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Area postrema syndrome – a challenge for differential diagnosis between multiple sclerosis and neuromyelitis optica spectrum disorders

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ABSTRACT

Area postrema syndrome (APS) manifested with hiccups, nausea and vomiting is one of the core clinical findings in neuromyelitis optica spectrum disorders (NMOSD). We report the case of a 41-year-old woman, with no significant prior medical history, who presented with left upper limb paresthesias. The patient revealed two prior episodes, one 5 years ago, with paresthesias and mild paresis on the right side of the body and the other a few month ago, with right peripheral facial palsy, right facial anesthesia, headache, nausea and emesis. This led us to suspect area postrema syndrome and, possibly, NMOSD. Brain MRI did not show typical lesions for NMOSD, apart from a left periaqueductal lesion. Other potential diagnoses were excluded through laboratory workup. Serum anti-AQP4 antibody were negative, while CSF analysis was positive for oligoclonal bands. Based on clinical and paraclinical findings, a diagnosis of MS was made. This case illustrated that APS may also be present in MS and not only in NMOSD.

Keywords: multiple sclerosis, NMOSD, area postrema, periaqueductal

Abbreviations (in alphabetical order):
AQP4 – Aquaporin 4
ANA – Antinuclear antibodies
ANCA – Anti-neutrophil cytoplasmic antibodies
CSF – Cerebrospinal fluid
CCP – Cyclic Citrullinated Peptide
dsDNA – double stranded DNA
HBV – Hepatitis B virus
HCV – Hepatitis C virus
HIV – Human immunodeficiency virus
HBP – High blood pressure
LETM – Longitudinally extensive transverse myelitis
MRI – Magnetic Resonance Imaging
MS – Multiple sclerosis
NMOSD – Neuromyelitis optica spectrum disorders
PAL – Periaqueductal lesion
RF – Rheumatoid factor

INTRODUCTION

Area postrema syndrome (APS) with unexplained hiccups, nausea and vomiting is one of the core clinical characteristics in the 2015 diagnostic criteria for neuromyelitis optica spectrum disorders (NMOSD) and have been encountered in non-NMOSD myelopathies extending to the region of area postrema. We present the case of a multiple sclerosis (MS) patient presenting a relapse manifested with APS and a demyelinating lesion located in the periaqueductal gray matter. NMOSD are a group of inflammatory demyelinating disorders, affecting predominantly the spinal cord and optic nerves. The distinction between NMOSD and MS is well established, especially after discovery of anti-AQP4 antibodies (1). This has led to a broadening of the clinical picture traditionally associated with NMO (2) and today, brain lesions are well recognized, especially in territories that highly express AQP4 (brainstem and diencephalon) (3). Although diagnostic criteria for NMOSD have been estab-

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lished, there are still anti-AQP4 positive patients outside the spectrum (4), and some authors have even suggested changing the name into autoimmune aquaporin-4 channelopathy (3), as well as anti-AQP4 negative patients fulfilling the criteria for NMOSD.

CASE REPORT

We report the case of a 41-year-old woman, non-smoker, casual alcohol consumer, known with HBP stage I and no family medical history, who presented with left upper limb paresthesias.

The patient revealed an episode of paresthesias and mild paresis on the right side of the body, with 6 months duration and spontaneous remission, approximately 5 years ago. A second episode, which took place at the beginning of 2017, consisted of right peripheral facial palsy and right facial anesthesia, accompanied by headache, nausea and emesis. The patient was admitted to our hospital at approximately 6 months after this episode.

Clinical examination revealed an erythematous eruption affecting the left L4 dermatome, residual right peripheral facial palsy, right-sided hearing loss, right Babinski sign and hypoesthesia on the left side of the body.

Brain MRI was performed, revealing demyelinating lesions at the right middle cerebellar peduncle (Fig. 1), right thalamus, in the subcortical white matter of the right frontal lobe and in the left mesencephalic periaqueductal gray matter (Fig. 2). **Spinal cord MRI** indicated a demyelinating lesion affecting the left posterior tracts at the C3-C4 level. None of these lesions was Gadolinium-enhancing.

