Area Postrema Syndrome Presenting as Intractable Hiccups and Vomiting: An Isolated Initial Manifestation of Aquaporin-4 Positive Neuromyelitis Optica Spectrum Disorder – A Case Report

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a potentially disabling autoimmune inflammatory disease of the central nervous system that is marked by the occurrence of recurrent attacks in the optic nerves, spinal cord, brainstem, and periventricular regions. Persistent nausea, vomiting and hiccups are one of the central clinical features of NMOSD, which is often misdiagnosed due to gastrointestinal symptoms being nonspecific, and termed area postrema syndrome (APS).

Case Presentation: A 30-year-old woman presented with three weeks of intractable hiccups and persistent vomiting, but no neurological deficits. The gastrointestinal investigations were normal except for significant length. Brain magnetic resonance imaging (MRI) revealed a hyperintense lesion on T2-weighted images in the area of the dorsal medulla and involving the area postrema. Immunoglobulin G (IgG) aquaporin-4 (AQP4) was strongly positive in serum testing. MRI of the spinal cord and ophthalmological examinations were normal. The patient had the initial symptoms of NMOSD as isolated APS. The complete clinical recovery observed at 12 months follow-up was obtained with high dose intravenous methylprednisolone and oral corticosteroid taper plus rituximab.

Conclusion: APS could be the first and the purest form of AQP4-positive NMOSD. Early diagnosis and immediate immunotherapy are key to avoid permanent neurological damage. In a patient with unknown persistent hiccups, vomiting post exclusion of gastrointestinal causes, NMOSD should be considered.

Keywords: Neuromyelitis optica spectrum disorder; Area postrema syndrome; Aquaporin-4 antibody; Intractable hiccups; Vomiting; Brainstem; Case report

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, serious autoimmune inflammatory disorder of the central nervous system (CNS) primarily targeting the optic nerves, spinal cord and

specific areas of the brain. The disease is marked by periodic attacks of inflammation caused by pathogenic immunoglobulin G (IgG) antibodies against aquaporin-4 (AQP4), the major water channel protein found on astrocytic end-feet. The identification of AQP4-IgG has transformed the knowledge of NMOSD from a diagnosis of exclusion to a diagnosis made by serological testing and has also helped to differentiate NMOSD from multiple sclerosis. If treatment is not provided in a timely fashion, persistent immune-mediated astrocyte injury results in activation of the complement system, secondary demyelination, neuronal damage, and progressive neurological dysfunction (1).

APS has now been identified as one of the 6 essential clinical features in the 2015 International Consensus Diagnostic Criteria for NMOSD. The area postrema is an extremely specialized circumventricular structure situated in the dorsal medulla in the floor of the fourth ventricle. It is the only region of CNS that does not have a blood brain barrier and it contains high levels of aquaporin-4 channels, which is why it is so vulnerable to circulating AQP4 antibodies. When there is autoimmune inflammation of this region, the central emetic pathways are impaired, leading to chronic nausea, recurrent vomiting and intractable hiccups, often unhelpful by classical gastrointestinal treatment (2).

Gastrointestinal symptoms of APS can occur before classic neurologic symptoms, like optic neuritis or longitudinally extensive transverse myelitis. As a result, affected individuals often have repeated gastrointestinal evaluations (abdominal imaging, endoscopy), before neurological evaluation is considered. This delay in diagnosis can further delay the time to starting immunotherapy and increase the risk of permanent neurological damage from new onset of disease activity. Clinicians involved in emergency medicine, gastroenterology, and/or neurology therefore need to be aware of the possibility of an isolated presentation of APS.

The typical appearance in MRI is T2-weighted hyperintense lesions of the dorsal medulla around the fourth ventricle, and the ability to detect AQP4-IgG in the serum offers a highly specific confirmation of the diagnosis of NMOSD. High dose corticosteroid followed by long term immunosuppressive treatment, such as rituximab or other targeted biological therapy, has been demonstrated to achieve a decrease in relapse rates and neurological response in the long term (3,4).

This patient's first clinical manifestation of AQP4-positive NMOSD was recurrent vomiting and persistent hiccups. This case emphasizes the need to think of autoimmune neurological disorders in patients with refractory gastrointestinal symptoms that are unexplained, and the value of early neuroimaging and serologic testing for early diagnosis and treatment.

