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CASE REPORT

A diagnostic challenge in a young woman with intractable hiccups and vomiting: a case of neuromyelitis optica

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Intractable nausea and vomiting along with hiccups is a commonly encountered problem on any general medicine or gastroenterology service. These symptoms are usually not appreciated as the possible initial manifestation of neuromyelitis optica (NMO). Missing diagnosis at this early stage will lead to a delay in the treatment, and hence, irreversible complications including blindness and paraplegia could occur. We report a case of a 22-year-old young female who presented with intractable hiccups and vomiting. After extensive evaluation, she was found to have NMO which involved the area postrema, the vomiting center of the brain. Early diagnosis from the clinical picture aided by aquaporin-4 serologic testing is extremely important to allow early initiation of immunosuppressive therapy. Immunosuppression gives an opportunity to modify the disease at an earlier stage rather than waiting for evolution of disease to fulfill the diagnostic criteria of NMO.

Keywords: *hiccups*; *vomiting*; *neuromyelitis optica*; *aquaporin-4 antibody*; *area postrema*

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A 22-year-old African-American woman who was 3 months post-partum presented with 2 months history of intractable hiccups and vomiting. She had four emergency room visits at various hospitals. Evaluation revealed normal blood counts and metabolic profile. She was never admitted. She was prescribed various anti-emetics, including thorazine, and advised to follow up with a gastroenterologist. Her initial examination was unrevealing.

On her fifth presentation, she was admitted to our hospital for intractable hiccups and a new complaint of drooling and trouble swallowing. She admitted a weight loss of 20 pounds in 2 months. The patient was hemodynamically stable. On physical examination, the patient looked thin and was constantly having hiccups. Oral examination was normal. Abdominal exam was unremarkable. No neurological deficits were noted. Routine laboratory showed that she had normal liver, kidney, thyroid functions, and cell counts. CT scan of the neck was normal, ruling out mechanical obstruction causing drooling and dysphagia. Myasthenia gravis was considered with bulbar muscle involvement. Serologies, including acetylcholine receptor antibodies, were subsequently negative. Neurologic consultation noted vertical nystagmus. MRI of the brain (T2-weighted and FLAIR) showed a hyperintense non-enhancing lesion in the posterior medulla as well as a hyperintense lesion in the splenium of corpus callosum (Figs. 1 and 2). However, these two lesions were distinct in nature. The medullary lesion was not visible on diffusion-weighted MRI image while the splenial lesion was clearly visible (Fig. 3). This led to further diagnostic dilemma. Lumbar puncture revealed cerebrospinal fluid having pleocytosis with lymphocytic predominance (WBC 160, lymphocytes 96%, monocytes 3%, and neutrophils 1%). No evidence of infections such as tuberculosis, HIV, listeria, herpes simplex, Cryptococcus, histoplasmosis, Lyme, infectious mononucleosis, and West Nile Virus was present. CSF angiotensin-converting enzyme level (for sarcoidosis) was normal. There were a total of three oligo-clonal bands in the cerebrospinal fluid (reference range zero) with zero bands in serum. CSF flow cytometry was negative for lymphoma. MRI of the spine did not reveal any lesions.

The patient was started on methyl prednisone (1 g/day) for possible multiple sclerosis (MS). Due to lack of response on day 4, neuromyelitis optica-spectrum disorder

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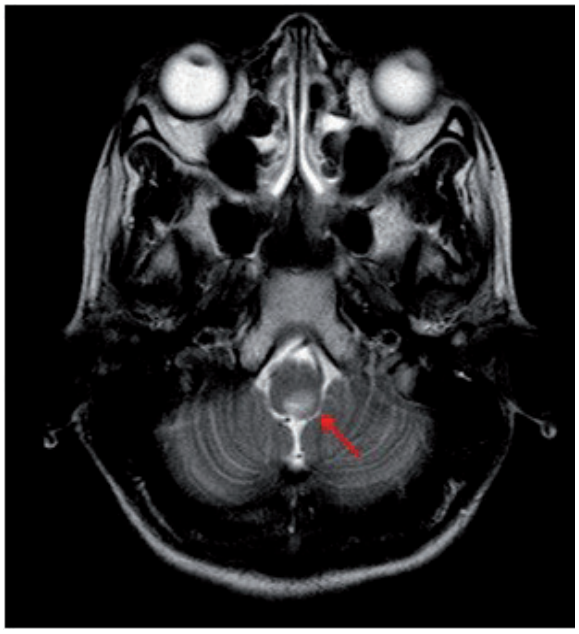


