


CASE REPORT

Wernicke's encephalopathy precipitated by neuromyelitis optica spectrum disorder and Graves' disease: A tale of clinical and radiological dilemmas

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD), an autoimmune astrocytopathy, may share common clinico-radiological features with Wernicke's encephalopathy (WE). A variant of NMOSD, known as area postrema syndrome (APS), that presents with intractable hiccups and associated vomiting, might lead to the depletion of nutrients if not detected and treated early. Autoimmune thyroid disorders (i.e., Graves' disease) may be associated with NMOSD. Rarely, thyrotoxicosis can give rise to thiamine depletion and WE.

Case presentation: Here, we present a case of untreated hyperthyroidism in an Indian female who presented with thyrotoxicosis and later developed WE, possibly also contributed by NMOSD (APS)-induced recurrent vomiting. The patient recovered with antithyroid drugs, parenteral thiamine, and immunomodulatory therapy. The possible pathogenic mechanisms have been discussed.

Conclusion: Our case establishes the importance of considering NMOSD variants in metabolic encephalopathy, especially if neuroimaging is suggestive and in the backdrop of another autoimmune disorder.

KEYWORDS

area postrema syndrome, astrocytopathy, neuromyelitis optica, thyrotoxicosis, Wernicke's encephalopathy

1 | INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune astrocytopathy against aquaporin-4 (AQP4) water channels. Area postrema syndrome (APS) is an NMOSD variant characterized by recurrent intractable hiccups and vomiting.^{1,2} Acute brainstem

syndrome is another recently described variant that presents with disturbances of arousal, cranial nerve deficits, and neuroophthalmological syndromes.^{1,2}

Involvement of the periaqueductal region, mammillary bodies and dorsomedial thalamus are classically described in Wernicke's encephalopathy (WE).³⁻⁵ Nonalcoholic associations of WE may be

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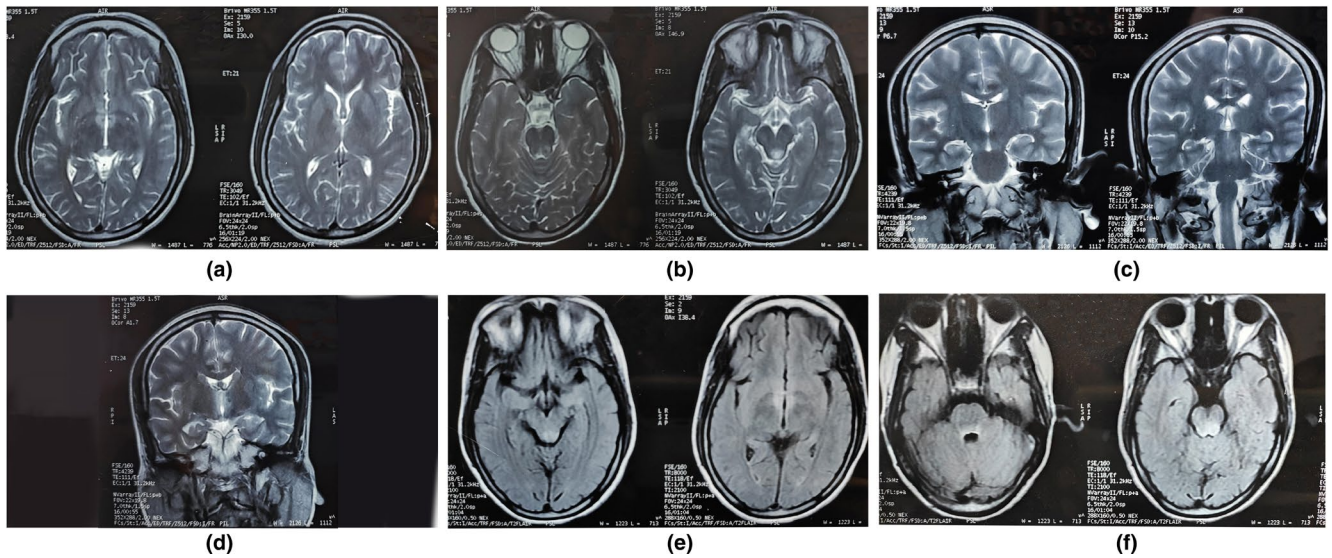


FIGURE 1 Brain MRI revealing nonenhanced hyperintensities on T2-weighted imaging (A–D) and fluid attenuated inversion recovery sequences (E,F) at the brainstem, periaqueductal regions, mammillary bodies, and ventromedial aspect of bilateral thalamus

dialysis-related thiamine loss, gastrointestinal surgery, malignancy, hyperemesis gravidarum,⁴ and, albeit rarely, hyperthyroidism.⁶

The authors herein report a case of a young Indian female who had inadvertently stopped treatment for hyperthyroidism and presented with a thyroid storm. During her course in the hospital, she was diagnosed with WE, likely precipitated by untreated hyperthyroidism and recurrent vomiting due to APS/NMOSD. With the reinstatement of antithyroid drugs, thiamine replenishment, and immunomodulatory therapy, she had an excellent recovery.

