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Pearls & Oy-sters: A cause of intractable vomiting

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PEARLS

1. Intractable vomiting or hiccups is fairly common in neuromyelitis optica spectrum disease (NMOSD) due to involvement of the area postrema that houses the medullary vomiting centers.
2. MRI lesions in the periependymal areas involving the hypothalamus and periaqueductal brainstem regions are more specific for NMOSD.
3. The presence of neuromyelitis optica (NMO)–immunoglobulin G (IgG) strongly supports the diagnosis of NMOSD and indicates a more aggressive disease course.

OY-STERS

1. NMOSD has a high rate of relapse and patients should be followed for an appropriate length of time.
2. NMOSD relapses frequently result in severe disability and thus treatment with disease-modifying therapy should be initiated early to help ameliorate the damage.

A 50-year-old Chinese woman with hypertension and hyperlipidemia presented with 2 months of progressive intractable vomiting. She was previously evaluated by 2 gastroenterologists who found no abnormalities on esogastroduodenoscopy and diagnosed her with a functional disorder. Her symptoms progressed to dysphagia to solids and liquids as well as spastic dysarthria over the week prior to neurologic evaluation. At that time, her clinical examination revealed a hyperactive gag reflex with tongue fasciculation and a left hypoglossal palsy. She had spastic dysarthria but a normal jaw jerk reflex. The remainder of her neurologic examination revealed no further deficits. CSF analysis revealed a mild pleocytosis (13 lymphocytes) with normal glucose and protein concentrations. No oligoclonal bands were detected. A metabolic screen was unremarkable when first performed by a gastroenterologist 2 months prior and a repeat test was also normal. Brain MRI showed a nonenhancing hyperintense lesion involving the medulla and bilateral hypoglossal nuclei (figure, A). Serologic analysis was positive for NMO-IgG (ELISA) (figure, B).

The patient underwent a 5-day course of IV corticosteroids with acute relief of her symptoms and she was transitioned to oral corticosteroids and azathioprine. Seven months later, she presented with left optic neuritis (ON) that recovered with minimal residual deficits following a second course of IV steroids The dose of azathioprine was increased and she has not had any relapses since then.

DISCUSSION NMO or Devic disease is a CNS demyelinating disease characterized by attacks of ON and destructive longitudinally extensive transverse myelitis (LETM) >3 vertebrae. While superficially similar to multiple sclerosis (MS), the 2 disease entities have divergent epidemiologies, pathogeneses, and treatments.

Whereas MS is the archetypal demyelinating disease afflicting predominantly white patients, NMOSD form a significant proportion (approximately 40%) of CNS demyelinating disorders in Asian populations and is more prevalent in female patients, with a female to male ratio of 6.5:1.[1,2] Relapses are more severe than those seen in MS and commonly cause residual deficits with a stepwise accumulation of disability.

NMO-IgG is an antibody directed against aquaporin-4, a water channel present in high concentrations at ependymal and brain CSF interfaces. Binding of NMO-IgG to aquaporin-4 initiates a cascade of complement-mediated cell damage and necrosis. Unlike MS lesions, eosinophils and neutrophils are common in the inflammatory infiltrates of active NMOSD lesions. Immunoglobulin and complement are deposited in a vasculocentric rim and rosette pattern in active NMO and NMOSD lesions.[3] NMO-IgG is detectable in the serum of patients with NMO and related disorders, with current assays achieving sensitivities and specificities of 75% and near 100%, respectively.[4] The presence of NMO-IgG in the serum is predictive of an aggressive disease course.[5]