Case Presentation

This woman, aged 30, complained of persistent nausea, recurrent vomiting and persistent hiccups of 3 weeks duration to the emergency department. The symptoms progressed and gradually worsened despite treatment with proton pump inhibitors, antiemetics and prokinetics that were prescribed locally at health care facilities. The vomiting was about 10-15 times a day, unrelated to feeding. The hiccups kept him from sleeping, eating, and living normally, and caused him to lose weight by himself, about 5 kg, in the previous three weeks. No history of fever, diarrhea, abdominal pain, hematemesis, vertigo, headache, visual disturbance, sensory deficits, bladder dysfunction or bowel incontinence was present and there was no history of gait instability.

There was no significant medical history apart from seasonal allergic rhinitis. There was no history of previous neurological disease, autoimmune disease, diabetes mellitus, hypertension, malignancy, or recent infection. There was no family history of autoimmune or neurological diseases. She reported not smoking or drinking any alcohol or recreational drugs.

The patient was admitted looking quite lethargic and slightly dehydrated but still conscious and alert. She had a blood pressure of 112/70 mmHg, a heart rate of 96 beats per minute, a respiratory rate of 18 breaths per minute, a temperature 36.8°C and 99% saturations on room air. General physical examination was normal including no lymphadenopathy, skin rash or peripheral oedema. The cardiovascular, respiratory and abdominal examinations were normal.

A neurological examination showed normal higher mental functions and speech. Cranial nerve examination revealed intact extraocular movements, normal visual fields, normal pupillary reflexes

and visual acuity. Hearing, gag reflex and palatal movement was intact, facial sensation and motor function were normal. There was no change of muscle tone, bulk or strength in all four limbs (Medical Research Council grade 5/5). Deep tendon reflexes were symmetrical and plantar responses flexor bilaterally. Sensory examination was normal – no loss of pain, temperature, vibration or proprioception. There was also no abnormality in cerebellar function and gait.

Laboratory tests showed a mild hypokalemia (3.2 mmol/L), probably due to the repeated vomiting, and were otherwise within normal range including complete blood count, renal and liver function tests, serum glucose, thyroid function tests, and serum calcium, vitamin B12 and inflammatory markers. Gastroesophageal endoscopy revealed normal esophagus, stomach and duodenum with no evidence of ulceration or obstruction. Abdominal ultrasound and contrast enhanced computed tomography were normal.

Due to the continuing symptoms in the gastrointestinal tract, with no obvious cause, magnetic resonance imaging (MRI) of the brain was done. T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences revealed a focal hyperintense area of the dorsal medulla at the area postrema adjacent to the floor of the fourth ventricle with no significant mass effect or hemorrhage. This radiological pattern is suggested as typical of area postrema syndrome in the context of neuromyelitis optica spectrum disorder (5,2). The MRI of the cervical and thoracic spine did not show the presence of longitudinally extensive transverse myelitis or other demyelinating lesions.

No fundoscopy, visual field examination, optical coherence tomography or visual evoked potentials were performed to exclude optic neuritis. CSF showed mild lymphocytic pleocytosis (5 cells/mm^3) and slightly elevated CSF protein concentration (58 mg/dL) with CSF glucose levels normal. No oligoclonal bands were found, which ruled out multiple sclerosis (6).

Given the typical MRI findings, serum work-up for autoimmune demyelinating diseases was ordered, using a live cell-based assay. Anti-Aquaporin-4 (AQP4-IgG) antibodies were strongly positive and anti-myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) were negative. Other autoimmune markers were negative, such as antinuclear antibodies, anti-double-stranded DNA antibodies, extractable nuclear antigen profile, rheumatoid factor and antiphospholipid antibodies. The patient met the 2015 International Consensus Diagnostic Criteria for AQP4-positive NMO spectrum disorder (1) based on the presence of isolated area postrema syndrome, characteristic dorsal medullary MRI abnormalities and positive AQP4-IgG serology.

Immediately after the onset of the treatment was started with intravenous administration of methylprednisolone (1 g/day) for five consecutive days followed by an oral taper. Clinical improvement was noticed within 72 hours, vomiting rate decreased and hiccups gradually disappeared. At the conclusion of the corticosteroid treatment, the child was able to eat without symptoms. Given the high risk of relapse in AQP4-positive NMOSD, maintenance immunotherapy with rituximab (1000 mg intravenous infusion on days 1, 15 and every 6 months) was started as recommended (7,8).

No area postrema syndrome, optic neuritis, transverse myelitis or other NMOSD symptoms were observed at follow-up visits after 1, 6 and 12 months. A follow-up brain MRI showed almost complete resolution of the dorsal medullary lesion and the patient's Expanded Disability Status Scale (EDSS) score remained 0, representing full function recovery.