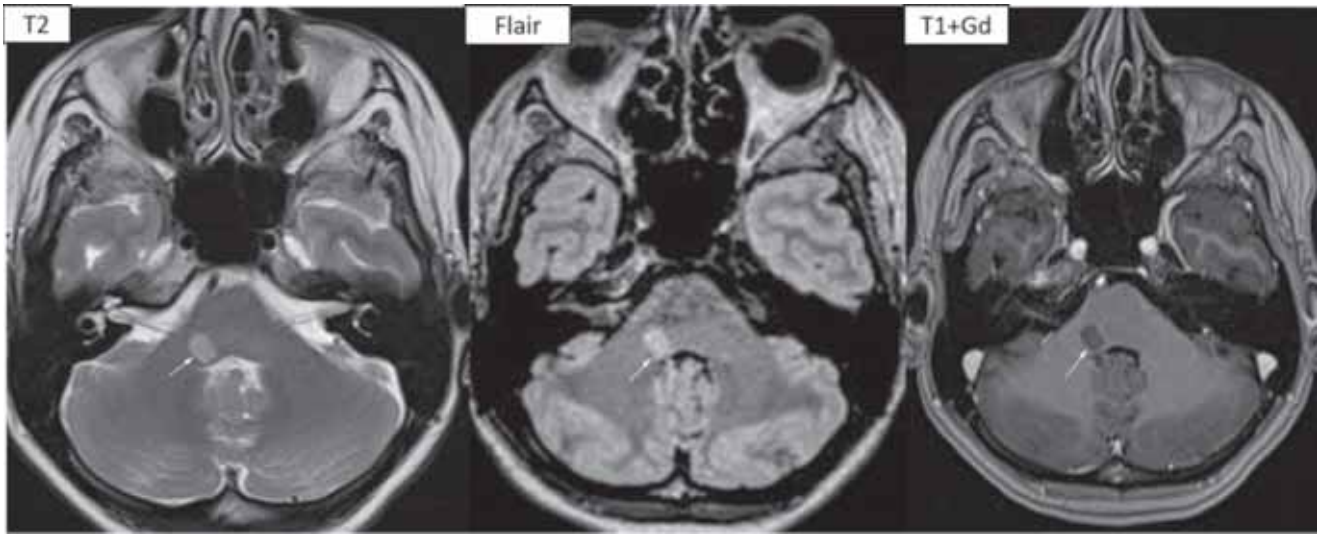

FIGURE 1. *Axial images revealing hyperintense lesion on T2 and FLAIR and hypointense non-enhancing on T1+Gd, located in the right middle cerebellar peduncle*

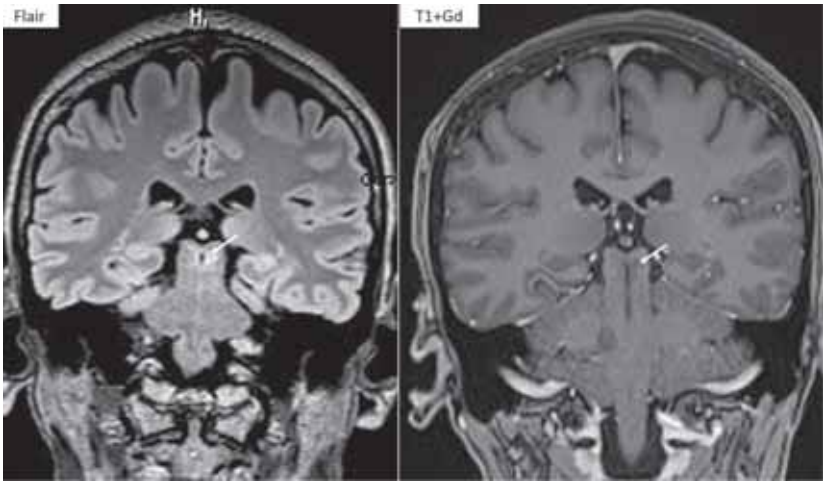

FIGURE 2. *Coronal images revealing small hyperintense lesion on FLAIR, non-enhancing on T1+Gd, located in the left periaqueductal gray.*

