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Area postrema syndrome

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

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Abstract

Objective

To define the frequency, duration, and severity of intractable nausea, vomiting, or hiccups in aquaporin-4–immunoglobulin G (AQP4-IgG)-positive neuromyelitis optica spectrum disorder (NMOSD) and propose diagnostic criteria and a severity scale for area postrema syndrome (APS).

Methods

An International NMOSD database was interrogated for frequency of APS. Patients with AQP4-IgG–positive NMOSD completed an APS symptom questionnaire. Nausea and vomiting severity was derived from the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score. The diagnostic criteria, severity scale, and immunotherapy response was applied to a prospective validation cohort of patients from multiple centers.

Results

Analysis of an international database for AQP4-IgG–seropositive NMOSD (n = 430) revealed a high prevalence of isolated APS attacks (onset 7.1%–10.3%; subsequent 9.4%–14.5%) across continents. For 100 patients with 157 episodes of APS, nausea (n = 127, 81%) lasted for a median of 14 days (range 2–365), vomiting (113, 72%) with a median of 5 episodes/d (2–40) lasted 1–20 minutes, and hiccups (102, 65%) lasted a median of 14 days (2–365). Symptoms consistently and completely resolved following immunotherapy. Data were used to propose APS diagnostic criteria and repurpose PUQE score (hiccups severity grade based on symptom duration). The clinical utility was demonstrated in a prospective validation cohort.

Conclusion

Isolated APS attacks are frequently encountered both at onset and during the NMOSD course. The diagnostic criteria proposed here will assist clinicians in recognizing APS. Diagnosis of an APS attack earlier than 48 hours is possible if a dorsal medulla lesion is detected. Accurate diagnosis and evaluation of APS attack severity will assist in outcome measurement in NMOSD clinical trials.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

AP = area postrema; **APS** = area postrema syndrome; **AQP4** = aquaporin-4; **HG** = hyperemesis gravidarum; **IgG** = immunoglobulin G; **INVH** = intractable nausea, vomiting, or hiccups; **NMOSD** = neuromyelitis optica spectrum disorder; **ON** = optic neuritis; **PAGI-SYM** = Patient Assessment of Upper Gastrointestinal Disorders–Symptoms Severity Index; **PUQE** = Pregnancy-Unique Quantification of Emesis and Nausea; **TM** = transverse myelitis.

Neuromyelitis optica spectrum disorders (NMOSD) are a clinically and radiologically defined group of CNS inflammatory autoimmune demyelinating diseases, the majority of which are associated with a pathogenic antibody specific for the aquaporin-4 (AQP4) water channel.[1–3] NMOSD-typical brain MRI lesions occur in AQP4-enriched areas[4,5] including the area postrema (AP), an emetic reflex center[6] at the floor of the fourth ventricle that is penetrated by convoluted capillaries that lack tight endothelial junctions.[6,7] The AP, via hypothalamic/brainstem connections, regulates fluid balance, osmoregulation, immunomodulation, and other important physiologic systems,[8] and also has chemo-sensitive neurons mediating hiccups.[9]

NMOSD lesions in the AP are associated with loss of AQP4 immunoreactivity and with inflammation, but different from spinal and optic lesions, lack demyelination and necrosis. This difference may explain the almost universal complete remission of symptoms from such lesions.[5,10,11] Experimental ablation arrests intractable vomiting,[12] and an increase in neuronal firing is associated with projectile vomiting.[13] Attacks of intractable nausea, vomiting, or hiccups (INVH), in the context of a lesion in the dorsal medulla, are known as AP syndrome (APS).[14] Up to 30% of patients will have an APS during their illness.[5,14–16]

APS is included as a core clinical criterion for NMOSD; however, the APS phenotype (onset, frequency, duration, severity, associated symptoms, and treatment response) is not well described. Herein, we define the frequency, duration, and severity of INVH in AQP4-IgG–positive NMOSD and propose diagnostic criteria and a severity scale for APS.

Methods

Standard protocol approvals, registrations, and patient consents

All patients in our study consented to the use of their medical record for research purposes. All patients responded to a telephone questionnaire and provided informed written consent. The study was approved by each center's ethics committee as follows. In the United Kingdom: National Research Ethics Service (London-Hampstead) REC reference 15/LO/1433, Project ID 180720; Oxford Research Ethics Committee C Ref: 10/H0606/56. In Japan: ethical committee of Tohoku University School of Medicine (no. 2013-1-30). In the United States: institutional review board of Mayo Clinic, Rochester, MN (IRB no. 08-007846).

