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Intractable Nausea and Vomiting from Autoantibodies Against a Brain Water Channel

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Drs. Iorio, Farrugia and Pasricha report no disclosure.

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Dr. Lennon is named inventor on two patent applications filed by Mayo Foundation for Medical Education and Research that relate to NMO (aquaporin-4) antibody and its application to cancer and functional assays for detecting AQP4-IgG. A patent issued for technology related to NMO-IgG testing has been licensed to a commercial entity. Dr. Lennon and Mayo Clinic have received royalties that exceed the federal threshold for significant financial interest from licensing of the above listed technology and have rights to receive future royalties. Serological testing for neural autoantibodies is offered on a service basis by Mayo Collaborative Service, Inc, an agency of Mayo Foundation. Neither Dr. Lennon nor her laboratory benefit financially from this testing.Dr Lennon has received research support from the Guthy-Jackson Charitable Foundation and the National Institutes of Health (R01 DK71209 and PO1 DK068055).

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Abstract

Background & Aims—Antibodies against the water channel protein aquaporin (AQP)-4 cause a spectrum of inflammatory, demyelinating, central nervous system disorders called neuromyelitis optica spectrum disorders (NMOSDs); these primarily affect the optic nerves and spinal cord, but also the brain. Symptoms of intractable nausea, vomiting and hiccups reflect involvement of AQP4 in the brainstem area postrema and account for gastroenterologic presentations. We investigated the frequency of intractable nausea, vomiting, or hiccups in patients with NMOSD who tested positive for immunoglobulin-G against AQP4 (AQP4-IgG). We also analyzed sera from patients with idiopathic nausea or vomiting for the presence of AQP4-IgG.

Methods—We reviewed the Mayo Clinic AQP4-IgG positive NMOSD database (n=70) to identify patients who presented with vomiting, focusing on results from gastroenterologic evaluations. We also tested serum samples (from the Gastroparesis Clinical Research Consortium repository) from patients who presented with idiopathic nausea or vomiting for AQP4-IgG (controls n=318 with gastroparesis and 117 without gastroparesis).

Results—Ten AQP4-IgG-positive patients diagnosed with NMOSD (14% of patients in the database) initially presented with intractable vomiting. Extensive gastroenterological evaluation was non-informative. AQP4-IgG was not detected in any of the controls.

Conclusions—Though NMOSDs are rare, tests for AQP4-IgG should be considered for patients that present with unexplained, intractable vomiting. Detection of the antibody before the development of optic neuritis or transverse myelitis allows patients to receive immunosuppressive therapy before the development of neurologic disabilities.

Keywords

diagnosis; chronic nausea and vomiting; central nervous system; aquaporin-4 antibody

Introduction

Autoantibodies targeting astrocytic aquaporin-4 (AQP4) water channels are a sensitive and specific biomarker, and the putative cause, of neuromyelitis optica (NMO). Detection of AQP4-IgG in serum or spinal fluid predicts a relapsing inflammatory demyelinating disorder of the central nervous system, and distinguishes NMO spectrum disorders (NMOSD) from multiple sclerosis.[1,2,3] AQP4 is the principal water channel in the central nervous system,[4,5] and is highly concentrated in astrocyte foot processes abutting microvessels and pia.[6,7] NMO-typical brain MRI lesions occur in AQP4-enriched areas,[8] including the fourth ventricular floor which contains the chemosensitive nausea and vomiting center (area postrema). Intractable nausea, vomiting and hiccups are recognized symptoms of NMOSD.[9,10,11]

We recently reported recognition of intractable vomiting as the heralding symptom of NMOSD in 12% of patients.[9] These patients commonly undergo extensive, but non-revealing, evaluations on presentation to internists and gastroenterologists who are largely unaware of this emerging neurological entity.

Here we describe 10 previously unreported patients with intractable nausea and vomiting as the initial symptom of an NMOSD. Investigation and subsequent clinical course revealed vomiting of central origin, reflecting an immune attack against brainstem AQP4.