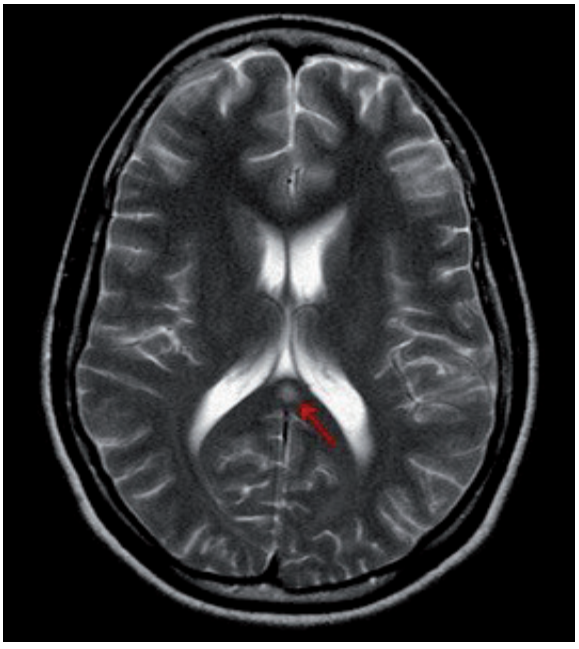
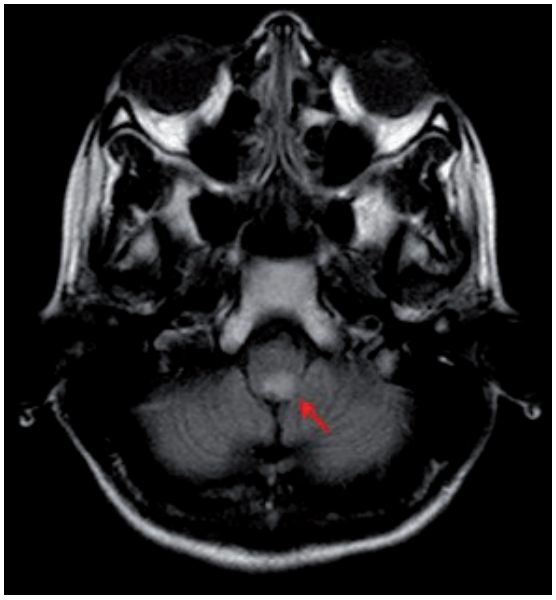


Fig. 1. T2-weighted MRI of the brain shows hyperintense lesion in the dorsal medulla and in the splenium of corpus callosum.



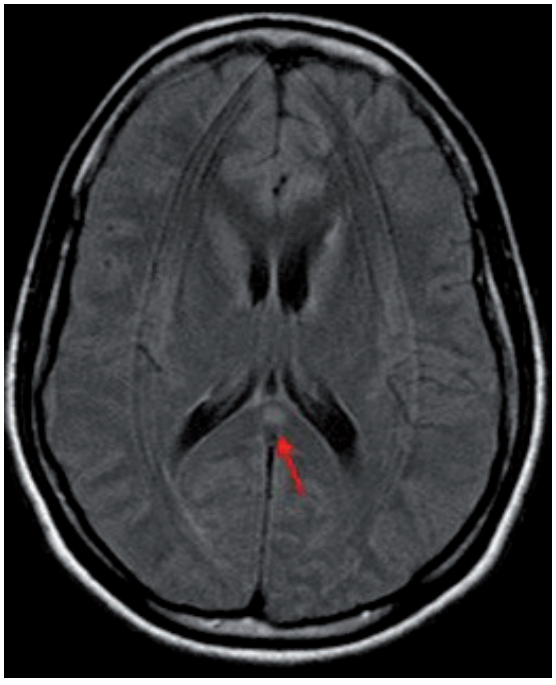


Fig. 2. Axial FLAIR MRI sequence of the brain again shows hyperintense lesion in the dorsal medulla and in the splenium of corpus callosum.

