A Missed Case of Area Postrema Syndrome Presenting with Neuromyelitis Optica Spectrum Disorder

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Patient: Female, 33-year-old
Final Diagnosis: Neuromyelitis optica
Symptoms: Altered mental status • ataxia • fever • hiccups • hypersomnolence • nausea • vomiting
Medication: —
Clinical Procedure: Aquaporin-4 antibody serological testing • cerebrospinal fluid analysis • electroencephalogram
Specialty: Gastroenterology and Hepatology • Neurology • Radiology

Objective: Rare disease
Background: Neuromyelitis optica spectrum disorder (NMOSD), which is also known as Devic disease, is a chronic disorder of the brain and spinal cord that includes inflammation of the optic nerve and spinal cord. Area postrema syndrome (APS) is due to involvement of the bulbar emetic reflex center, and has previously been described in NMOSD. Patients with APS may present with nausea, vomiting, or hiccups. This report is of a 33-year-old Asian American woman with history of APS who presented with NMOSD.

Case Report: A 33-year-old Southeast Asian woman, 2 months postpartum, presented with fever, hypersomnolence, altered mental status, and difficulty ambulating. Neurological examination revealed a lethargic woman with poor attention span, broad-based gait ataxia, and positive Romberg’s sign. Laboratory work-up showed sodium 123 milliequivalent/L (mEq/L). Brain magnetic resonance imaging (MRI) with contrast revealed bilateral, non-enhancing, patchy fluid-attenuated inversion recovery (FLAIR) hyperintensities in the anteroinferomedial thalamus extending to the mammillary bodies. Additional history revealed hospitalization for intractable nausea, vomiting, and hiccups 2 years ago. NMOSD was confirmed with positive AQP-4 antibody, prompting treatment with intravenous (i.v.) methylprednisolone, followed by plasmapheresis. Repeat brain MRI showed mild improvement of bilateral thalamic FLAIR hyperintensities and no clinical recurrence was reported with Rituximab treatment.

Conclusions: This case highlights the importance of the diagnostic diligence required for NMOSD diagnosis. Multiple etiologies can mimic the clinical presentation of acute diencephalic syndrome; thus, a broad differential needs to be considered. This report presents the diagnostic work-up and management of a patient with a complex neurological condition that was diagnosed as NMOSD.

Keywords: Aquaporin 4 • Area Postrema • Diencephalon • Neuromyelitis Optica • Wernicke Encephalopathy

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Neuromyelitis optica spectrum disorder has significant diagnostic complexity due to its myriad of clinical presentations. The spectrum of core clinical characteristics includes optic neuritis, longitudinally extensive transverse myelitis, area postrema syndrome, acute cerebral syndrome, acute brainstem syndrome, and acute diencephalic syndrome [1]. Each of these characteristics can be caused by a plethora of conditions; thus, a broad differential needs to be considered.

Prompt initiation of long-term immunosuppression is imperative to prevent progression and recurrence. Consequences of untreated NMOSD are dire, as 50% of cases develop residual deficits with chronic disability, while the mortality rate is 33% within 5 years of developing initial symptoms [2].

This report is of a 33-year-old Asian American woman with a history of APS who presented with NMOSD.

**Case Report**

A 33-year-old Southeast Asian woman, 2 months postpartum, actively breast-feeding, with a past medical history of chronic episodic migraines, experienced fever and sweats. Testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via polymerase chain reaction (PCR) and antibody was negative. The patient presented to the Emergency Department (ED) with a 7-day history of severe hypersomnolence, altered mental status, and difficulty walking. Her husband reported she had tangential thought patterns and flight of ideas. Four weeks previously, the patient went to her primary care physician, reporting nausea and diaphoresis, with a fever of 38.6°C. She had an abnormal urinalysis result, for which ciprofloxacin was initiated due to a suspected urinary tract infection (UTI) and she was also advised to adequately hydrate. She denied any current headaches, fever, and dizziness. She also denied a history of alcohol, smoking, and illicit drug use. Additionally, the patient denied recent vaccination or infection. Vital signs taken on arrival were blood pressure 123/92 millimeters of mercury (mmHg), heart rate 98 beats per minute, respiratory rate 18 breaths per minute, temperature 37.1°C, and SpO₂ 98% on room air. Cardiopulmonary examination results were within normal limits, except for sodium 123 mEq/L. Non-contrast brain computed tomography (CT) showed no signs of acute infarct, hemorrhage, or other intracranial abnormalities.