Methods

The study, approved by the Mayo Clinic Institutional Review Board, involved retrospective chart review of 70 consenting AQP4-IgG seropositive Mayo Clinic patients identified through the Neuroimmunology Laboratory's NMO database since our initial report of intractable vomiting as the initial presentation of NMOSD in 8 of 69 (12%) patients. [9] As controls we tested sera from 435 patients enrolled in the Gastroparesis Clinical Research Consortium (GpCRC) repository, using a transfected cell-binding assay (Euroimmun, Luebeck, Germany) to detect AQP4-IgG. These patients included 318 with gastroparesis and 117 with nausea or vomiting without gastroparesis

Results

Intractable Nausea and Vomiting in AQP4-IgG Positive Patients

Ten of 70 newly identified AQP4-IgG-positive patients (14%) had nausea and vomiting as the initial presenting symptom of NMOSD.

Table 1 summarizes clinical, serological and neuroimaging characteristics. Nine were women; mean onset age 47 years (range 26-72). Seven patients (70%) required in-patient intravenous hydration. Nausea and Vomiting was generally continuous and non-cyclic in all patients, it occurred day and night and was not preceded by headache. None had cyclic vomiting. Hiccups accompanied intractable vomiting in 3 patients. All presented to a gastroenterologist or internist; 6 (85%) underwent extensive gastroenterological evaluation including gastroscopy with biopsy, small bowel X-ray and abdominal ultrasound. Abdominal CT was performed in 2 patients (#1 and #2 in the table); patient #1 had a wireless capsule endoscopy. Inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, were all within the normal range.

Brain MRI (5 patients, within 2 months of vomiting onset) revealed a focus of T2 signal abnormality in the area postrema (3 patients), multiple foci of T2 signal abnormality in the deep white matter (fourth patient) and no abnormality (fifth patient).

Diagnoses were unspecified viral illness (4 patients) and gallbladder polyp (1 patient). The mean interval from onset of vomiting to a classical NMO symptom (optic neuritis or longitudinally-extensive transverse myelitis [LETM]) was 111 weeks (range 0-720).

Intractable vomiting recurred in 4 patients (#1, 4, 5 and 7; Table 1) during a subsequent NMO-typical relapse. AQP4-IgG was detected in serum (9) or cerebrospinal fluid (1). At last follow-up (mean follow-up period 56.6 months; range 11-180), 8 patients had fulfilled 2006 diagnostic criteria for NMO and 2 patients fulfilled criteria for NMOSD (relapsing LETM and AQP4-IgG seropositivity, without optic neuritis).[4] Summarized clinical histories follow, for 2 representative cases (patients #1 and #2; Table 1).

Case 1

A woman aged 41 was hospitalized locally with severe, intractable nausea and vomiting with hiccups. Symptomatic treatment yielded only partial benefit. Continuing post-discharge symptoms necessitated University Hospital admission. Extensive but non-revealing gastroenterologic evaluation included CT of abdomen and pelvis, pelvic and liver ultrasound, upper GI endoscopy, gastroscopic biopsy, gastric emptying study and wireless capsule endoscopy. MRI head and cerebrospinal fluid testing (protein and cells) were negative. Four weeks after onset, she was transferred to our institution's Intensive Care Unit for management of bradycardia and hypotension. She reported a 10 pound weight loss. Blood pressure stabilized after intravenous rehydration. Extensive blood tests were negative

(except for antinuclear antibody). Prochlorperazine (5 mg *p.o.*, once daily) and diphenhydramine (25 mg *p.o.*, 6 hourly) partially improved the nausea; upon discharge she tolerated oral intake. Nausea and vomiting persisted for 3 months.

One week after nausea and vomiting had subsided, she experienced optic neuritis involving the right eye; this improved after *i.v.* methylprednisolone (1g/day, 3 days). Left optic neuritis developed 3 weeks later, and resolved following a second course of *i.v.* methylprednisolone (1 g/day, 5 days). One month later, nausea and vomiting recurred. A repeated gastric emptying test was normal. The patient complained of foot paresthesias, gradually ascending to the torso; urinary retention and constipation followed. Spinal cord MRI (T2 weighted imaging) revealed signal abnormality extending from the cervicomedullary junction to upper thoracic cord (Figure). Post-gadolinium T1 weighted images revealed mild patchy enhancement. The clinical and radiological findings were consistent with the diagnosis of NMO. Serum AQP4-IgG was positive. Plasmapheresis and methylprednisolone (1g/day, 5 days) were initiated. Gait, sensory complaints and bladder function improved after the fifth plasma exchange.

