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Case Report

Area postrema syndrome: an atypical presentation of primary Sjogren's

Sonam Tanwar[1]*, Rahul Jadhav[1], Jyotsna Oak[1], Tushar Raut[2]

[1]Department of Medicine, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, Maharashtra, India
[2]Department of Neurology, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Sonam Tanwar,
E-mail: sonamtanwar1902@gmail.com

ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune condition characterized by antibodies against serum aquaporin-4 (AQP4), primarily affecting the optic nerves and spinal cord. This case report sheds light on the diagnostic challenges of area postrema syndrome (APS) as the initial manifestation of Sjogren's syndrome, often misidentified due to its diverse symptomatology. APS, seen in 10% of NMOSD cases, manifests as persistent nausea, vomiting, and uncontrollable hiccups. Left untreated, APS can progress to optic neuritis and longitudinally extensive myelitis, emphasizing the need for early intervention with corticosteroid therapy and immunomodulators. NMOSD commonly coexists with other autoimmune diseases like Sjogren's syndrome and systemic lupus erythematosus. Recent evidence also highlights NMOSD's impact on peripheral organs, particularly skeletal muscles, with elevated creatine kinase levels during acute phases. Understanding the relationship between NMOSD and autoimmune diseases is vital for accurate diagnosis and management, especially in cases of seronegative NMOSD and recurrent attacks, emphasizing comprehensive clinical evaluations and a broader diagnostic approach.

Keywords: Area postrema syndrome, Longitudinal extensive transverse myelitis, NMOSD, Primary Sjogren's syndrome, AQP4-Ab

INTRODUCTION

This case report unveils a unique scenario wherein area postrema syndrome (APS) served as the primary indicator of underlying primary Sjogren's syndrome (SS) in a patient later diagnosed with neuromyelitis optica spectrum disorder (NMOSD). NMOSD is an uncommon autoimmune condition characterized by the presence of AQP4 antibodies, which manifests in the optic nerves and spinal cord.[1] APS, observed in 10% of NMOSD cases, manifests as persistent nausea, vomiting, and uncontrollable hiccups, signifying an early onset of NMOSD.[2] This report underscores the significance of comprehensive clinical evaluations and acknowledges the potential implications of autoimmune comorbidities in NMOSD.

CASE REPORT

A previously healthy 24-year-old male presented with acute onset intermittent episodes of intractable nausea, vomiting, hiccups, abdominal discomfort, and generalized weakness for 25 days. He reported a history of 3-4 kg weight loss. He denied any complaints of fever, chest pain, urinary problems, rash, oral ulcers, joint pains, dysphagia, regurgitation, or recurrent pulmonary symptoms. On general examination, his BP was 120/80 mmHg with a pulse rate of 80 bpm and respiratory rate of

16 breaths per minute. Systemic examination yielded normal results. Routine investigations including erythrocyte sedimentation rate, C-reactive protein, and Thyroid function test were unremarkable including viral hepatitis workup except for the liver function test; aspartate aminotransferase 357 U/l, alanine aminotransferase-85 U/l, total bilirubin 0.47 mg/dl, alkaline phosphatase 74 U/l. His abdominal ultrasound showed no abnormalities. Due to persistent weakness, fatigue, and elevated aspartate transaminase disproportionate to alkaline phosphatase, a total creatine phosphokinase was done which unveiled significantly high levels at 7357 U/l along with aldolase levels of 52.6 U/l. The patient improved with symptomatic treatment, though hiccups and constipation persisted. Endoscopy and chest CT revealed a small hiatus hernia, and no dilatation of the esophagus was observed, which was incongruent with symptom severity. Abnormal liver function and high total creatine phosphokinase prompted rheumatological evaluation of the patient which showed positive anti-nuclear antibody (ANA) by indirect immunofluorescence using Hep-2 cells with 1:1000 speckled pattern. ANA blot was positive for Ro-52, SS-A, weakly for ds DNA, ANF 1:320 speckled, with negative Anti-neutrophil cytoplasmic antibodies and autoimmune hepatitis panel. Other tests including serum angiotensin-converting enzymes (ACE) and complement levels were normal (C3-112.51 mg/dl, C4 30.96 mg/dl). Although he did not complain of dryness of eyes or mouth, Schirmer's test was positive. Subsequent electromyography showed normal findings despite the elevated creatinine phosphokinase. The patient was diagnosed as a case of primary SS with gastroparesis and myositis based on the 2016 ACR-EULAR classification criteria for SS. On the commencement of the oral steroids, he showed gradual improvement in symptoms and blood parameters until the seventh day, when he started to develop gradual right-sided weakness, rendering the patient unable to walk or stand. His bowel and bladder movements were intact. CNS examination showed no nystagmus, muscle tone was normal, power of Right upper limb 4/5, right lower limb 2/5, and left upper and lower limb strength was 5/5, DTR 3+, right plantar extensor. There were no associated higher mental function abnormalities, difficulty in speech, or cranial nerve or cerebellar involvement. MRI revealed longitudinally extensive intramedullary altered signal from C5 to T9 vertebral levels with sparing of the conus medularis (Figure 1). Another short segment with altered signal intensity was present at the cervicomedullary junction at the obex (Figure 2 and 3). There was no expansion of the cord, abnormal intramedullary or leptomeningeal enhancement. The CSF analysis revealed normal findings along with the absence of oligoclonal bands, while the serum and CSF AQP4IgG, analyzed through a cell-based assay, were found to be positive. Other tests on CSF were normal (red blood cells-nil; no organisms in culture and staining). Thus, the patient also fulfilled the international consensus diagnostic criteria for NMOSD, 2015. His evaluation for optic nerve involvement was done and no abnormality was found (normal fundus, normal visual evoked potential). He received treatment with intravenous methylprednisolone at a dosage of 1 gram daily for three days, followed by a regimen of high-dose oral steroids gradually tapered down, in conjunction with mycophenolate mofetil, an immunomodulator. His gastrointestinal symptoms gradually diminished, and with ongoing physiotherapy and the administration of immunomodulator medications, substantial progress was evident within 2-3 weeks. The patient achieved significant improvement, being able to walk up to 100 meters with minimal support.