(NMO-SD) was considered as was vasculitis causing stroke or CNS Bechet's disease. A CT angiogram of the brain was normal. Autoimmune workup showed strongly positive Sjogren's antibody (SS-A: 163 units) and weakly positive ANA (1:160). She did not have any sicca symptoms like dry eyes or mouth; hence, CNS Sjogren's was less likely. She was started on IV immunoglobulins (0.4 g/kg/day) for 5 days for potential NMO-SD. NMO antibody levels of blood and CSF were sent out. After two cycles of IV immunoglobulins, her hiccups and vomiting had subsided. Her secretions were decreasing. A PEG tube was placed due to oropharyngeal dysfunction on barium fluoroscopy. Rituximab (1 g infusion) was added to her regimen. NMO titers with ELISA testing were subsequently positive (9.9 Units/ml) (Table 1). A repeat MRI showed resolution of splenial lesion with persistent medullary lesion. A repeat lumbar puncture showed improvement: WBC 79, lymphocytes 99%, neutrophils 1%, and zero oligoclonal bands. The midline splenial lesion was suspected to be posterior reversible encephalopathy syndrome (PRES),

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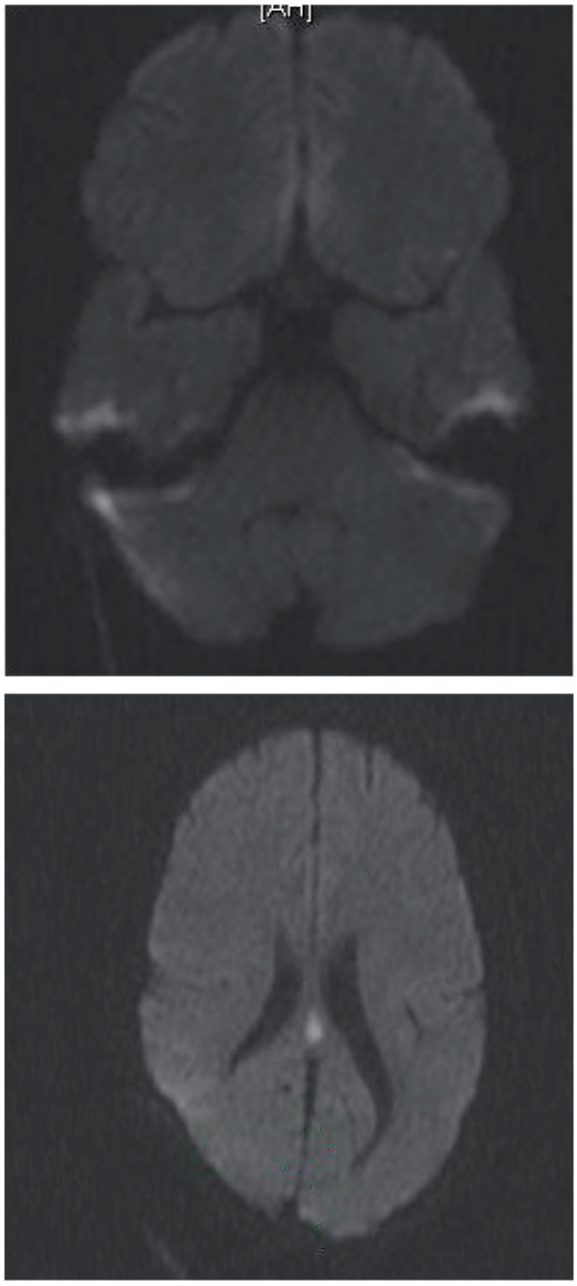

Fig. 3. Diffusion-weighted MRI of the brain shows the presence of the lesion in the splenium; however, it does not show the lesion in the dorsal medulla seen on T2 and FLAIR images. This shows that the two lesions are distinct in their etiology.

which has been associated with NMO. A diagnosis of NMO-SD with isolated medullary involvement without optic neuritis and transverse myelitis was made. She completed two cycles of rituximab. At her 1 month follow-up her dysphagia had significantly improved.