Case 2

Continuous nausea and vomiting without associated abdominal pain developed in a previously healthy 40-year-old woman. Extensive gastroenterological evaluation (upper GI endoscopy with biopsy, small bowel X-ray, CT of abdomen) revealed no cause; ultrasound revealed a tiny gallbladder polyp. Laparoscopic cholecystectomy was uncomplicated; nausea and vomiting worsened. Vomiting continued 1-3 times daily for 3 months despite anti-emetic therapy. Blood tests, including liver function, were unremarkable except for mild hypokalemia and anti-nuclear antibody. Weight loss was 30 pounds. Two months later a subacute gait disorder evolved over several days, with ataxia, bilateral lower extremity weakness, left upper extremity dysesthesias, constipation, urinary retention, and incomplete voiding. She complained additionally of diplopia, vertigo, and dysarthria. Brain MRI revealed a lesion in the posterior medulla at the obex level, which extended into the upper cervical cord. The spinal cord MRI lesion extended from the lower medulla to the mid-T5 body with slight cervical cord expansion compatible with a diagnosis of LETM. Her condition improved while receiving *i.v.* methylprednisolone (1g/day, 5 days); oral prednisone therapy followed. Two years later, with alternate day prednisone doses of 10 mg and 5 mg, nausea, vomiting, diarrhea and urinary urgency began, necessitating hospitalization. Spastic paraparesis worsened, and bilateral lower extremity hyperreflexia and extensor plantar responses continued unabated. Another relapse, 5 years later, was characterized by LETM, posterior reversible encephalopathy syndrome and a fatal respiratory crisis. AQP4-IgG testing, unavailable at the time of clinical evaluation, was detected subsequently in archival serum.

AQP4-IgG Frequency in Patients with Gastroparesis or Idiopathic Nausea and Vomiting

We used AQP4-transfected cell-binding assay (Euroimmun, Luebeck, Germany) to test serum from 435 patients enrolled in the NIH-funded Gastroparesis Clinical Research Consortium (GpCRC) repository. Demographics and clinical characteristics are summarized in Table 2. Nausea and vomiting were the predominant symptoms prompting gastroparesis evaluation. No patient (among 158 and 100, respectively) was seropositive for AQP4-IgG.

Discussion

Intractable vomiting may be the initial and isolated presenting symptom of an NMOSD.[9] Thus internists and gastroenterologists need to be aware of the entity of AQP4 autoimmunity. Contemporary evidence supports these disorders being organ-specific

autoimmune diseases mediated by IgG targeting astrocytic AQP4 water channels in the central nervous system.[1,4]

We previously reported intractable nausea and vomiting as the initial presenting symptom of AQP4 autoimmunity in 12% (8 of 69) of AQP4-IgG-seropositive NMOSD patients.[9] The present study brings our total cohort of AQP4-IgG-seropositive NMO patients to 139, with a 13% prevalence rate of nausea and vomiting as the heralding symptom of NMO. With timely MRI imaging[8,9] (or immunohistopathologic evaluation of autopsied tissues[10]) the symptomatology is demonstrably associated with discrete lesions in the area postrema, the AQP4-rich emetic reflex center of the medulla.[12] Astroglial cells in this specialized sensory region are accessible to circulating IgG because the capillaries are fenestrated.[13]

Seventy percent of the patients in this study initially presented to a gastroenterologist or to an internist, but extensive investigation revealed no gastroenterological explanation for emesis. Imaging of a gallbladder polyp in 1 case led to unnecessary surgery. Although NMOSDs are not common, AQP4-IgG seropositivity predicts with high probability relapsing attacks of optic neuritis and transverse myelitis with a cumulative neurological morbidity.