Three separate NMOSD patient cohorts (all AQP4-IgG–positive by cell-based assays) were evaluated for this study as follows.

Aim 1: To report the frequency of isolated APS attacks across continents and in different ethnicities, by analyzing a large international NMOSD attack database

An international database defining dates and types of NMOSD attacks in 430 patients from the United Kingdom, Japan, and the United States was interrogated.

Aim 2: To further characterize the APS phenotype and propose guidelines for APS diagnosis and investigate the utility of a repurposed nausea and vomiting in pregnancy severity scale (Pregnancy-Unique Quantification of Emesis and Nausea) with addition of a hiccups component for NMOSD

From the Mayo Clinic NMOSD database, 100 patients (none from the international database) with a total of 157 APS-compatible symptoms otherwise unexplained (e.g., medication side effects, anorexia nervosa, gastrointestinal disorder, pregnancy, or other comorbid condition) were interviewed. Clinical information collected during telephone interview included symptom type and onset, frequency, duration, associated symptoms (e.g., weight loss, yawning, menstrual irregularity, and headache), severity, timing of other NMOSD core attacks (e.g., optic neuritis [ON], transverse myelitis [TM], brainstem), and symptomatic (antiemetic medications) and immunotherapy treatment responses. We documented any initial gastroenterology diagnosis from patients' records. All available brain MRIs at the time of APS were reviewed. Utilizing these data, we defined clinical criteria for APS diagnosis in AQP4-IgG–seropositive NMOSD.

The severity scale for APS was modified from a validated score: the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score (table 1). Nausea and vomiting severity was based on duration of nausea and frequency of vomiting episodes in accordance with validated PUQE criteria, demonstrated to be correlated with quality-of-life measures over a 24-hour period of symptoms. Since hiccups are not included in the PUQE criteria, a separate hiccups section based on duration of symptoms was added.

Aim 3: To validate the revised NMOSD PUQE scale in a prospective multicenter cohort of patients with NMOSD

These criteria and the severity scale were applied to a different subgroup of 25 patients with NMOSD who had recent APS

Table 1 PUQE form

Pregnancy-unique quantification of emesis and nausea				
1. On average in a day, for how long do you feel nauseated or sick to your stomach?				
>6 h	4–6 h	2–3 h	≤1 h	Not at all
5 points	4 points	3 points	2 points	1 point
2. On average in a day, how many times do you vomit or throw up?				
≥7 h	5–6 times	3–4 times	1–2 times	Not at all
5 points	4 points	3 points	2 points	1 point
3. On average in a day, how many times have you had retching or dry heaves without bringing anything up?				
≥7 h	5–6 times	3–4 times	1–2 times	Not at all
5 points	4 points	3 points	2 points	1 point

Abbreviation: PUQE = Pregnancy-Unique Quantification of Emesis and Nausea.
Total score (sum of replies to 1, 2, and 3): mild nausea and vomiting in pregnancy (NVP) ≤6; moderate NVP 7–12; severe NVP ≥13. Quality of life question: On a scale of 0–10, how would you rate your well-being? 0 = worst possible; 10 = as good as you felt before pregnancy. PUQE form modified from Koren et al., Am J Obstet Gynecol, with permission.[23]

attacks identified by coinvestigators at multiple international centers. The utility of the severity scale applied at APS nadir, post symptomatic therapy, and post immunotherapy was evaluated.

Statistical analysis

Univariate and post hoc analysis of continuous variables between antibody subgroups was performed using 1-way analysis of variance. Nominal variables were analyzed using the χ^2 test (IBM SPSS 23; IBM Corp., Armonk, NY). Because of the retrospective and exploratory nature of the study, no adjustment for multiple comparisons was made.

Data availability statement

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Results

APS attacks (isolated or accompanying other symptoms) in patients with AQP4-IgG–seropositive NMOSD are common and occur with similar frequency across continents and ethnicities

A total of 430 patients (59 males, 371 females) were evaluated from 3 different countries (Japan, n = 69; United Kingdom, n = 169; United States, n = 192) (figure 1, A–F). Age at symptom onset in patients from Japan (median age 40 years [range 13–73 years]), the United Kingdom (median age 47 [range 3–79 years]), and the United States (median age 43 years [range 5–76 years]) was comparable (p = 0.680). The frequency of isolated APS at NMOSD onset was 7.1% in UK, 8.7% in Japanese, and 10.3% in US patients with NMOSD (p = 0.163). The frequency of APS occurring in association (<30 days in between) with other symptoms (e.g., ON or TM) at onset attack was 11.2% in UK, 15.9% in Japanese, and 8.2% in US patients (p = 0.332). APS attacks also occurred frequently during the course (not onset attack) of NMOSD; isolated APS occurred as noninaugural attacks in 11.2% in UK, 14.5% in Japanese, and 9.4% in US patients (p = 0.331) and in association with other symptoms in 12.4% in UK, 18.8% in Japanese, and 8.9% in US patients (p = 0.043). The frequency of APS attacks at onset and during the course of NMOSD stratified according to ethnicity across 3 continents is illustrated in figure 1.