2 | CASE REPORT

A 38-year-old Indian female was brought to the emergency in an utterly confused mental state with behavioral abnormalities following episodes of intractable hiccups and vomiting for the past 18 days. According to her caregivers, she was diagnosed with hyperthyroidism 2 years previously and was prescribed carbimazole (30 mg/day) and propranolol (80 mg/day), which she discontinued without the physician's advice for the past year. She lost about 10 kg of weight and became lean recently (over the past 1 year). She also had unevaluated chronic loose stool for the past 4 months, excessive sweating, heat intolerance, palpitations, and irritability. On prompt initial evaluation, she had tachycardia (140 bpm, regular), tachypnea (22/min), moderate dehydration, cachexia (BMI 16.8 kg/m²), bilateral pitting pedal edema, faint bibasilar rales, fever (101°F), and altered and fluctuating sensorium. Bedside random capillary blood glucose was 148 mg/dL, and an arterial blood gas analysis revealed mild hyponatremia (Na⁺ 132mEq/L) and no acid-base disequilibrium. An emergent electrocardiogram ruled out cardiac arrhythmia and myocardial ischemia. Cardiac troponin-T, as well as SARS-CoV-2 RT-PCR, were negative. She had a visible goiter and features of Graves' ophthalmopathy. The initial

working diagnosis was thyroid storm precipitated by noncompliance and inadvertent stoppage of antithyroid medications. As per the caregivers' she had never suffered from any similar or other neuropsychiatric or cardiac illness previously and had no addictions (including alcoholism) or nonprescription drug use. She was kept on maintenance intravenous fluids, intravenous dexamethasone (16 mg/day), propranolol (80 mg/day), acetaminophen, low-dose ramipril (1.25 mg/day), and low-dose toremide (5 mg/day). Her thyroid profile revealed elevated unbound T3, unbound T4 levels and reduced serum TSH levels along with positive TRABS (TSI) anti-TPO and anti-TG antibodies suggestive of Graves' disease with thyrotoxicosis. She was put on carbimazole (45 mg/day), and her vitals and biochemical profile were continuously monitored. Complete blood count revealed neutrophilic leukocytosis and elevated erythrocyte sedimentation rate. Liver function tests showed mild elevation (<2 times ULN) of transaminases, reduced albumin (3.0 g/dL), and normal PT-INR. N-terminal pro-BNP was elevated. Serum electrolytes, calcium, magnesium, and 24-hour urinary free cortisol were within the normal range. Fasting and postprandial plasma glucose were 120 mg/dL and 188 mg/dL, respectively. HbA1c level was 6.3%. Blood and urine cultures and viral serology (HBV, HCV, and HIV-1,2) ruled out infectious etiologies. After 96 h of treatment, although her vital parameters got significantly stabilized, her sensorium showed no improvement. Brain magnetic resonance imaging (MRI) revealed nonenhanced hyperintensities on T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR) sequences at the brainstem, periaqueductal regions, mammillary bodies, and ventromedial aspect of bilateral thalamus without mass effect and diffusion restriction (Figure 1). Salient findings on neuroimaging, clinical course (chronic diarrhea, involuntary weight loss and untreated hyperthyroidism, behavioral abnormalities, and recurrent vomiting, followed by encephalopathy with normal electrolytes) and encephalopathic