The patient was admitted and subsequent neuroimaging with brain MRI with contrast revealed bilateral, non-enhancing, patchy fluid-attenuated inversion recovery (FLAIR) hyperintensities in anteroinferomedial thalamus extending to the mammillary bodies (Figure 1). A provisional diagnosis of non-alcoholic Wernicke’s encephalopathy was made and the patient was empirically started on intravenous (i.v.) thiamine 500 milligrams (mg) 3 times daily. Her pre-infusion thiamine level was reported as 158 nanomoles/liter (nmol/L). Despite post-infusion thiamine levels reaching 1200 nmol/L, the patient remained symptomatic. Brain and neck magnetic resonance angiography without contrast showed no evidence of stenosis in the extra- or intracranial circulation. Brain magnetic resonance venography without contrast showed no thrombosis or hemodynamically significant stenosis, apart from a small left transverse sinus suspected to be a normal anatomical variant.

Electroencephalogram revealed mild diffuse slowing (7 Hertz) with no epileptiform discharges, intermixed with disorganized
and poorly sustained sleep architecture. Hypercoagulable pan-
el revealed low partial thromboplastin time (22.4 s) and high protein C (177). Autoimmune panel, human immu-
nodeficiency virus, and Mycobacterium tuberculosis were neg-
itive. Cerebrospinal fluid (CSF) opening pressure was within normal range (17 centimeters of water [cmH₂O]), while analy-
sis revealed red blood cell count 2 cells/millimeter³, nucleated cells 11 cells/millimeter³, lymphocytes 99 cells/millimeter³, pro-
tein 51 grams per deciliter (g/dL), albumin 27.9 g/dL, glucose 70 milligram per deciliter (mg/dL), lactate 2.6 mg/dL, and im-
umoglobulin G (IgG) 4.0 (serum IgG 922 mg/dL). No oligoclo-
bands were found and the IgG index was 0.5. Cerebrospinal fluid PCR for Cryptococcus, Enterovirus, Herpes simplex I/II, and Treponema pallidum were negative. On day 4 of admission, the hyponatremia improved with water restriction (sodium 135 mEq/L). She was started on modafinil 200 mg twice daily.

On re-interrogation of the patient, she revealed she had been hospitalized 2 years ago for intractable nausea, vomiting, and hiccups that lasted for 3 weeks. Esophagogastroduodenoscopy at that time revealed mild gastritis. Brain MRI with and without contrast revealed no acute ischemia, hemorrhage, or hydrocephalus. The symptoms self-resolved with no recurrence, and the underlying etiology remained undetermined. Based on this additional information, the suspicion of NMOSD was raised, for which serological work-up for AQP-4 antibodies was initiated. The AQP-4 immunoglobulin G (IgG) antibody test result came back positive and myelin oligodendrocyte glycopro-
tein (MOG) antibody was negative. Her current symptomatolo-
gy was consistent with acute diencephalic syndrome, a subset of NMOSD. A 5-day course of high-dose i.v. methylprednisolone sodium succinate treatment was initiated and modafinil was switched to armodafinil 250 mg once in the morning for per-
sistent hypersomnolence. The patient was given 5 sessions of plasmapheresis, which led to improvement in her altered men-
tal status and ataxia, but she remained symptomatic with hy-
personmnlence. After a discussion with the patient and fam-
ily regarding risks and benefits, and due to health insurance limitations, she was started on rituximab. At 3-month follow-
up, the patient reported no clinical flare-up despite remain-
ing symptomatic with hypersomnia. A repeat brain MRI with and without contrast showed mild improvement of the bilat-
eral thalamic FLAIR hyperintensities.

Discussion

Here we discuss an interesting and complex case of a 33-year-
old, Southeast Asian woman, 2 months postpartum, who pre-
covered with fever, hypersomnolence, altered mental status, and difficulty ambulating. We will be addressing the challeng-
es faced in the diagnosis and management of neuromyelitis optica spectrum disorder.

Neuromyelitis optica spectrum disorder continues to mesmerize physicians across various disciplines due to overlapping clinical manifestations. The diagnostic criteria for NMOSD have evolved over the last 2 decades [1]. The latest criteria, proposed by Wingerchuk et al in 2015, has increased NMOSD diagnostic sensitivit
ity by 76% by incorporating diverse clinical manifestations and radiological findings along with the AQP-4 antibody status [1,3].

