Area postrema syndrome
Frequency, criteria, and severity in AQP4-IgG–positive NMOSD

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Study objective
To determine the frequency, duration, and severity of intractable nausea, vomiting, or hiccups (INVH) in aquaporin-4 (AQP4)–immunoglobulin G (IgG)–positive (AQP4-IgG+) neuromyelitis optica spectrum disorder (NMOSD) and provide diagnostic criteria and a severity scale.

Summary results
Patients with AQP4-IgG + NMOSD commonly experience isolated area postrema syndrome (APS) attacks characterized by INVH occurring over several days to weeks. When APS is the presenting symptom, the diagnosis is commonly missed.

What is known and what this paper adds
APS attacks are among the core clinical criteria for NMOSD, but the APS phenotype remains poorly characterized. This study provides a phenotype characterization that allowed development of diagnostic criteria as well as a severity scale, both of which may be helpful in the clinic and drug trial setting.

Participants and setting
This study used a database of 430 patients (86.3% female) with AQP4-IgG + NMOSD from the US (n = 192), the UK (n = 169), and Japan (n = 69). This study also included a cohort of 100 patients (91% female) with AQP4-IgG + NMOSD treated at Mayo Clinic (Rochester, Minnesota).

Design, size, and duration
This study determined the country-specific prevalences of APS attacks (isolated or in association with other symptoms) using the trinational database. The APS phenotype was further characterized by interviewing the Mayo Clinic patients about their symptoms. APS severity was measured using a scoring system, modified from the Pregnancy-Unique Quantification of An Emesis (PUQE) scale, and a separate validation was performed.

Primary outcome measures
The primary outcomes were the frequencies, durations, and severities of INVH symptoms in APS attacks.

Main results and the role of chance
There was a high prevalence of isolated APS attacks [onset 7.1%–10.3% and subsequent 9.4%–14.5%] and APS attacks occurring in association with other symptoms [onset 8.2%–15.9% and subsequent 8.9%–14.5%] that were similar between countries (p = 0.332). The 100 Mayo Clinic patients experienced 157 APS attacks that included nausea (81%; median duration, 14 days), vomiting (72%; median frequency, 5 episodes/d), and hiccups (65; median duration, 14 days). Based on these phenotypic characteristics, the diagnostic criteria for APS were developed.

Bias, confounding, and other reasons for caution
The PUQE scale was developed for pregnant women. This is a validated measure that was modified, with the addition of a hiccups severity score, for use in APS.

Generalizability to other populations
The applicability of these results to patients with non–AQP4-IgG + NMOSD is unclear.

Study funding/potential competing interests
This study was funded by the NIH, the Guthy-Jackson Charitable Foundation, Mayo Clinic, and Alexion Pharmaceuticals. Some authors report serving on journal editorial boards; receiving personal fees, advisory board appointments, and funding from various healthcare companies; receiving patent royalties; and receiving funding from various foundations and government agencies. Go to Neurology.org/N for full disclosures.

Table
Area postrema syndrome criteria in AQP4-IgG-seropositive neuromyelitis optica spectrum disorder

| 1. Acute or subacute NVH (single or combined symptoms), episodic or constant |
| 2. Persistent for ≥48 h,* with lack of complete resolution after symptomatic therapy |
| 3. Exclusion of other etiology* |

Abbreviations: AQP4-IgG = aquaporin-4-immunoglobulin G; NVH = nausea, vomiting, and hiccups.

*A Shorter duration (<24 hours) may be considered if MRI shows new area postrema involvement (figure 1, B).

*IV fluid, antiemetics, hiccups treatments.

*Metabolic (e.g., hyponatremia, liver dysfunction, renal dysfunction), gastrointestinal, biochemical, CNS structural lesions (e.g., tumor, stroke), mediastinal lesions, classic migraine, or psychiatric eating disorders.

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