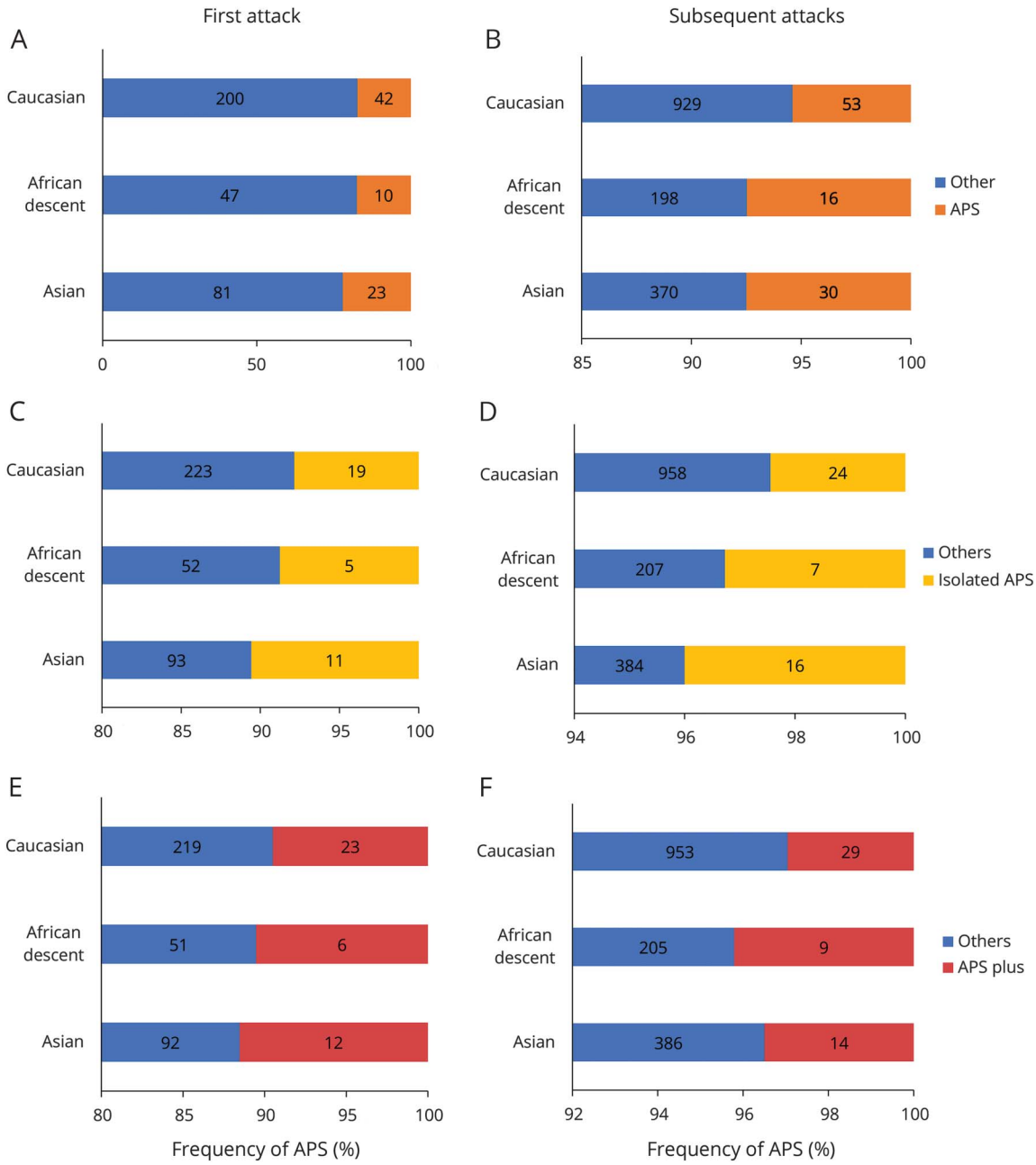
The APS attack phenotype

Of 100 patients (91 of whom were women), 45 Caucasian, 37 African American, 8 Asian, 7 Hispanic, and 3 others experienced 157 APS attacks (table 2). APS attacks were the inaugural symptoms in 54 patients. Of 157 APS attacks, 64 (40%) occurred without other neurologic symptoms and 91 (58%) preceded another NMO-typical relapse (19 ON, 58 TM, 9 ON/TM, 4 brainstem, 1 cerebral) by a median of 10 days (0–90). In only 2 patients did the APS symptoms follow an NMO-typical relapse (2 TM). Brain MRIs performed within 21 days (2–90) of APS onset revealed increased T2/fluid-attenuated inversion recovery or abnormal enhancement involving the dorsomedial medulla including the AP (figure 2).

APS is frequently evaluated by gastroenterologists and misdiagnosis is common

Forty-four patients presented initially to gastroenterologists and underwent extensive workup including upper gastrointestinal endoscopy, transit studies, and abdominal CT. The cause was not identified by the gastroenterologist in any of these patients. Twenty percent were given an incorrect diagnosis for their APS: gastroparesis (4), food poisoning (2), gastroesophageal reflux disease (2), *Helicobacter pylori* infection (2), cholecystitis (2), Crohn disease (1), pancreatitis

Figure 1 Frequency of APS in patients with NMOSD stratified according to ethnicity