Early diagnosis, aided by serological testing, allows early initiation of immuno-suppressant therapy and an opportunity to modify the course of this severe neurological disorder rather than awaiting relapse to fulfill 2006 diagnostic criteria for NMO.[14] Natural history studies have established that 50% of untreated patients are blind in 1or both eyes or confined to a wheelchair within 5 years of disease onset.[4]

The importance of the area postrema as the first point of attack in NMOSDs is illustrated convincingly by the histopathological finding of selective AQP4 loss in the medullary floor of the fourth ventricle and area postrema.[9, 10] This is accompanied by tissue rarefaction, inflammation, variable deposition of terminally activated complement components, and non-lytic alterations in GFAP-positive reactive astrocytes (nondestructive lesions with relative preservation of neurons, axons and myelin).[10,]

The pathophysiological mechanisms linking astrocyte dysfunction to nausea and vomiting are yet to be determined. It has been documented experimentally that ablation of the area postrema arrests intractable vomiting,[15] and that an increase in firing of area postrema neurons is associated with projectile vomiting.[16] The binding of NMO-IgG to AQP4 *in vitro* triggers diverse molecular outcomes by cross-linking and internalizing AQP4 and its membrane partner molecules. These outcomes include impaired water fluxes and, if active complement is present, plasma membrane lysis.[17, 18] The astrocytic excitatory amino acid transporter 2 (EAAT2), which accounts for 90% of synaptic glutamate reuptake, is linked non-covalently to AQP4. AQP4-IgG induces internalization of both AQP4 and EAAT2 and reduces glutamate uptake.[19] Increased extracellular glutamate concentration would lead to excessive stimulation of calcium-permeable glutamate receptors. However, unlike the spinal cord, the area postrema lacks EAAT2.[10, 20] The non-destructive pattern of pathology and the rapid reversal of symptoms and medullary MRI abnormalities by immunotherapy suggest that NMO-IgG binding to AQP4 in this region does not activate complement efficiently, i.e., astrocytic “injury” is sublytic.[9] The conspicuous lack of AQP4 immunoreactivity in the affected area postrema is consistent with IgG-induced down-regulation of AQP4. AQP4 loss and resulting alteration/disruption of water or neurotransmitter homeostasis presumably activates area postrema neurons and vomiting ensues.

The estimated prevalence of NMO and its spectrum disorders is 0.5 to 4.4 per 100,000 population.[21,22] Given the rarity of NMO and the fact that intractable nausea and vomiting herald its onset in only 1 of 8 cases, it is not surprising that none of the control patients with

idiopathic nausea and vomiting was seropositive for AQP4-IgG. The negative results obtained in this large control group of patients with gastroparesis and other vomiting disorders of presumed peripheral origin implies it unlikely that AQP4 in the proximal gut is involved in gastrointestinal dysmotility. Nevertheless, AQP4 autoimmunity can be added to diagnosable central causes of intractable nausea and vomiting in patients presenting with unexplained intractable nausea and vomiting for which gastric emptying studies do not reveal evidence of gastroparesis.

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Abbreviations used in this paper

AQP4	aquaporin-4
EAAT2	excitatory amino acid transporter 2
LETM	longitudinally-extensive transverse myelitis
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorders

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TABLE 1

Clinical Characteristics of 10 Patients Whose Initial NMO Spectrum Disorder Symptom Was Intractable Vomiting (with Nausea)