changes in EEG pointed toward a diagnosis of Wernicke's encephalopathy (WE). A serum sample was sent for thiamine level estimation, and she was put on high-dose intravenous thiamine (1000 mg as starting dose [on day 6 of admission], 500 mg daily for the next 5 days, and then 100 mg/day). Serum thiamine level (HPLC) came out to be extremely low. After 72 h (day 9 of admission), her sensorium started showing some improvement, and by day 5 (day 11 of admission), she was fully conscious and oriented to time, place, and person. At this point, her detailed neurological examination revealed anterograde amnesia, affect problems, infrequent confabulation, and ataxic gait. On day 14 of her admission, she complained of acute onset-weakness of all four limbs, acute urinary retention, and again recurrent bouts of hiccups, vertigo, and frequent vomiting, forcing her to be bedridden once again. She also complained of loss of sensation to all modalities below her chest. Rapid neurological examination revealed acute-onset cervical myelopathy with dorsal medullary involvement. MRI of the spine revealed a longitudinally extensive hyperintense lesion on T2-weighted imaging and STIR with patchy contrast enhancement from the medulla to D8 level, predominantly involving the central cord (Figure 2). She was urgently put on high-dose intravenous methylprednisolone (day 15 of admission, 1 g/day for 5 days). Complete metabolic panel was resubmitted, and serum and cerebrospinal fluid (CSF) samples were sent for anti-AQP4-antibodies, anti-MOG-antibodies, IgG index, and oligoclonal bands. Routine CSF study revealed mild pleocytosis and raised protein concentration (cells 10/ μ L, all lymphocytes, protein 68 mg/dL). Relevant tests for neurosyphilis, neurotuberculosis, and neurosarcoidosis, including serum angiotensin-converting enzyme levels, were negative. On day 20 of admission, her neurological features showed some improvement (power improved from MRC grade 1/5 to 3/5 and hiccups resolved but complained of frequent dysesthetic pain [tract pain] in bilateral lower limbs along with painful flexor spasms). Cell-based assay for anti-AQP4-antibodies was positive, establishing this to be a case of seropositive NMOSD. She was put on cyclical rituximab therapy (one cycle every 6 months for 2 years) for relapse prevention (started on day 30 of admission). She was discharged after the first cycle of rituximab and kept under close follow-up and rigorous physiotherapy training. For the next 6 months of follow-up, she had no relapse of the neurological symptoms. Neurological findings improved further (i.e., motor strength returned to 4/5, voluntary bladder control returned to normal). She has remained euthyroid on medications (carbimazole 20 mg/day, propranolol 40 mg/day). Oral thiamine supplementation was stopped after 6 months.

3 | DISCUSSION

Acute-onset hiccups and vomiting, followed by encephalopathy and ataxia, in a young female with untreated Graves' disease point toward a working diagnosis of acute brainstem syndromes. With further help of neuroimaging, differential diagnosis was curtailed to



FIGURE 2 MRI of the spine revealing longitudinally extensive lesion, hyperintense on T2-STIR imaging, extending from dorsal medulla (area postrema) to lower dorsal cord, suggestive of long-segment demyelination

demyelinating pathologies,^{1,2} metabolic encephalopathies,^{3,6} thyroid storm, and anti-TPO/anti-TG antibody-related neurologic disorders responsive to steroids (ATANDS).⁷ Vascular (ischemic/hemorrhagic stroke, cavernomas), infiltrative, autoimmune, infective, and toxic etiologies should also be kept in mind.^{1,2} It is worth noting that the initial intractable hiccup and vomiting was likely because of NMOSD, but not WE. Therefore, it was important to notice the initial APS symptoms in this case.

The presenting features and historical backdrop were suggestive of an acute endocrinological emergency, i.e. thyroid storm. Dilemmas arrived when even after satisfactory stabilization of the thyrotoxic crisis and stable hemodynamics, metabolic parameters, and negative "sepsis screen," her mental status did not improve. At this juncture, diagnosis of ATANDS was thought of, and

positivity of anti-thyroid antibodies; CSF picture and EEG findings further had substantiated this diagnosis. However, brain MRI revealed the involvement of periependymal regions surrounding the ventricular system, including affection of the periaqueductal area, dorsomedial thalami, and mammillary bodies. These regions are infamous for getting involved in both autoimmune astrocytopathy, i.e. NMOSD and WE.^{1-4,7}

The involvement of the periependymal regions around the third and fourth ventricles and the cerebral aqueduct is due to the abundance of AQP4 channels in the astrocytic foot processes in these regions, as demonstrated by the recent advancements in neuroimaging, neuropathological, and immunohistochemical techniques.^{8,9} Thiamine deficiency impairs energy metabolism and leads to the accumulation of lactic acid in brain cells,^{3,6} which may mediate AQP4 overexpression leading to cytotoxic edema to be picked up by traditional brain MRI.¹⁰ Again, as AQP4 are avidly expressed by astrocytic foot processes in the vicinity of the CSF-laden ventricular system, even in WE, make this is particularly affected.^{8,11} Hence, in this case, the possibilities of both disorders were kept. Since, unfortunately, in our setup, cell-based assay for anti-AQP4 antibodies take around 7 to 14 days to be finally reported, we had to start intravenous immunomodulatory therapy with corticosteroids even before the receipt of the positive anti-AQP4 antibodies report. However, after receiving the positive

report, we decided to put her on cyclical rituximab therapy for long-term control of disease and prevention of relapse.