Frequency of APS, total number of attacks (A, B), either isolated APS (C, D) or along with other neurologic disorders (APS-plus: APS with optic neuritis and/or transverse myelitis and/or cerebral lesions [E, F]) during initial attack or subsequent relapses based on ethnicity in a multicenter international NMOSD database from 3 different countries (Japan [69 Asian descent patients], United Kingdom [118 Caucasian, 23 African descent, 16 Asian patients], and United States [122 Caucasian, 33 African descent, 19 Asian]). Note that details of APS on some patients included in this database may have been published in the context of single-center case series. APS = area postrema syndrome; NMOSD = neuromyelitis optica spectrum disorder.

(1), fatty liver (1), *Clostridium difficile* (1), and psychogenic (3).

The phenotypic spectrum of APS includes intractable nausea, vomiting, and/or hiccups and is broader than previously recognized

Seventy-three patients (73%) had a single APS attack during their NMOSD course. Twenty-seven (27%) had multiple APS attacks with a median APS attack frequency of 2 (1–9) (table 2). All 3 symptoms (nausea, vomiting, and hiccups [NVH]) were present in 68 of 157 attacks (43%, 45 patients), 2 symptoms (NV [38], NH [8], VH [4]) in 50 attacks (32%, 32 patients), and a single symptom (N [14], H [22], V [3]) in 39 (25%, 23 patients).

Nausea

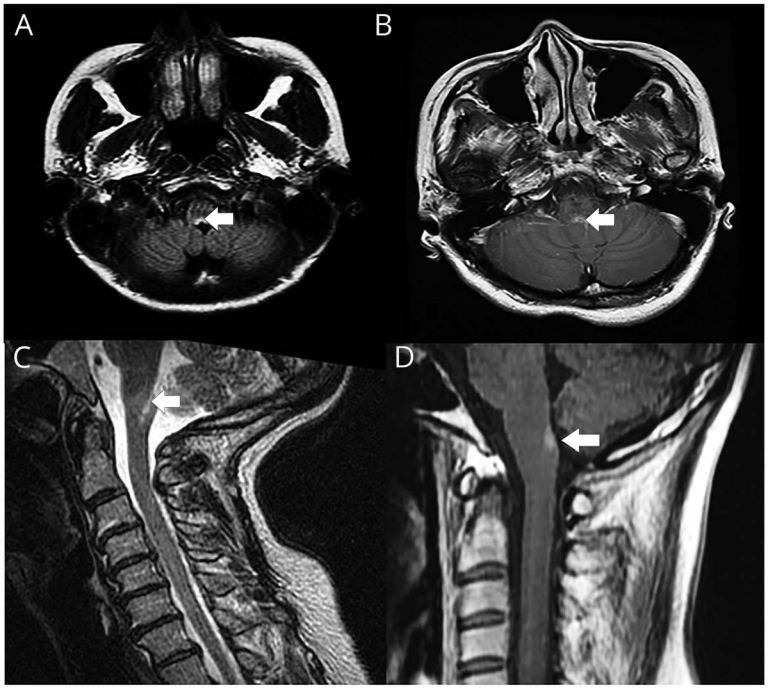
Nausea was acute in 73 attacks (57%). Daily duration of nausea episodes was ≤6 hours in 45 (35%) and >6 hours in 83 (65%).

