score, spinal cord lesion extension and presence of brain MRI lesions, in a cohort of ten NMOSD patients [6].

Concerning PTS presentation, the onset is abrupt, lasting few seconds, and can be precipitated by a stimulus such as sudden movement, particularly after a long resting period, or triggered by emotional factors [5]. In a recent review, it was reported that PTS can involve one side of the body (3/13 patients, 23%), the four limbs (8/13 patients, 61.5%) and, more rarely, the neck and upper limbs exclusively [12]. No major differences were observed between NMOSD and MS patients in terms of clinical presentation and movement disorder's characteristic. These paroxysmal events are usually painful (9/13, 69%), constituting a major source of disability [12] as it occurred in our patient. Table S1 (supplementary material) summarises the clinical features and therapy used in neuromyelitis optica patients with PTS.

Treatment response of PTS in NMOSD is remarkable while administering phenytoin, topiramate, benzodiazepine, gabapentine and, specially, CBZ [6,10]. However, several studies show higher efficacy of topiramate and CBZ versus gabapentin or pregabalin [6,13]. The response observed with CBZ, usually occurs within the first week, achieving cessation of PTS in most cases [6,9,10]. Similarly, our patient fully responded to low doses of CBZ remission immediately after treatment onset, but not to topiramate and/or pregabaline. CBZ and topiramate are anti-epileptic drugs blocking voltage-gated sodium channels, limiting inward flux of sodium, and stabilizing the membrane [14]. Through these mechanisms the abovementioned drugs can achieve inhibition of the ephaptic transmission occurring at the level of demyelinated lesions.

We reported and recorded a case of PTS during recovery phase after an NMOSD relapse. Our goal is to increase awareness on this not so infrequent symptom appearing in association with NMOSD and responding to CBZ administration.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2023.100443.

Funding sources

No targeted funding reported.

Declaration of Competing Interest

SL has nothing to disclose. AML received consulting fees for ADC therapeutics SA not related to this study. PHL received honoraria for speaking for Biogen-Idec, CSL Behring, Merck Serono, Novartis, Sanofi-Aventis, TEVA, Roche; consulting fees from Biogen-Idec, Geneuro, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, TEVA; research grants from Biogen-Idec, Merck Serono, Novartis nonrelated to this study.

Acknowledgments

We would like to express our gratitude to Dr. Marjolaine Uginet for her assistance during the video recording. We thank the participant who volunteered for this case presentation.

References

[1] D.M. Wingerchuk, B. Banwell, J.L. Bennett, et al., International consensus diagnostic criteria for neuromyelitis optica spectrum disorders, Neurology 85 (2015) 177–189.
[2] W.B. Matthews, Tonic seizures in disseminated sclerosis, Brain 81 (1958) 193–206.
[3] P.O. Ostermann, C.E. Westerberg, Paroxysmal attacks in multiple sclerosis, Brain 98 (1975) 189–202.
[4] C. Candeias da Silva, D.B. Bichuetti, S.M.C. Azevedo Silva, et al., Movement disorders in multiple sclerosis and neuromyelitis optica: a clinical marker of neurological disability, Parkinsonism Relat. Disord. 51 (2018) 73–78.
[5] L. Abaroa, S.A. Rodriguez-Quiroga, L. Melamud, et al., Tonic spasms are a common clinical manifestation in patients with neuromyelitis optica, Arq. Neuropsiquiatr. 71 (2013) 280–283.
[6] S.M. Kim, M.J. Go, J.J. Sung, et al., Painful tonic spasm in neuromyelitis optica: incidence, diagnostic utility, and clinical characteristics, Arch. Neurol. 69 (2012) 1026–1031.
[7] K.A. Ekbom, C.E. Westerberg, P.O. Osterman, Focal sensory-motor seizures of spinal origin, Lancet 1 (1968) 67.
[8] D. Maimone, A.T. Reder, F. Finocchiaro, E. Recupero, Internal capsule plaque and tonic spasms in multiple sclerosis, Arch. Neurol. 48 (1991) 427–429.
[9] E. Carnero Contentti, F. Leguizamon, J.P. Hryb, et al., Neuromyelitis optica: association with paroxysmal painful tonic spasms, Neurologia 31 (2016) 511–515.
[10] N. Usmani, G. Bedi, B.L. Lam, W.A. Sheremata, Association between paroxysmal tonic spasms and neuromyelitis optica, Arch. Neurol. 69 (2012) 121–124.
[11] C.F. Lucchinetti, Y. Guo, B.F. Popescu, et al., The pathology of an autoimmune astrocytopathy: lessons learned from neuromyelitis optica, Brain Pathol. 24 (2014) 83–97.
[12] H. Abboud, H.H. Fernandez, M.A. Mealy, M. Levy, Spinal movement disorders in neuromyelitis optica: an under-recognized phenomenon, Mov. Disord. Clin. Pract. 3 (2016) 596–602.
[13] J. Liu, Q. Zhang, Z. Lian, et al., Painful tonic spasm in neuromyelitis optica spectrum disorders: prevalence, clinical implications and treatment options, Mult. Scler. Relat. Disord. 17 (2017) 99–102.
[14] S. Iida, M. Nakamura, R. Wate, et al., Successful treatment of paroxysmal tonic spasms with topiramate in a patient with neuromyelitis optica, Mult. Scler. Relat. Disord. 4 (2015) 457–459.