Discussion

Intractable nausea and vomiting along with hiccups is a commonly encountered problem on any general medicine or gastroenterology service. These symptoms are usually not appreciated as the possible initial manifestation of NMO. Diagnostic criteria for NMO were initially published in 1999, with revised criteria in 2006 making it an entity distinct from MS (Table 2). The criteria included the presence of both optic neuritis and transverse myelitis as an absolute requirement for the diagnosis of NMO. New insights into this disease are being made.

The prevalence of NMO in various parts of the globe ranges from 0.5 to 5/100,000. The basic pathophysiology of NMO is the development of antibodies against aquaporin-4 channels in the central nervous system. Aquaporin-4 channels are predominantly expressed on optic nerves, subpial and subependymal area, hypothalamus, immediate periventricular regions, and gray matter of the spinal cord. Recently, the area postrema (vomiting center) in the medulla has been identified as another important area rich in these channels. It lacks a blood brain barrier which is why antibodies may gain access to the central nervous system at this site and cause symptoms described in this report. Consequently, this may be the first target in NMO (1). As in this case, early MRI imaging shows a discrete lesion in the area postrema. With the increase in awareness there have been very few case reports of intractable hiccups and vomiting as initial presentation of NMO (2). Iorio et al. recently reported recognition of intractable vomiting as the heralding symptom

Table 1. Summary of various CSF and serum tests

CSF studies	
WBC 160 with 90% lymphocytes	
Oligoclonal bands: 3	
Tuberculosis, HIV, listeria, herpes simplex, Cryptococcus, histoplasmosis, Lyme, infectious mononucleosis, West Nile Virus.	Negative
Angiotensin-converting enzyme level	
Flow cytometry	
Serologies	
Acetylcholinesterase receptor blocking and modulating antibodies	Negative
Aquaporin-4 (NMO) antibody, Sjogren's antibody, ANA	Positive

Table 2. Diagnostic criteria of NMO

Absolute criteria (all required)

1. Optic neuritis
2. Transverse myelitis

Supportive criteria (any two or three should be present)

1. Negative brain MRI at onset
2. Spinal cord MRI with contiguous T2-weighted signal abnormality extending over three or more vertebral segments
3. NMO IgG seropositivity

of NMO in 12% (8/69) of patients (3). These patients underwent unrevealing investigations by internists and gastroenterologists.

In 2007, the term NMOSD was introduced to include AQP4-IgG-seropositive patients with limited or commencing forms of NMO (e.g., first-attack LETM or recurrent or bilateral optic neuritis) who were at high risk for future attacks. However, still at that time area postrema lesions causing intractable vomiting and hiccups were not well recognized.

The presence of two different natures of brain lesions created further diagnostic dilemma. PRES has been reported in association with NMO (4). Usually PRES involves bilateral cerebral hemispheres; however, it may be central involving the splenium. These two different lesions may illustrate the dual nature of the pathogenesis of brain lesions in NMO: functional changes in brain water channels and blockade of water flux from the CNS leading to symmetric cerebral vasogenic edema vs. inflammatory attack of target aquaporin-4 leading to areas of persistent T2 signal abnormality and possibly focal neurologic signs at the other extreme (4).

Misdiagnosis has been frequently observed in NMO. MS is a common misdiagnosis in NMO. These diseases have common demographic namely young females. This can lead to grave disability since NMO is treated by immunosuppressant therapy while MS is treated by immunomodulation. Immunomodulators such as interferon b, natalizumab, and fingolimod that are used in MS have shown to worsen NMO (5). We have tried to show important differences between NMO and MS that may help general clinicians distinguish them (Table 3).

The patient in our report was 3 months post-partum. Post-partum period is a particularly high-risk time for initial presentation of NMO especially the first 3 months post-partum (6). This finding justifies close medical monitoring of females in early post-partum for any symptom suspicious of NMO.

Our patient had positive titers of Sjogren's antibody without clinical picture of Sjogren's syndrome. It is important to note that presence of SSA-Ab is highly associated with seropositivity for aquaporin antibody in patients with NMOSD (7). This may cause misdiagnosis as CNS Sjogren's syndrome if not appropriately investigated for NMO.