Table 2 APS phenotype of 157 attacks in 100 AQP4-IgG–positive patients with neuromyelitis optica spectrum disorder

	APS symptoms in 157 attacks		
	Nausea (N), 83 patients	**Vomiting (V),[a] 75 patients**	**Hiccups (H)[b] 64 patients**
No. (%) with APS symptoms	127 (81)	113 (72)	102 (65)
No. (%) in isolation	14 (9)	3 (2)	22 (14)
No. (%) with 1 other	NV 38 (24), NH 8 (5), VH 4 (3)		
No. (%) with all *3*	68 (43)		
Median duration, d (range)	14 (2–365)	10 (2–365)	14 (2–365)
Continuous symptoms, n (%)	83 (65)	—[c]	30 (30)
Episodic symptoms, n (%)	45 (35)	113 (100)	72 (70)
Episodes/d (range)	5 (2–30)	5 V/d (2–40)	10 (2–50)
Median duration of each episode, min (range)	10 (2–120)	2 (1–20)	15 (2–300)[d]
Awakened due to symptom onset	35	36	46
Weight loss (>3 lbs in 3 d), n	75		
Median, lbs (range)	17 (3–70)		

Abbreviations: APS = area postrema syndrome; AQP4-IgG = aquaporin-4–immunoglobulin G.
Twenty-seven patients reported migraine-like headaches in association with APS symptoms, characterized by severe throbbing headache, over the temples or back of the head with radiation to frontal regions that failed to respond to standard analgesia; 23 denied prior migraines or other headache history. Cardiac arrhythmias and fluctuations in blood pressure were reported in 16. Secondary amenorrhea was reported by 6 women during the course of the APS attack, 4 (2–10) months. Rare symptoms such as purposeful yawning unrelated to sleep or fatigue were reported in 2 patients, and generalized itching in another 2.
[a] Of 100 patients, 91 of whom were women, 45 were Caucasian, 37 African American, 8 Asian, 7 Hispanic, and 3 others.
[b] In no patient was hiccups triggered by food or drink. Hiccups improved in 15% of patients when supine.
[c] All vomiting attacks were episodic, even if it continued all day. Food and drink triggered vomiting in 9 patients. Vomiting was described as projectile by 8 patients.
[d] Median interval between episodes was 10 minutes (1–480 minutes).

Figure 2 MRI abnormalities in AQP4-IgG–seropositive neuromyelitis optica spectrum disorder patients with APS



MRI head demonstrates a hyperintense lesion in the area postrema adjacent to the 4th ventricle on axial fluid-attenuated inversion recovery (A, arrow) in a patient with APS. In a separate patient, an enhancing lesion is noted the same region on axial T1-weighted head MRI postgadolinium administration (B, arrow). In a third patient a T2-hyperintense lesion in the area postrema is best seen on sagittal T2-weighted MRI of the cervical spine MRI (C, arrow). In a fourth patient, enhancement in the area postrema is demonstrated on sagittal T1-weighted cervical spine MRI post gadolinium (D, arrow). APS = area postrema syndrome; AQP4-IgG = aquaporin-4–immunoglobulin G.

Vomiting

All vomiting attacks were episodic, even when persistent. The number of vomiting episodes in APS attacks was ≤4/d in 46 (41%), 5–7 in 43 (38%), and ≥8 in 24 (21%). Food and drink triggered vomiting only in 9 patients. Vomiting was described as projectile by 8 patients.

Hiccups

Onset was acute in 55 attacks (54%). Daily duration of hiccups in APS attacks was ≤3 hours in 31 (30%), 4–12 hours in 27 (27%), and >12 hours in 44 (43%). Hiccups were reported as constant ("nonstop" for >24 hours) in 31 (30%) APS attacks. While episodic in the remainder, the median interval between episodes was 10 minutes (1–480 minutes). In no patient was hiccups triggered by food or drink. Hiccups improved in 15% of patients when supine.

Hospitalization is common, and symptomatic therapies are generally ineffective

Because of symptom severity, 78 patients (78%) required frequent emergency room visits for APS attacks. One hundred four attacks were treated with symptomatic treatments (i.e., antiemetics: Primperan [metoclopramide], ondansetron, promethazine) or IV rehydration only; partial improvement was reported in only 11 of these attacks (11%) in the emergency room. APS symptoms led to hospitalization in 59 patients. For many patients, the symptoms would fluctuate over months and in some stopped spontaneously.