Apart from low levels of vitamin D, **laboratory findings** were within normal range, including autoimmune markers (ANA, anti-dsDNA, c-ANCA, p-ANCA, anti-CCP, RF, anti-Ro and anti-La), thyroid hormones, tumoral markers, coagulation, proinflammatory markers and serology for HBV, HCV, HIV, syphilis and Borrelia Burgdorferi.

CSF analysis after lumbar puncture was positive for oligoclonal bands.

Visual evoked potentials presented with morphology, amplitude and latencies at the upper limit of normal in both eyes.

Anti-AQP4 antibody in serum were negative. Based on the 2010 McDonald criteria and additional positive oligoclonal bands, relapsing remitting MS was diagnosed.

DISCUSSIONS

Although most of the clinical and imaging features are consistent with MS, the patient presented during the second episode intractable nausea and vomiting, which raised the suspicion for area postrema syndrome, usually associated with NMOSD (5,6).

Moreover, MRI showed a demyelinating periaqueductal lesion (PAL), which is also characteristic for NMOSD. This can be explained by the high concentration of AQP4 in the ependymal cells lining the aqueduct (7).

PAL have also been confirmed in MS. In one study, PAL were detected in 48 of 257 patients on MRI (8) and there are several studies relating presence of PAL with headache/migraine in MS patients (9-11). The periaqueductal gray is thought to contain an antinociceptive neural network, which, in case of dysfunction, may lead to migraine (12).

The current diagnostic criteria for NMOSD differ according to presence/absence of AQP4-IgG autoantibodies (13).

In case of positive AQP4-IgG antibodies, diagnosis is based on ≥1 core clinical feature and exclusion of other diagnoses.

In case of negative/unknown status of antibodies, diagnosis is based on presence of ≥ 2 different core clinical features, of which ≥ 1 must be optic neuritis, acute LETM or area postrema syndrome, supported by additional MRI criteria and exclusion of other causes.

TABLE 1. *Core clinical features*

Op c neuri s
Transverse myeli s
Area postrema syndrome
Acute brainstem syndrome
Acute diencephalic syndrome with NMOSD-typical diencephalic MRI lesions
Symptoma c cerebral syndrome with NMOSD-typical brain MRI lesions

TABLE 2. *Additional MRI criteria*

For acute op c neuri s:	(1) Normal MRI or nonspecific white ma er lesions
	(2) T2-hyperintesity or T1-Gadolinium enhancing lesion affec ng more than one-half of op c nerve length or involving op c chiasm
For transverse myeli s	(1) MRI spinal lesion extending ≥ 3 con guous segments
	(2) Spinal atrophy extending ≥ 3 con guous segments in a pa ent with history sugges ve of acute myeli s
For area postrema syndrome	Associated area postrema lesions
For acute brainstem syndrome	Associated periependymal brainstem lesions

Based on these criteria, our patient presented with 2 clinical core features, of which one was compatible with area postrema syndrome, the other being an acute brainstem syndrome. However no area postrema lesion was detected on brain MRI, only a mesencephalic periaqueductal demyelianting lesion.

No optic nerve involvement was detected, and the spinal lesion was more suggestive of MS (i.e. incomplete and asymmetrical). Spinal cord involvement in NMOSD tends to involve most of the cross-sectional area and ≥ 3 continuous segments. It should be noted that some NMOSD patients can present with shorter involvement of spinal cord (14).

CONCLUSIONS

In conclusion area postrema manifestations may present as an overlap syndrome in MS and NMOSD and the neuroimaging findings associated with dosage of oligoclonal bands and anti-AQP4 antibodies are important tools in establishing the correct diagnosis.

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