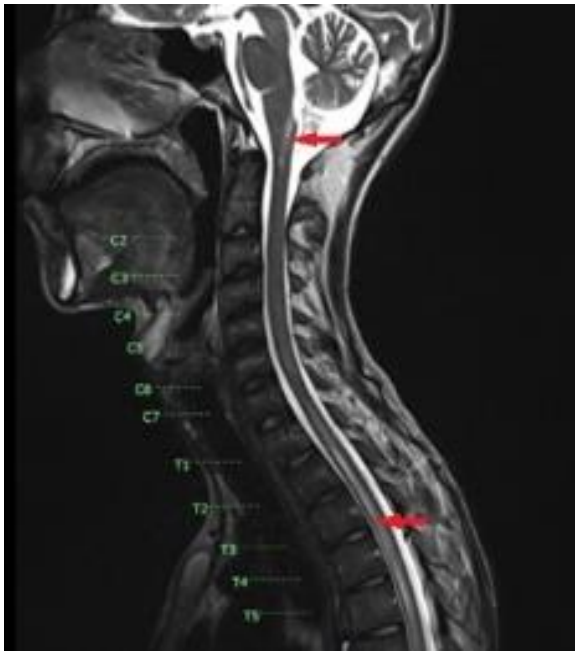

Figure 1: Hyper-intense signal on T2W MRI at the cervico-medullary junction and C5-T9.

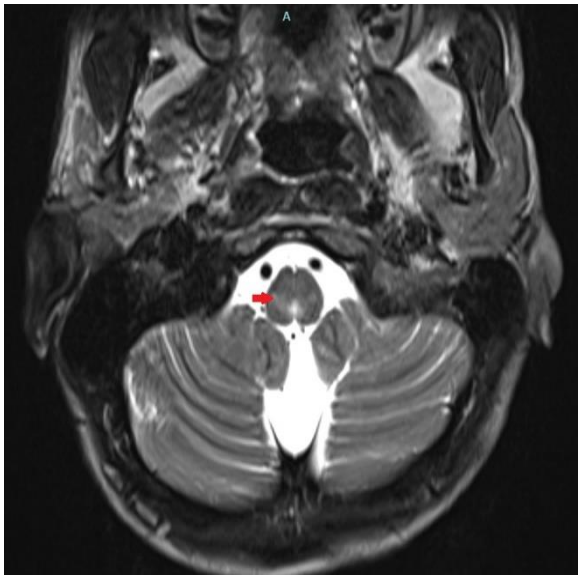

Figure 2: Axial T2W MRI brain with hyper-intense signals at cervico-medullary junction at the obex.