Immunotherapy resulted in rapid cessation of symptoms in nearly 90% of patients treated

Eighty-four APS attacks (in 51 patients) were treated with IV methylprednisolone (69 attacks) or plasmapheresis (15 attacks): 88% of APS attacks ceased within 2 days. In 10, symptoms partially improved, but eventually resolved with maintenance immunotherapy (azathioprine, mycophenolate mofetil, or rituximab).

APS diagnostic criteria will assist in clinical diagnosis, attack identification, and classification for NMOSD clinical trials

The criteria outlined in table 3 require AQP4-IgG seropositivity and acute or subacute onset of intractable nausea, vomiting, or hiccups. Single or combined symptoms are allowed. Symptoms must persist for at least 48 hours. Lack of response to symptomatic therapies may be a clue to APS. APS may only be diagnosed earlier than 48 hours if brain MRI reveals a new focus of signal abnormality in the AP given the broad differential diagnosis and the rarity of APS as a cause of vomiting and hiccups in the general population. APS can only be diagnosed after exclusion of other etiologies.

Repurposing the PUQE scale for use in APS

Nausea and vomiting severity was based on duration of nausea and frequency of vomiting episodes in accordance with validated PUQE criteria (tables 1 and 4). Using hiccups phenotype data, a separate hiccups section based on duration of symptoms was added (table 4). The severity of each symptom type (nausea, vomiting, or hiccups) is graded on a 0 to 3 scale. An overall severity, defined as mild, moderate, or severe, is based on combinations of symptom grades. For example, a patient with hiccups lasting 3 hours or less and less than 4 episodes of vomiting in a 24-hour period would be considered "mild." In contrast, constant hiccups or nausea or more than 7 vomits per day would be considered "severe." In 100 US patients with NMOSD who had 157 APS attacks, 30 (19%) were mild, 37 (24%) were moderate, and 90 (57%) were severe.

Table 3 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,[a] with lack of complete resolution after symptomatic[b] therapy
3. Exclusion of other etiology[c]

Abbreviations: AQP4-IgG = aquaporin-4–immunoglobulin G; NVH = nausea, vomiting, and hiccups.
For patients fulfilling criteria 1 to 3, it is strongly recommended to test for AQP4-IgG if unknown.
[a] Shorter duration (<24 hours) may be considered if MRI shows new area postrema involvement (figure 1, B).
[b] IV fluid, antiemetics, hiccups treatments.
[c] 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.

Validation cohort

Among the 25 NMOSD patients with APS, the majority, 20 (80%), fulfilled criteria for severe APS; only 2 (8%) were classified as mild and 3 (12%) as moderate at APS attack nadir. Seventeen patients received symptomatic therapies: 12 (75%) experienced no benefit; 4 (25%) reported partial improvements, as was observed in the 100-patient cohort, and the overall APS severity grade dropped from severe to moderate in 3 and moderate to mild in 1 (figure 2). Eighteen patients received immunotherapy (IV methylprednisolone [12], plasma exchange [6]), 17 patients (95%) experienced complete resolution of APS symptoms and their score returned to zero, and the other patient improved from severe to mild (figure 3). APS was isolated in 8 (32%), and preceded typical NMOSD attacks in 17 patients (68%): 11 (44%) TM, 4 (16%) ON, and 2 (8%) brainstem.

Discussion

This multicenter, international, collaborative study provides new clinical and diagnostic insights into APS in AQP4-IgG–positive NMOSD. APS is commonly encountered in AQP4-IgG–positive NMOSD across different ethnicities and continents, either in isolation or accompanying other symptoms (mostly ON or TM), at onset or during the course of the NMOSD illness. The phenotypic spectrum across 100 patients with 157 APS attacks is described. These

Table 4 Area Postrema Severity Scale

Over past 24 h	% of 157 APS attacks in 100 patients[a]
Nausea grades	
0: None	19
I: Total duration[b] ≤3 h	15
II: Total duration 3–6 h	13
III: >6 h or constant	53
Vomiting grades	
0: None	28
I: ≤4 episodes/d	29
II: 5–7 episodes/d	28
III: ≥8 episodes/d[c]	15
Hiccups grade	
0: None	35
I: Total duration[b] ≤3 h/d	20
II: Total duration 3–12 h/d	17
III: >12 h or constant[c]	28
APSS	
Normal: grade 0	0
Mild: 1 or 2 grade I	19
Moderate: 1 or 2 grade II, or 3 grade I	24
Severe: ≥1 grade III, or 3 grade II	57

Abbreviations: APS = area postrema syndrome; APSS = Area Postrema Severity Scale.
[a] APSS measured at APS nadir.
[b] May be episodic.
[c] Or experienced dehydration, electrolyte imbalance, or life-threatening condition.

observations facilitated proposal of diagnostic criteria for APS in NMOSD. Based on these phenotypic data, we propose an APS severity scale based on a previously validated severity scale for hyperemesis gravidarum (HG).