Investigations

Initial laboratory testing was done to rule out gastrointestinal, metabolic, infectious, and inflammatory causes for the patient's ongoing complaints of nausea, vomiting, and intractable hiccups. All complete blood count, liver function test, renal function test, serum electrolytes, fasting blood glucose, thyroid function test and serum calcium levels were within normal range. Blood tests were also performed, with the erythrocyte sedimentation rate (ESR) slightly elevated at 28 mm/hour but the C-reactive protein (CRP) was normal, meaning there was no major systemic inflammation.

Table 1. Initial Laboratory Investigations

Investigation	Result
Complete blood count	Normal
Liver function test	Normal

Renal function test	Normal
Serum electrolytes	Normal
Thyroid function test	Normal
ESR	Mildly elevated (28 mm/hour)
CRP	Normal

The upper gastrointestinal endoscopy revealed normal oesophageal, gastric and duodenal mucosa with no evidence of peptic ulcer disease, gastritis, gastric outlet obstruction and malignancy. Abdominal ultrasound and computed tomography (CT) scan of the abdomen showed no structural abnormality of the liver, pancreas, gall bladder, kidneys or gastrointestinal tract. With ongoing gastrointestinal evaluation and management, the patient's symptoms remained without explanation, so a neurological consultation was sought.

Brain MRI demonstrated a well-defined T2-weighted and fluid-attenuated inversion recovery (FLAIR) hyperintense lesion of the dorsal medulla at the area postrema adjacent to the floor of the fourth ventricle. The lesion was minimally enhanced with none of the diffusion restriction or hemorrhage. The imaging findings were very suggestive of area postrema syndrome, known as one of the classical clinical features of NMO spectrum disorder (NMO-SD) (5,2).

There were no findings of longitudinally extensive transverse myelitis or any other demyelinating lesions on MRI of the cervical and thoracic spinal cord. All ophthalmological examination was normal, including visual acuity testing, fundoscopy, optical coherence tomography and visual evoked brain potentials, excluding optic nerve involvement.

Lumbar puncture was then performed to obtain cerebrospinal fluid (CSF) for analysis. CSF was clear and colorless, and showed mild lymphocytic pleocytosis (5 cells/mm^3) and slightly elevated protein concentration (58 mg/dL), but the glucose concentration was normal. The lack of oligoclonal bands decreased the chances of multiple sclerosis (6).

Table 2. Cerebrospinal Fluid Findings

Parameter	**Result**
Appearance	Clear
White blood cells	Mild lymphocytic pleocytosis
Protein	Mildly elevated
Glucose	Normal
Oligoclonal bands	Negative

The serum autoantibody test was conducted based on the characteristic brain MRI, and a live cell-based immunofluorescence assay was used. Myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) was negative while aquaporin-4 immunoglobulin G (AQP4-IgG) was strongly positive. All other autoimmune tests were negative (antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA) and extractable nuclear antigen (ENA) profile).

Table 3. Autoimmune Serological Investigations

Test	**Result**
Aquaporin-4 IgG	Strongly Positive
MOG-IgG	Negative
ANA	Negative
Anti-dsDNA	Negative
ENA Profile	Negative

The patient met the 2015 International Consensus Diagnostic Criteria for AQP4-positive Neuromyelitis Optica Spectrum Disorder (1) in the context of isolated area postrema syndrome, typical dorsal medullary MRI abnormalities, and positive AQP4-IgG serology.

Differential Diagnosis

The patient's long-term gastrointestinal symptoms led to the consideration of a number of non-neurological diseases. Acute gastroenteritis, peptic ulcer disease, gastroparesis, gastroesophageal reflux disease, metabolic and vestibular disorders were among the differential diagnoses. These conditions

were however unlikely, because the patient did not respond to standard antiemetic treatment and the normal gastrointestinal endoscopy, abdominal imaging, and laboratory investigations.

Neurological causes were then taken into account. Because of the lack of evidence for acute ischemia on DW MRI, brainstem infarction was excluded. Multiple sclerosis was suspected but was less likely due to lack of typical periventricular lesions, CSF oligoclonal bands and AQP4-IgG antibody positivity. The absence of a MOG-IgG serology excluded myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Other considerations included brain stem tumor and paraneoplastic syndromes, which were ruled out by the MRI, lack of systemic abnormalities, and the absence of malignancy-related laboratory abnormalities.

Ultimately, the diagnosis of AQP4-positive neuromyelitis optica spectrum disorder (1,7) was made, based on isolated area postrema syndrome, typical dorsal medullary MRI findings, and a strongly positive AQP4-IgG antibody test result.