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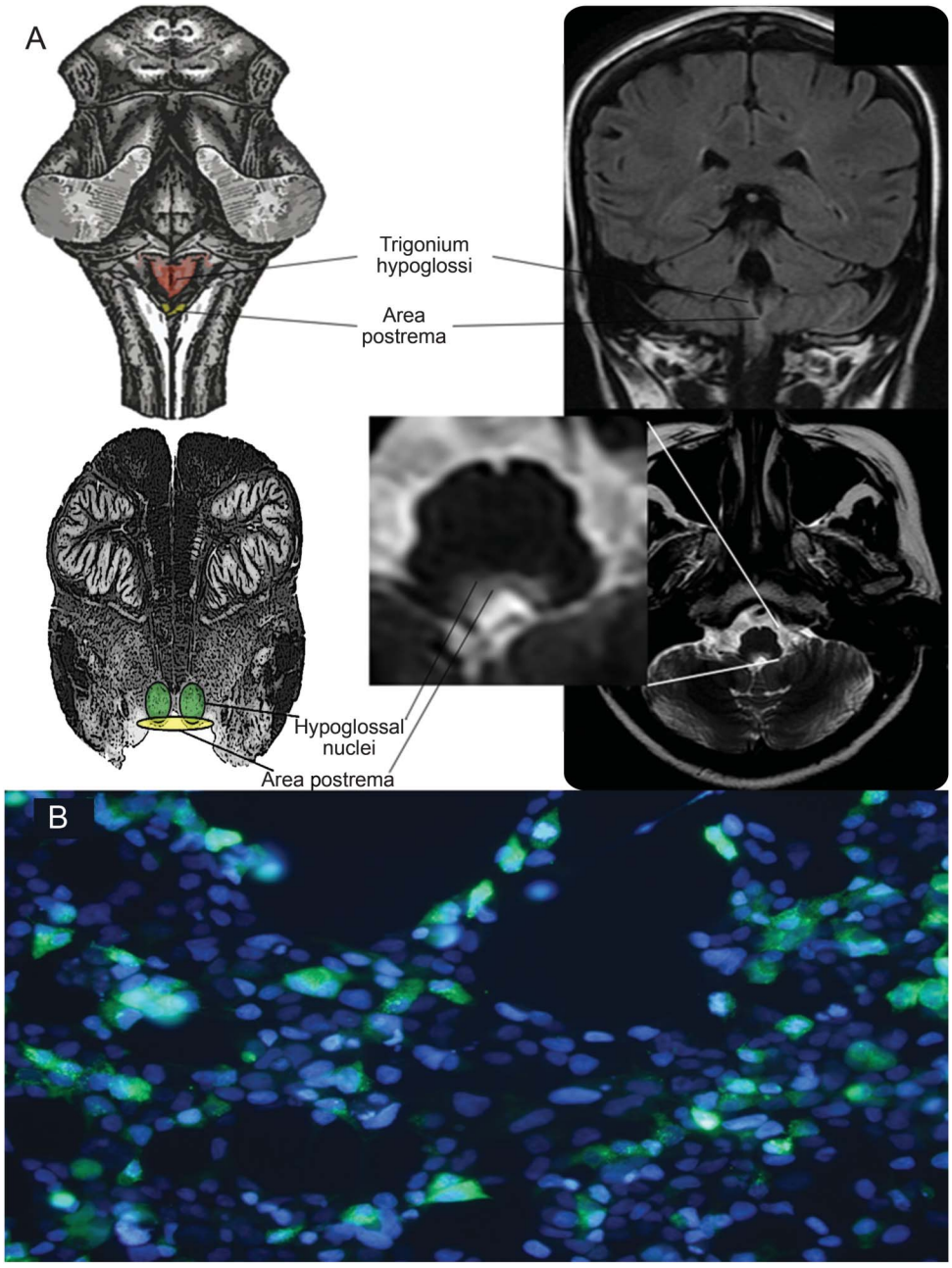
Figure Neuromyelitis optica antibodies, brain MRI involvement, and corresponding diagrams



(A) The patient's coronal and axial brain MRI reveal abnormalities in the dorsal medulla and area postrema. Appended anatomical diagrams illustrate the structures involved. (B) neuromyelitis optica–immunoglobulin G antibodies (APQ4) immunofluorescence.