Although our patient presented with features consistent with acute diencephalic syndrome, etiological diagnosis remained a challenge due to broad differentials (Table 1). Acute dienceph-
cephalic syndrome can present with varying combinations of symptoms including hypersomnia, ataxia, anorexia, inapprop-
riate diuresis, temperature dysregulation, and endocrinolog-
ical abnormalities, including secondary amenorrhea, galactor-
rhea, hyperprolactinemia, and hypothryroidism [4-6].

Excessive daytime sleepiness was the main presenting fea-
ture of our patient. Hypersomnia in NMOSD can present as both an isolated symptom or as part of acute diencephalic syn-
drome [7]. The pathogenesis involves damage to orexin neu-
rons along the central projections secondary to hypothalamic lesions, and is usually associated with low CSF orexin levels [7]. Pathological hypersomnia can be extremely disabling and refractory to treatment, as seen in our patient.

Another disabling symptom in our patient was broad-based gait ataxia, requiring 1-person assist. A neurological exami-
nation revealed positive Romberg sign and difficulty in per-
forming heel-to-shin, but she had intact finger-to-nose test-
ing and was absent specific cerebellar signs including scanning speech, nystagmus, and dysdiadochokinesia. Sensory ataxia can result from pathologies along the neuraxis at multiple lev-
els. The thalamus is vulnerable to insults from multiple etiolo-
gies and, being the main sensory relay station, this can cause severe sensory gait ataxia [8].

Our patient’s vital signs revealed a maximum temperature of 38.6°C, which was initially attributed to her urinary tract in-
fecion. Temperature dysregulation, as a symptom of acute diencephalic syndrome, can occur in NMOSD [9]. Inflammation around the preoptic nucleus of the hypothalamus, mediated by the AQP-4 antibody complex, can raise the set-point for core body temperature [9]. Fever of unknown origin with or with-
out other hypothalamic symptoms, especially in young wom-
en, should be investigated for NMOSD [9].

Our patient presented with moderate to severe hyponatremia (123 mEq/L), which was initially thought to be associated with psychogenic polydipsia. Significant hyponatremia has been well described in patients with NMOSD, both during the initial attack, as well during relapse, with 60.8% presenting with levels less than 125 mEq/L [10]. The pathogenesis of the hyponatremia...
is either dilutional via syndrome of inappropriate diuretic hormone secretion, or depletional via cerebral salt wasting syndrome [10]. These etiologies should be differentiated promptly to initiate appropriate treatment such as fluid restriction or resuscitation [10]. Our patient’s hyponatremia responded to water restriction and she was discharged on salt tablets.

Wernicke’s encephalopathy was the initial diagnosis considered due to our patient’s clinical and neuroradiological presentation. Our patient denied alcohol use, but did fulfill 2 of the 4 Caine’s criteria, with findings of ataxia and altered mental status [11]. Our patient’s brain MRI was reviewed by 2 independent American board-certified neuroradiologists, who raised the possibility of Wernicke’s encephalopathy as the primary diagnosis. Our group has previously reported isolated “pulvinar/hockey stick sign” in patients with non-alcoholic Wernicke’s encephalopathy [8]. Our patient did not respond to thiamine supplementation. Additionally, the pre-infusion thiamine levels available on day 4 of hospitalization were normal, refuting the possibility of non-alcoholic Wernicke’s encephalopathy.

Cerebral venous thrombosis (CVT) was another possible differential in our patient due to her potential hypercoagulable state and abnormal MRI FLAIR findings of thalamic hyperintensities. However, the absence of thrombosis and normal venous anatomy with congenital variation on magnetic resonance venography ruled out CVT in our patient.

Other differential diagnoses that were considered included site-restricted acute disseminated encephalomyelitis, myelin oligodendrocyte glycoprotein antibody disorders, extrapontine osmotic demyelination syndrome, and multiple sclerosis. These diagnoses were ruled out in our patient through appropriate history, physical examination findings, and relevant diagnostic testing.

Two years ago, our patient presented with a 3-week history of intractable nausea, vomiting, and hiccups of unexplained origin, that later subsided without treatment and recurrence. Brain MRI with contrast at the time was unremarkable, although no formal neurological or serological evaluation was pursued.