APS was included as a core clinical criterion of NMOSD in the revised 2015 NMOSD diagnostic guidelines and as 1 of 3 characteristic clinical manifestations, of which at least one was required in patients seronegative for AQP4-IgG.[17] However, lack of specificity of these symptoms and absence of a rigorous definition leads to substantial subjectivity in its application by the treating physician, which may be problematic when comparing attack outcomes in clinical trials, of which there are currently 3 ongoing (MEDI-551 [anti-CD19], SA 237 [anti-IL-6 receptor], eculizumab [anti-C5]).[18,19]

Given the high frequency of APS attacks in NMOSD and the increasing numbers of clinical trials aimed at reducing attack frequency (and severity), accurate diagnosis, especially of isolated APS, is important. Based on the APS phenotype reported here and defined through telephone questionnaire of prior APS attacks, diagnostic criteria for APS were developed. To enhance specificity, 48 hours was the minimum duration of symptoms allowed to make an APS diagnosis after exclusion of other etiologies and in the absence of a new MRI lesion in the AP. Although AP lesions are not specific for NMOSD, presence of intractable nausea, vomiting, and hiccups is highly specific for AQP4-IgG–seropositive NMOSD, which emphasizes the importance of clinical rather than MRI features of APS.[20] Although in a clinical trial setting in which patients are encouraged to report symptoms as soon as they occur, we propose that diagnosis of INVH as an APS earlier than 48 hours of onset is possible only when a dorsal medulla lesion is detected on MRI.

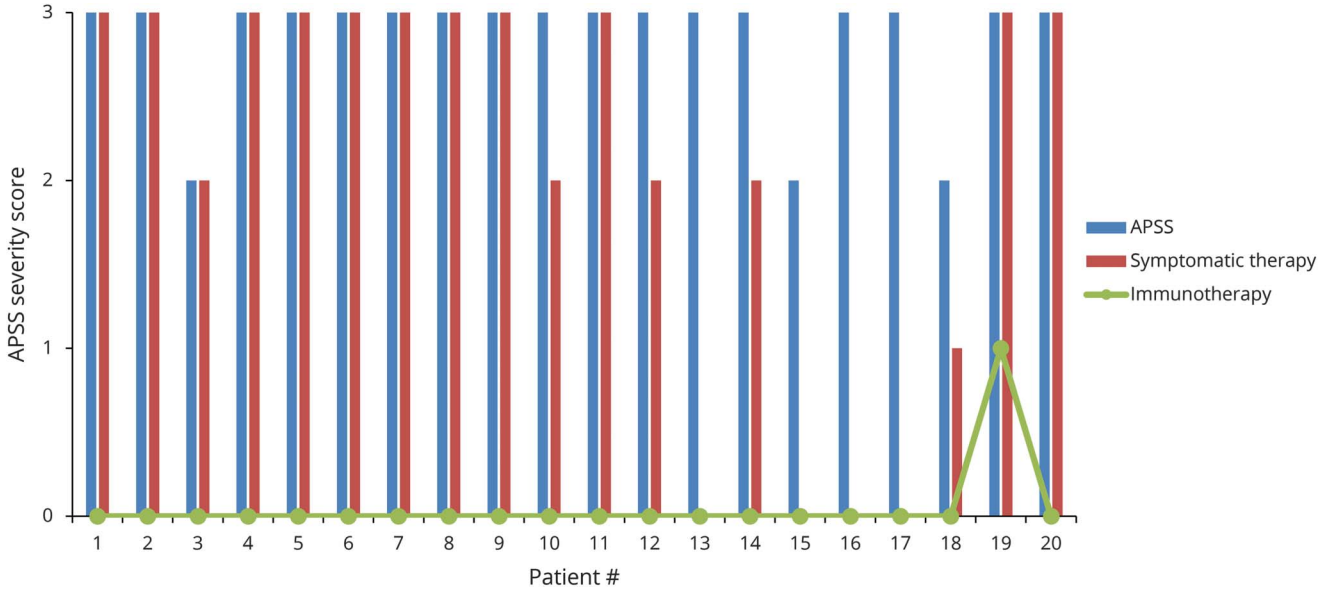
Given that 75% of patients reported weight loss, up to 70 pounds, we suspect that anorexia was a contributing factor in our cohort. Lesions in the AP in animal models can induce hypophagia and weight loss without alteration in intestinal transit or gastric retention.[21]