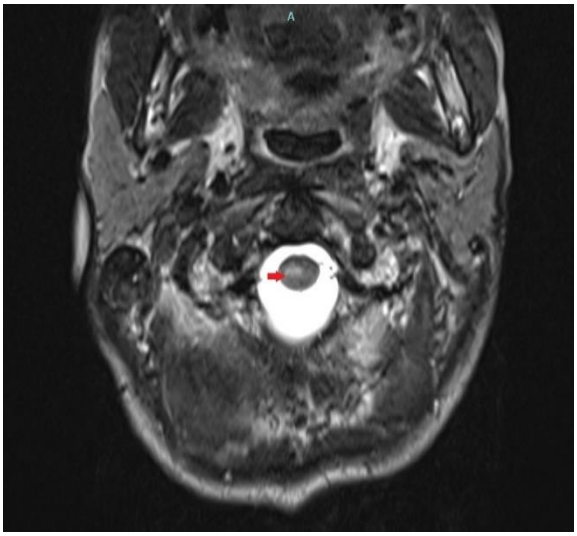

Figure 3: Axial T2W MRI with hyper-intense signals at C5.

DISCUSSION

NMOSD is a rare autoimmune condition characterized by antibodies against serum AQP4, affecting the optic nerves and spinal cord.[1] One of the initial symptoms, area postrema syndrome, presents with persistent nausea, vomiting, and uncontrollable hiccups, observed in 10% of NMOSD patients.[2] This case report illustrated the complexity of diagnosing area postrema syndrome as the primary presentation of SS. The patient's response to corticosteroid therapy and an immunomodulator emphasizes the importance of prompt intervention in managing such cases. These individuals often face misdiagnoses, commonly being erroneously identified as having GIT abnormalities such as gastroparesis, gastroesophageal reflux disease, and occasionally even psychogenic conditions. The presence of APS serves as a crucial warning sign. If left untreated, this syndrome can progress, eventually leading to optic neuritis and longitudinally extensive myelitis. Therefore, recognizing APS in these cases becomes paramount as it signifies the potential trajectory toward severe neurological complications if not appropriately managed.

NMOSD lesions in the area postrema (AP) show a unique profile, marked by the loss of AQP4 immunostaining and inflammation. Unlike spinal and optic lesions, AP lesions lack demyelination and necrosis, potentially explaining the near-complete remission of symptoms from such lesions.[2,3]

NMOSD often coexists with immune-mediated diseases, predominantly antibody-mediated conditions. Notably, SS and systemic lupus erythematosus (SLE) are most frequently associated with NMOSD among systemic autoimmune diseases. Furthermore, myasthenia gravis in neurological diseases and autoimmune thyroid diseases in non-neurological organ-specific autoimmune diseases are commonly reported comorbidities in NMOSD.[3]

This coexistence between NMOSD and autoimmune diseases implies shared underlying pathology, potentially due to genetic tendencies toward an abnormal immune system. Wang et al concluded in their study that MHC class I-related processes and interferon-gamma-mediated signaling pathways may play a role in NMOSD pathogenesis when coexisting with autoimmune thyroid disease (AITD), SLE, and SS.[4] While Chuk et al 2012 proposed that NMOSD might be one facet of a genetic tendency towards humoral autoimmunity and susceptibility to various autoimmune conditions.[5] In contrast, a study conducted by Wang et al using MR (Mendelian randomization) analysis suggested a distinct perspective. They proposed a causal link between autoimmune disorders and NMOSD susceptibility but did not support the reverse association.[4]

Distinct neurological manifestations in primary SS compared to NMOSD alone indicate a higher incidence of peripheral neuropathy in the former. Conversely, when NMOSD and Sjogren's coexist, patients tend to exhibit a higher frequency of brain abnormalities than those with singular autoimmune diseases.[6,7]

The lack of sicca symptoms in our patients might be clarified by studies conducted by Pittock et al 2008 Gökçay et al 2007 and Qiao et al 2015 indicating that Sicca symptoms (related to dryness of mucous membranes) tend to be relatively mild in NMOSD patients with coexisting autoimmune diseases.[4,8-10] Javed et al confirmed severe salivary gland inflammation in this cohort, suggesting that even without clinical signs specific to Sjögren's disease, inflammation is evident in the salivary glands of NMOSD patients.[11]

In our case study, cerebrospinal fluid (CSF) analysis yielded normal results, contradicting Zhang et al.'s findings, which reported higher CSF white blood cell count, protein levels, serum C-reactive protein (CRP), and immunoglobulin G (IgG) in NMOSD patients with autoimmune diseases. This disparity might suggest a more active immune status in patients with autoimmune diseases compared to those without.[12]

New findings underscore the peripheral organ involvement, particularly skeletal muscle, in NMOSD. Chen et al 2017 investigated serum CK levels in NMOSD patients during acute and stable phases compared to healthy controls, revealing significantly elevated CK levels during the acute phase.[13] Muscle pathology in these patients exhibited characteristics consistent with complement-activating IgG targeting sarcolemmal AQP4, affirming NMOSD's influence on muscles.[14,15] This understanding may help elucidate the elevated CPK levels in our patients.