The area postrema, a circumventricular organ, is an emetogenic center found in the dorsal medulla, at the caudal end of the 4th ventricle [4,12,13]. The area postrema, unlike other areas of the brain affected by AQP-4 IgG antibodies, lacks

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**Table 1. Differential diagnoses of acute/subacute diencephalic syndrome.**

| Etiology                | Diagnosis                                                                 |
|-------------------------|---------------------------------------------------------------------------|
| Immune-mediated         | Atypical multiple sclerosis                                               |
|                         | Site-restricted acute disseminated encephalomyelitis (Pediatrics)         |
|                         | Neuro-Behcet’s syndrome                                                   |
|                         | Sjogren’s syndrome                                                        |
| Infectious              | Human immunodeficiency virus                                              |
|                         | Cytomegalovirus                                                           |
|                         | Cysticercosis                                                             |
|                         | Variant Creutzfeldt-Jakob disease                                         |
|                         | Influenza A                                                               |
|                         | Parainfluenza                                                             |
|                         | Mycoplasma pneumoniae                                                     |
|                         | John Cunningham virus (JC virus) (progressive multifocal leukoencephalopathy) |
|                         | Mycobacteria tuberculosis                                                  |
| Paraneoplastic/neoplastic| Anti-Ma2 encephalitis                                                     |
|                         | Craniopharyngioma                                                         |
|                         | Glioblastoma multiforme                                                   |
|                         | Gliomatosis cerebri                                                       |
|                         | Primary central nervous system lymphoma                                    |
| Metabolic               | Osmotic demyelination syndrome                                             |
|                         | Wilson’s disease                                                           |
|                         | Krabbe’s disease                                                           |
|                         | Fabry’s disease                                                            |
|                         | Gangliosidosis                                                             |
|                         | Fahr’s disease                                                             |
| Vascular                | Artery of percheron stroke                                                |
|                         | Meso-diencephalic syndrome                                                 |
|                         | Top of the basilar syndrome                                                |
|                         | Cerebral venous sinus thrombosis                                           |
|                         | Vein of Galen (infarct or arteriovenous fistula)                           |
|                         | Subacute diencephalic angioencephalopathy                                  |
| Nutritional             | Wernicke’s encephalopathy                                                 |
| Toxic                   | Carbon monoxide poisoning                                                  |
|                         | Chemotherapy/Radiation therapy                                             |
|                         | Lead poisoning                                                             |
| Multifactorial          | Paroxysmal autonomic instability with dystonia (PAID) syndrome             |
The treatment protocol for acute management for NMOSD includes high-dose steroids (1 g i.v. methylprednisolone daily, followed by oral prednisone taper) [2]. The acute treatment of acute diencephalic syndrome and area postrema syndrome follows similar treatment guidelines, with area postrema syndrome patients showing a more robust symptomatic response compared to other core subsets of NMOSD [14]. Plasmapheresis is the preferred immunomodulatory treatment for patients refractory to steroid treatment [2]. There have been recent advancements in the long-term management of NMOSD, with the approval of 3 immunomodulatory agents, including eculizumab (complement factor C5 inhibitor), inebilizumab (CD-19 inhibitor), and satralizumab (IL-6 receptor inhibitor) [15,16]. Rituximab has also shown a beneficial effect, with a relapse prevention rate of up to 67% [16]. Other commonly used immunosuppressants include azathioprine, mycophenolate mofetil, and tocilizumab [15]. Specific monoclonal antibodies, including ublituximab, which targets CD-20, and aquaporumab, which binds to AQP-4 directly, are in the early stages of development and require large-scale clinical trials before use in clinical practice [15]. In our patient, rituximab was the drug of choice, resulting in no clinical or radiological relapse for 4 months.

Approximately 50% of patients with untreated NMOSD are left with chronic disabilities such as wheelchair dependency [2]. The mortality rate is 33% within 5 years of a NMOSD attack in untreated patients [2]. In our patient, earlier diagnosis at the onset of area postrema syndrome and initiation of appropriate treatment could have prevented the development of acute diencephalic syndrome.

Conclusions

We presented a case of NMOSD in which lack of serological work-up on the initial presentation of intractable nausea, vomiting, and hiccups resulted in delayed diagnosis. Secondly, a broad differential needs to be considered due to a wide range of clinical entities associated with acute diencephalic syndrome. This case report has highlighted the need for increased awareness of NMOSD to be considered as a diagnostic possibility to prevent a potentially debilitating prognosis.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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