Treatment

Once a diagnosis is confirmed, acute immunotherapy was started with intravenous methylprednisolone 1g/day for 5 days as first-line treatment for acute NMOSD attacks (7,9). Patients began to show clinical signs of improvement on the third day of therapy, when their vomiting decreased in frequency and their persistent hiccups resolved. At the end of corticosteroid treatment, the patient was able to eat solid food without difficulty and nausea had completely disappeared.

The patient was then discharged on a slowly weaning dose of oral prednisolone for three months, to reduce the likelihood of early relapse. Given the frequent reoccurrence rate of AQP4-positive NMOSD, maintenance treatment with Rituximab was started. The two doses of Rituximab were given as 1,000 mg intravenous infusion two weeks apart, then at six-month intervals as per standard treatment guidelines (9,10).

Supplemental therapy consisted of intravenous fluids to replace losses due to dehydration, antiemetic agents for symptomatic treatment, proton pump inhibitors (PPIs) to provide gastric protection during corticosteroid therapy, and electrolyte replacement for mild hypokalemia from vomiting.

Outcome and Follow-Up

Throughout the hospital stay, the patient's clinical condition continued to improve and she was discharged in a stabilized condition, with the resolution of all the symptoms of nausea, vomiting and hiccups. She was totally asymptomatic and returned to her baseline activities at 1 month follow-up.

A follow-up brain MRI six months after treatment revealed no new inflammatory abnormalities and near-complete resolution of the dorsal medullary lesion. Follow-up visits were made at regular intervals and serial neurological examination remained normal.

During the 12 months' follow-up period, the patient had no further case of area postrema syndrome, optic neuritis, transverse myelitis, or other signs of neuromyelitis optica spectrum disorder. Her visual function remained normal, spinal MRI continued to show no evidence of myelitis and there were no complications noted with the treatment. The Expanded Disability Status Scale (EDSS) functional assessment stayed at 0 (no disability/100% neurological recovery). The diagnosis was made early and the treatment with immunotherapy started in time and was effective, allowing the prevention of disease progression and a very good prognosis in the long-term.

Discussion

Neuromyelitis optica spectrum disorder (NMOSD) is a profound autoimmune astrocytopathy that affects recurrently the optic nerves, spinal cord, brainstem and certain periventricular areas of the central nervous system (CNS). Since the discovery of aquaporin-4 immunoglobulin G (AQP4-IgG), the disease is known as a separate clinical entity and not a subpopulation of multiple sclerosis. Neurological dysfunction is caused by the autoantibody-induced damage of astrocytes leading to complement activation, inflammatory cell infiltration and secondary demyelination. Recurrent attacks can cause irreversible disability if diagnosed too late, which is especially important for the early diagnosis (11,12).

Area postrema syndrome (APS) is among the six main clinical features of the 2015 International Consensus Diagnostic Criteria for NMOSD. APS is defined clinically as chronic nausea, vomiting and

inexplicable hiccups that persist for more than 48 hours, for which there is no obvious gastrointestinal cause. APS has been increasingly acknowledged, but is underdiagnosed because it is a clinical presentation that is very similar to common gastrointestinal disease. Patients are therefore often subjected to multiple gastrointestinal evaluations prior to neurological evaluation (13).

This is a problem with diagnosis that is illustrated in the present case. Our patient had gastrointestinal symptoms in isolation, without visual impairment, sensory deficits, weakness of the limbs or involvement of the spinal cord. Further investigations of the gastrointestinal tract, including upper gastrointestinal endoscopy and imaging of the abdomen, did not reveal a cause. Magnetic resonance imaging was performed only after a prolonged follow-up period of unsuccessful conventional therapy, and showed a typical dorsal medullary lesion. A serum AQP4-IgG was subsequently seen, which confirmed the diagnosis of AQP4-positive NMOSD in its exclusive area postrema form. This is a reminder that having a wide differential diagnosis is important when patients present with refractory vomiting and hiccups without an obvious cause.

The selective involvement of the area postrema in NMOSD is possible based on special anatomical and physiological properties. The area postrema is considered to be one of the circumventricular organs, which is devoid of a complete blood brain barrier and therefore AQP4 antibodies can directly contact astrocytes. In addition, a high density of aquaporin-4 channels is present in this area of the central nervous system. Complement activation by antibody binding allows the destruction of astroglia, leading to regional inflammation and neural pathway disruption of emesis and diaphragmatic reflexes. This mechanism accounts for the fact that sustained nausea, vomiting and hiccups can precede more common neurological symptoms by weeks or months (14,15).