Both, optic neuritis and transverse myelitis should be present per the revised diagnostic criteria of NMO. However based on recent case studies, it is important to note that it is now being recognized that brain stem lesions may antedate other neurologic involvement by months to years (8). Early diagnosis from the clinical picture aided by serologic testing is extremely important to allow early initiation of immunosuppressive therapy. Immunosuppression gives an opportunity to modify the disease at an earlier stage rather than waiting for evolution of disease to fulfill the diagnostic criteria of NMO. Studies have shown

Table 3. The distinguishing characteristic features of NMO and MS

	Neuromyelitis optica	Multiple Sclerosis
Basic pathophysiology	Antibody-mediated disease with astrocytolysis	T cell-mediated demyelination
Antibodies	Aquaporin-4 (AQP-4)	No antibodies present
Cross reactive antibodies	SLE and Sjogren's antibodies frequently present and may cause misdiagnosis	None
Population affected	More common in non-whites but any population group affected	More common in whites, less common in Asia and tropical climates
Sex (F:M)	9:1	2:1
Symptoms	Symptoms correlate well with specific lesion in the CNS	Subjective complaints and objective signs that frequently are not attributable to one specific lesion in the CNS
Severity of symptoms	Symptoms more severe in an NMO attack	Symptoms are mild in an MS attack. They can be cumulative in repeated attacks
Disabilities	Disabilities can arise from single acute attack with irreversible tissue destruction	Disabilities may arise from single acute attack with reasonable recovery
Affected areas in CNS	Optic nerve, spinal cord, area postrema, periventricular, and subependymal regions (rich in aquaporin receptors)	Supratentorial (periventricular, callososeptal, juxtacortical area) and infratentorial (multiple cranial nerves, cerebellum) and spinal cord
Oligoclonal bands presence	15–30%	85%
Radiologic characteristics	Lesions on MRI can be patchy, extensive, or confluent involving three or more vertebral segments	Lesions are linear or ovoid rarely continuous as in NMO
Treatment	Immunosuppressive agents	Immunomodulating agents (can worsen NMO)

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that 50% of untreated patients are blind in one or both eyes or confined to a wheelchair within 5 years of disease onset (9).

The NMO of today represents a relapsing spectrum of disease that is not necessarily restricted to the optic nerves and spinal cord and is very different from the monophasic disorder in which near simultaneous bilateral optic neuritis and transverse myelitis occur as was originally described. Aquaporin-4 antibody provides helpful prognostic information for patients presenting with a first-ever attack of NMO as they have a high relapse rate. In one study in patients presenting with transverse myelitis, seropositive patients have a greater than 50% risk of myelitis relapse or conversion to NMO over the subsequent 12 months (10).

A curative treatment for NMO does not exist to date. The main treatment goals are: 1) remission and improvement of relapse-associated symptoms, 2) long-term stabilization of disease course by means of relapse prevention. The treatment of acute attacks is methylprednisone (1 g/kg) for 5 days (11). If no improvement is seen then a trial of plasma exchange or IV IgG can be considered. As NMO takes a relapsing course in most cases, with often incomplete recovery and rapid accumulation of neurological deficits, long-term immunosuppressive treatment should be initiated once the diagnosis of NMO has been confirmed. Data on the long-term treatment (5 years) of NMO are limited, all retrospective, and mainly concern rituximab and azathioprine. Rituximab and azathioprine are currently the most widely used first-line therapies in NMO (11). Rituximab treatment can be given using either of two different regimens: two 1 g infusions of rituximab at an interval of 2 weeks or four weekly 375 mg/m^2 applications. Because most patients remain B-cell deficient for 6 months after rituximab treatment, re-dosing every 6 months is considered to be an adequate retreatment frequency. The second line agents for immunosuppression are mycophenolate mofetil, mitoxantrone, and methotrexate based on smaller case studies.

The International Panel on NMO Diagnosis is currently revising the diagnostic criteria of NMO/NMOSD, but a general consensus among NMO experts is that AQP4 antibody-positive patients can be diagnosed with NMO/NMOSD if they have one core clinical manifestation of NMO/NMOSD such as severe optic neuritis, longitudinally extensive transverse myelitis, and some brain stem symptoms unique to NMO/NMOSD, and there are no better explanation than NMO/NMOSD. Experts also agree that AQP4 antibody seropositivity alone without typical clinical features does not suffice the diagnosis.

Conflicts of interest and funding

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