In support of the specificity of this syndrome as a manifestation of NMOSD, AQP4-IgG was not detected in 435 patients (enrolled in the NIH-funded Gastroparesis Clinical Research Consortium repository) who presented with idiopathic nausea or vomiting.[16] The 435 patients enrolled in the Gastroparesis Clinical Research Consortium Registry cohort included 318 patients with gastroparesis, of whom 59% had vomiting or nausea as their predominant symptom that prompted gastroenterologic evaluation. Their Patient Assessment of Upper Gastrointestinal Disorders–Symptoms Severity Index (PAGI-SYM) scores (scale 0–5, where 0 = none and 5 = very severe) were 3.5 ± 1.2 for nausea and 2.2 ± 1.9 for vomiting. The frequency of vomiting or nausea as the predominant symptom that prompted gastroenterologic evaluation in those lacking gastroparesis was 60% for nausea and vomiting. Their PAGI-SYM scores were 3.4 ± 1.3 for nausea and 1.9 ± 1.9 for vomiting.[16]

However, recognizing the lack of specificity of nausea and vomiting, in the absence of detectable AQP4-IgG or for symptoms lasting less than 48 hours, the criteria for an APS attack requires a new T2 or enhancing MRI lesion in the AP for confirmation.

Most APS attacks (58% of the Mayo-only cohort and 68% of the international validation cohort) preceded (<30 days, thus considered the same attack) inflammatory involvement of the optic nerves or spinal cord, making APS an important warning sign. Early treatment of APS with steroids or plasmapheresis (or other acute attack immunotherapies) may not only reduce severity of APS attacks but may also prevent accompanying disabling attacks of ON or TM. Therefore, evaluating the severity may be important in NMOSD clinical trials. Sensitivity of outcome measures is particularly important for

Figure 3 APSS scores at nadir, and post therapy



Change in APSS scores after symptomatic and immunosuppressant therapies for 20 patients with both nadir and posttherapy scores. APSS = Area Postrema Severity Scale.

NMOSD studies that typically are "time to first event" studies with each patient contributing information only from a single attack before removal from the blinded phase of a clinical trial.

Up to 80% of all pregnant women report nausea and vomiting, and in some, this is associated with a reduced quality of life.[22] A more serious condition, HG, occurs in approximately 1% of pregnant women. HG bears some similarities to APS in NMOSD, and is defined as vomiting occurring before the 20th week of gestation of such severity as to require the patient's admission to hospital. The pregnancy-specific questionnaire PUQE score was developed to assess the severity of emesis (nausea and vomiting) in pregnancy.[23] It contains 3 questions regarding the time span of nausea, vomiting, and retching, respectively. The questionnaire has been modified to encompass 24 hours as well as the entire first trimester (table 1).[24] PUQE score has been validated to correlate with inability to take iron supplementation in pregnancy, risk of hospitalization due to HG or severe nausea and vomiting in pregnancy, increased health care costs attributable to nausea and vomiting in pregnancy, and reduced well-being/quality of life.[25] The PUQE questionnaire has also been used in several studies assessing the effect of antiemetic treatments for emesis and hyperemesis.[26,27] The severity scale for APS proposed herein is based on the nausea and vomiting questionnaire sections of the PUQE criteria. Intractable hiccups severity scale, based on duration of symptoms, is an additional component in the APS scoring system. In the multicenter validation cohort, the severity grades were similar to those in the 100-patient cohort. The APS severity scale detected improvements with both symptomatic therapy and immunotherapy, demonstrating the potential utility in drug trials. This study was restricted to patients with the immunopathologically distinct entity AQP4-IgG NMOSD. It remains unclear whether these data are applicable to APS that have been observed in patients with myelin oligodendrocyte glycoprotein autoimmunity.[1,28] The applicability to seronegative diseases remains unknown.

Author contributions

Conception and design of the study: S.J.P., B.W., E.S. Acquisition and analysis of data: all authors. Drafting a significant portion of the manuscript or figures: S.J.P., E.S., B.M.G., D.D.

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