Diagnosis of NMO rests on satisfaction of the Wingerchuk et al.[6] criteria. This requires the presence of both ON and myelitis and the satisfaction of 2 out of 3 following conditions: NMO-IgG seropositivity, MRI evidence of LETM, and absence of MS-like brain appearances on MRI. Whereas these criteria have high specificity for NMO, the use of the Wingerchuk et al.[6] criteria may fail to capture many disease entities within the NMO clinical-immunologic spectrum, such as nascent forms of NMO and isolated recurrent ON or LETM. These disease entities, while not fulfilling diagnostic criteria for NMO, represent members of the same pathologic family. The umbrella term NMOSD therefore encompasses NMO and related entities.[7] Additional evidence of relapsing activity in 95% of NMOSD justifies close follow-up and early treatment.[2]

While severe ON and transverse myelitis constitute the classic disease spectrum of NMOSD, other modes of presentation have been described. These include endocrinopathies (diabetes insipidus, prolactinemia) and posterior reversible encephalopathy

syndrome. Brainstem deficits may occur such as vertigo, hearing loss, cranial nerve palsies, ptosis, and nystagmus.[6] This is illustrated in our patient's case, as she did not fulfill any criteria for NMOSD at the point of presentation. The detection of NMO-IgG in her serum and the subsequent development of ON support the diagnosis of NMOSD. Moreover, her predominant presentation of intractable vomiting and lower cranial nerve involvement is consistent with reported clinical observations of the illness, although not classically thought of as presenting symptoms of NMOSD. In NMOSD, extension into the medullary vomiting centers in the area postrema results in intractable nausea and hiccups in up to one-fifth of all patients.[8] Other relevant clinical findings in our patient include a brisk gag reflex from involvement of the corticonuclear tracts as well as dysphagia and dysarthria from lesions involving the swallowing center and upper motor neuron findings of the tongue. The table summarizes the patient's symptoms and signs with anatomical localization and the figure, A, shows the MRI correlates.

Our patient's initial imaging did not reveal the typical LETM or optic nerve enhancement seen with NMOSD. Instead, T2 hyperintensities were observed in clinically eloquent areas of the medulla. A normal MRI of the brain was one of the minor criteria in previous diagnostic classifications, which has since been removed. The MRI brain scan can be and is frequently normal, especially in the early course of the disease; however, some MRI brain abnormalities appear to be more commonly found in NMOSD. In NMOSD, MS-like lesions that fulfill the criteria for dissemination in space can be seen rarely, but these lesions are often clinically silent. Lesions in the periependymal areas involving the hypothalamus and periaqueductal brainstem regions surrounding the ventricular system parallel midline AQP4-rich regions and are more specific to NMOSD.[6] Linear medullary lesions reported in 48% of Chinese patients discriminate between NMOSD and MS and our patient had such involvement of the medulla.[9]

Atypical presentations such as seen in our patient could delay a diagnosis of NMOSD. This may cause increased morbidity as each relapse is likely to result in disability. Early intervention is crucial in both treating the acute relapse and in averting future attacks. Acute episodes are treated with high-dose steroids, and plasmapheresis in the event of insufficient therapeutic response. While the evidence for immunosuppression arises predominantly from limited open-label studies, the expert consensus is that a combination of oral corticosteroid and a steroid-sparing agent (azathioprine and rituximab being first-line agents) significantly reduces relapse rate.[5,10] All such treatment must be embarked upon only after full, honest, and open dialogue with the patient.

The discerning practitioner should include NMOSD in the differential diagnosis of patients who present with unexplained intractable vomiting or hiccups, as this presentation is seen in an unexpectedly high proportion of patients with NMOSD. Current diagnostic criteria for NMO are not designed to capture the entire spectrum of the disease, and strict adherence to the criteria alone may result in delayed diagnosis and avoidable relapse-associated disability. A review of the diagnostic criteria may be timely.

Table Symptoms and anatomical correlates

Symptom	Anatomical correlate
Vomiting	Area postrema
Brisk gag reflex	Corticonuclear tract (upper motor neuron lesion of cranial nerve IX/X)
Dysphagia	Swallowing center at the bottom of the IVth ventricle
Slurring speech/tongue fasciculations	Upper motor neuron cranial nerve XII

AUTHOR CONTRIBUTIONS

L. Yeo: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision. N. Wieder: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. A.S. Wang: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. E. Ting: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. R. Rathakrishnan: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Dr. Soon: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and final approval.

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DISCLOSURE

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