CONCLUSION

Findings highlight a more severe trajectory of NMOSD when associated with SS compared to isolated NMOSD

cases. This compounded severity is characterized by increased debilitation, and higher recurrence rates, emphasizing the crucial need for early identification of accompanying comorbidities and autoimmune (AI) diseases. It's crucial to acknowledge that the AQP4 Ab test may not always yield positive results, leading to seronegative NMOSD, particularly in cases associated with autoimmune diseases. This highlights the necessity for a clinical understanding that a negative AQP4 Ab test doesn't rule out NMOSD in cases associated with autoimmune conditions. Even with an initial negative outcome, it is pivotal to conduct repeated diagnostic assessments for autoimmune disorders during each occurrence of NMOSD, and conversely. The significantly higher occurrence of positivity for SSA in cases of recurrent myelitis and neuromyelitis optica (NMO) underscores the importance of vigilance in recognizing autoimmune diseases during NMOSD occurrences, thereby emphasizing the need for comprehensive clinical evaluations and a broader diagnostic approach in managing these conditions.

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REFERENCES

1. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177-89.
2. Shosha E, Dubey D, Palace J, Nakashima I, Jacob A, Fujihara K, et al. Area postrema syndrome: Frequency, criteria, and severity in AQP4-IgG-positive NMOSD. Neurology. 2018;91(17):1642-51.
3. Shahmohammadi S, Doosti R, Shahmohammadi A, Mohammadianinejad SE, Sahraian MA, Azimi AR, et al. Autoimmune diseases associated with neuromyelitis optica spectrum disorders: a literature review. Multiple sclerosis and related disorders. Elsevier B.V.; 2019: 350-63.
4. Wang X, Shi Z, Zhao Z, Chen H, Lang Y, Kong L, et al. The causal relationship between neuromyelitis optica spectrum disorder and other autoimmune diseases. Front Immunol. 2022;13.
5. Wingerchuk DM, Weinshenker BG. The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease. Mult Scler. 2012;18(1):5-10.
6. Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, et al. Neurologic manifestations in primary Sjögren syndrome. Medicine. 2004;83(5):280-91.
7. Tzarouchi LC, Tsifetaki N, Konitsiotis S, Zikou A, Astrakas L, Drosos A, et al. CNS involvement in primary sjögren syndrome: assessment of gray and white matter changes with MRI and Voxel-based morphometry. Am J Roentgenol. 2011;197(5):1207-12.
8. Pittock SJ, Lennon VA, De Seze J, Vermersch P, Homburger HA, Wingerchuk DM, et al. Neuromyelitis optica and non organ-specific autoimmunity. Arch Neurol. 2008;65(1):78-83.
9. Gökçay F, Çelebisoy N, Gökçay A, Kabasakal Y, Öder G. Primary Sjögrens syndrome presenting as neuromyelitis optica. Pediatr Neurol. 2007;36(1):58-60.
10. Qiao L, Wang Q, Fei Y, Zhang W, Xu Y, Zhang Y, et al. The clinical characteristics of primary Sjogren's syndrome with neuromyelitis optica spectrum disorder in China: A STROBE-compliant article. Medicine. 2015;94(28).
11. Javed A, Balabanov R, Arnason BGW, Kelly TJ, Sweiss NJ, Pytel P, et al. Minor salivary gland inflammation in Devic's disease and longitudinally extensive myelitis. Mult Scler. 2008;14(6):809-14.
12. Zhang B, Zhong Y, Wang Y, Dai Y, Qiu W, Zhang L, et al. Neuromyelitis optica spectrum disorders without and with autoimmune diseases. BMC Neurol. 2014;14(1).
13. Chen HX, Zhang Q, Lian ZY, Liu J, Shi ZY, Miao XH, et al. Muscle damage in patients with neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm. 2017;4(6).
14. He D, Li Y, Dai Q, Zhang Y, Xu Z, Li Y, et al. Myopathy associated with neuromyelitis optica spectrum disorders. Int J Neurosci. 2016;126(10):863-6.
15. Guo Y, Lennon VA, Bogdan BF, Grouse CK, Topel J, Milone M, et al. Autoimmune aquaporin-4 myopathy in neuromyelitis optica spectrum. JAMA Neurol. 2014;71(8):1025-9.

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