Case	Sex/age at vomiting onset	Subspecialty consultations/ GI evaluation	Duration of vomiting (days)	Associated symptoms	No. vomiting episodes per day	Vomiting periodicity (cyclic vs non-cyclic)	Provisional diagnosis	Interval from vomiting onset to ON or LETUM (weeks)	AQP4-IgG titer *	Diagnosis at last follow-up	Duration of follow-up from vomiting onset (months)
1	F/41	Gastroenterology, Internal Medicine, Cardiology, Rheumatology, Gynecology; gastroscopy with biopsy, small bowel X-ray, abdominal ultrasound, abdomen and pelvis CT, wireless capsule endoscopy	90	Hiccups	15	Non-cyclic	Viral illness	12	30720	NMO	11
2	F/40	Gastroenterology; gastroscopy, small bowel X-ray, liver ultrasound, abdomen CT, cholecystectomy	90	None	N/A	Non-cyclic	Gallbladder polyp	20	240	rLETM	84
3	F/50	Neurology; none	7	Limb ataxia	N/A	Non-cyclic	Multiple sclerosis	0	30720	NMO	31
4	F/43	Gastroenterology; abdomen ultrasound, gastroscopy with biopsy, small bowel X-ray	7	Hiccups	N/A	Non-cyclic	None	18	7680	NMO	60
5	F/26	Gastroenterology; gastroscopy with biopsy, abdomen ultrasound, small bowel X-ray	28	Hiccups	N/A	Non-cyclic	Viral illness	260	960	NMO	84
6	F/45	None; none	1	None	N/A	Non-cyclic	None	20	15360	NMO	12
7	F/41	Gastroenterology; gastroscopy, abdomen ultrasound, small bowel X-ray None; none	21	None	N/A	Non-cyclic	None	720	1920	NMO	180
8	F/51		4	None	N/A	Non-cyclic	Viral illness	1	7680	NMO	36
9	M/60	Gastroenterology; gastroscopy with biopsy, small bowel X-ray, abdomen ultrasound	15	Hiccups	14	Non-cyclic	None	2	CSF only positive	NMO	42
10	F/72	Internal Medicine	3	None	20	Non-cyclic	Viral illness	64	960	rLETM	26

CT, computed tomography; F, female; M, male; ON, optic neuritis; CSF, cerebrospinal fluid; rLETM, relapsing longitudinally-extensive transverse myelitis; N/A, information not available; NMO, neuromyelitis optica.

* Ascertained by tissue-based immunofluorescence testing of serum.

TABLE 2

Demographic and Clinical Characteristics of 435 Patients Enrolled in the Gastroparesis Clinical Research Consortium Registry All of Whom Were Seronegative for AQP4-IgG by Cell Binding Assay

	Definite gastroparesis *	
	Yes	**No**
Patient characteristics	(N=318)	(N=117)
Gender		
Female	269 (85%)	94 (80%)
Male	49 (15%)	23 (20%)
Age, years	41.5 ± 13.9	42.5 ± 13.0
Hispanic ethnicity	16 (5.0%)	8 (6.8%)
Race		
White	278 (88%)	95 (82%)
Black	28 (9%)	13 (11%)
Other	8 (2.6%)	8 (6.9%)
Gastroparesis etiology		
Diabetes	106 (33%)	31 (27%)
Idiopathic	212 (67%)	86 (73%)
Gastroparesis severity *		
Grade 1, Mild	40 (13%)	27 (23%)
Grade 2, Compensated	167 (53%)	69 (59%)
Grade 3, Gastroparesis with gastric failure	108 (34%)	21 (18%)
Predominant symptom that prompted evaluation for gastroparesis		
Nausea		
Vomiting	110 (35%)	48 (41%)
Abdominal pain	78 (24%)	22 (19%)
Bloating	23 (7.2%)	9 (7.7%)
Gastroesophageal reflux symptoms	6 (1.9%)	4 (3.4%)
Postprandial fullness	7 (2.2%)	6 (5.1%)
Early satiety	61 (19%)	19 (16%)
Diarrhea	5 (1.6%)	1 (0.9%)
Weight loss	2 (0.6%)	2 (1.7%)
Constipation	1 (0.3%)	1 (0.9%)
Anorexia	5 (1.6%)	0 (0.0%)
Weight gain	1 (0.3%)	0 (0.0%)
Problems with management of diabetes	12 (3.8%)	4 (3.4%)
Other	1 (0.3%)	0 (0.0%)
	6 (1.9%)	1 (0.9%)
PAGI-SYM scores		
(scale 0-5, where 0=none and 5=very severe)		
Nausea	3.5 ± 1.2	3.4 ± 1.3
Retching	2.1 ± 1.7	1.8 ± 1.7

	Definite gastroparesis *	
	Yes	**No**
Vomiting	2.2 ± 1.9	1.9 ± 1.9

* Definite gastroparesis defined by gastric retention >60% at 2 hrs or >10% at 4 hrs.

† 2 patients in the “not gastroparesis” group had gastroparesis severity classified as a combination of grade 2 and grade 3.