Another pertinent point in this case is that he did not present with optic neuritis or longitudinally extensive transverse myelitis. Past observations suggested that these symptoms were important characteristics of the disease of neuromyelitis optica, but recent research has led to a realization that isolated brainstem involvement was a well-recognized subset of the NMOSD spectrum. There are several observational studies that have proven that patients who begin with APS often get optic neuritis or myelitis during subsequent relapses if disease-modifying immunotherapy is not started in a timely fashion. Thus, early detection of isolated APS offers a valuable opportunity for prevention of neurological disability in the future (16).

MRI still plays a crucial role in the evaluation of patients with a suspected diagnosis of APS. Dorsal medulla lesions adjacent to the fourth ventricle which demonstrate hyperintensity on T2-weighted and FLAIR are highly characteristic. In contrast to ischemic infarction or neoplastic lesions, inflammatory lesions that develop in the context of NMOSD tend to have minimal mass effect, with significant improvement after corticosteroid treatment. Follow-up MRI in this case showed almost complete resolution of the medullary lesion following immunotherapy, which was consistent with the inflammatory nature of the lesion and with complete clinical resolution (17).

Due to its high specificity, serological testing for AQP4-IgG has become the mainstay of the diagnosis of NMOSD. Cell-based assays have better diagnostic accuracy than previous immunofluorescence assays and are helpful in distinguishing from multiple sclerosis (MS) and from antibody to myelin oligodendrocyte glycoprotein (MOGAD). Strongly positive AQP4-IgG and negative MOG-IgG and the absence of CSF oligoclonal bands ruled out these other demyelinating diseases in our patient. Correct serological classification is important since the treatment and prognosis are markedly different between these diseases (18).

The patient responded very well to the high dose of intravenous methyl prednisolone along with maintenance rituximab. Corticosteroids are effective at quickly suppressing the acute inflammatory component of the disease and are the recommended first-line drugs for acute NMOSD attacks. The monoclonal antibody against CD20-positive B lymphocytes, rituximab, has been consistently shown to be effective at significantly reducing relapse rate and disability progression through its ability to limit the production of pathogenic AQP4 antibodies. The newer biological therapy agents that target complement activation, IL-6 signaling, and B-cell depletion agents, such as eculizumab, satralizumab

and inebilizumab, are also emerging as evidence-based treatments, especially for the relapsing form of the disease in patients with AQP4 receptor antibody-positive disease (19).

Physicians outside neurology must be more aware of this important learning point of this case. Autoimmune neurological disorders are often not suspected during the initial evaluation, especially when evaluating patients who have persistent nausea and vomiting complaints, who are seen by gastroenterologists, emergency physicians, and general internists. If vomiting or hiccups persist after thorough gastrointestinal work-up, even when they are responding to conventional treatment, early neurological consultation should be considered, particularly if they persist beyond a few days. Rapid brainstem and AQP4-IgG testing can significantly narrow the diagnostic delay, and prevent permanent neurological damage.

This report is on the successful clinical management but has some limitations. It is not a study of prevalence or causal relationships between imaging finding and clinical outcomes, and therefore can only be seen as one case. Moreover, long-term follow-up beyond one year is required as relapses can happen several years after diagnosis even with immunosuppressive therapy. However, this case adds to the evidence for isolated area postrema syndrome as an early sign of AQP4-positive NMOSD and reminds us that the development of atypical neurological symptoms should be considered during routine clinical practice.

Conclusion

This case emphasizes the diagnostic value of the identification of area postrema syndrome as a very early and isolated presentation of aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. Persistent nausea, recurrent vomiting, and intractable hiccups are often seen and are thought to be gastrointestinal diseases, leading to large investigation efforts and delayed neurological evaluation. Because of the absence of optic neuritis, transverse myelitis, or other focal neurological deficits at presentation, this is another reason why misdiagnosis can occur. In the present case, the characteristic magnetic resonance imaging (MRI) findings associated with the dorsal medulla and the presence of serum aquaporin-4 (AQP-4) antibodies allowed a timely diagnosis of the disease, before the onset of irreversible neurological complications.

Rapid clinical improvement, complete radiological resolution, and sustained remission without relapse were observed at the 1-year follow-up for prompt initiation of high dose corticosteroid therapy followed by maintenance treatment with rituximab. This good result highlights the importance of early detection and prompt immunisation to avoid progression of the disease and chronic disability. Physicians should also have a high clinical suspicion for NMO in those who have unexplained persistent vomiting and hiccups when other common gastrointestinal causes have been excluded, especially those in emergency medicine, gastroenterology and general internal medicine. Raising awareness of this unusual presentation will lead to earlier diagnosis, help avoid unnecessary investigations and aid long term neurological prognosis with timely commencement of the correct disease modifying therapy.

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