Thiamine is an essential cofactor for two enzymes involved in oxidative metabolism: pyruvate dehydrogenase and α -ketoglutarate dehydrogenase. It is hypothesized that thyrotoxicosis initiates a hypermetabolic state, which in turn necessitates increased thiamine utilization.^{6,12,13} In our case, intractable vomiting and hiccups on the one hand, and the increased thiamine demand due to decreased dietary intake on the other, may have precipitated WE in the setting of depleted thiamine stores.^{6,13} Although different neuropsychiatric disorders have been described in thyrotoxicosis, the role of thiamine deficiency in the synthesis of neuropsychiatric manifestations in thyrotoxicosis remains poorly explored. Furthermore, recent evidence of greater positivity rates of anti-thyroid antibodies among AQP4-positive than AQP4-negative patients¹⁴ and the presence of AQP4 in thyroid follicular cells¹⁵ are suggestive of a potential role of AQP4 in the genesis of thyroid abnormalities. Thus, although establishing a temporal relation as to which disease evolved first is difficult, the plethora of the symptoms in this patient can be attributed to the interrelated pathogenetic mechanisms of the three diseases.

Clinico-radiological similarities between WE and NMOSD (e.g., the clinical presentation of confusion, gait unsteadiness, and radiological evidence of involvement of areas around the ventricles,

TABLE 1 Dissimilarities between NMOSD and WE

Features	WE	NMOSD
Pathomechanism	Hemorrhage and cytotoxic edema in astrocytes and neurons, which can lead to breakdown of the blood brain barrier due to severe thiamine deficiency involving mainly the periventricular regions, especially mammillary bodies and thalamus	Astrocytic damage and demyelination caused by AQP4 antibody-mediated immune attack, predominantly involving periependymal regions
Historical background	h/o chronic alcohol abuse, gastrointestinal disorders (peptic ulcer disease, ulcerative colitis, Crohn's disease), surgeries (bariatric, intestinal resection, gastrectomy), cancers (colon cancer, non-Hodgkin's lymphoma, large B-cell lymphoma, gastric carcinoma, myeloid leukemia), repeated episodes of vomiting or chronic diarrhea etc., which may all lead to thiamine-deficient state	h/o other autoimmune disorders, e.g. systemic lupus erythematosus (SLE) and Sjogren's syndrome, inflammatory bowel disease etc.
Specific clinical features	Horizontal nystagmus on lateral gaze, lateral rectus weakness, conjugate gaze palsy, and rarely, ptosis	Optic neuritis, transverse myelitis, area postrema syndrome, acute brainstem syndrome, cerebral syndrome
Definitive diagnostic test/criteria	Decreased serum thiamine level (by HPLC method)	AQP4 positivity in paired sera or fulfillment of international consensus diagnostic criteria for NMOSD ¹⁷
CSF findings	Normal protein levels	Elevated protein levels along with pleocytosis and presence of neutrophils and eosinophils in acute cases
Specific MRI findings	Mammillary bodies are typically involved along with the tectal plate, periaqueductal region and dorsomedial thalamus, basal ganglia, and midline cerebellum may also be affected	Periventricular periependymal regions surrounding the CSF-filled spaces, e.g. hypothalamus, thalamus, brainstem, hemispheric white matter, periaqueductal region, long segment or posterior chiasmal region of the optic nerve, long segment involvement of preferentially central cord
Mainstay of treatment	Intravenous high-dose thiamine supplementation	Immunomodulatory therapy
Course	Medical emergency, which may lead to Korsakoff's syndrome, if left untreated	Typically recurrent with the development of severe disabilities if left untreated

periaqueductal gray, and thalamus in both) have often led clinicians to misdiagnose cases of NMOSD as WE.¹¹ To our knowledge, the simultaneous presence of WE and NMOSD has previously been reported only once.¹⁶ However, in contrast to the previous report where NMOSD preceded WE, our case exhibited an episode of WE triggered by NMOSD, making the diagnostic evaluation more exciting and challenging. Specific characteristics delineating the WE and NMOSD have been summarized in Table 1.

4 | CONCLUSION

This case again reestablishes the importance of considering cerebral syndrome, diencephalon syndrome, and area postrema syndrome variants of NMOSD while managing a case of metabolic encephalopathy, particularly if neuroimaging features are suggestive.

ETHICS

Written informed consent was taken from the patient for participating in this study.

AUTHORS' CONTRIBUTIONS

All authors are in agreement with the content of the manuscript in keeping with the latest guidelines of ICMJE. Conception and organization: RG, SD, AR, JBL. Manuscript Drafting: RG, SD, DR. Manuscript review, editing and critique: RG, SD, AR, DR, KD, AM, DN, BCS, AP, JBL.

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