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Single Case – General Neurology

Multifocal Stroke Complicating Anti-NMDA Receptor Encephalitis

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Adolescence · Autoimmune disease · Encephalitis · NMDA receptor · Stroke

Abstract
Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is an autoimmune form of encephalitis, first described in 2005 and now recognized as among the more common causes of encephalitis. While NMDARE can result in permanent neurologic deficits or even mortality, the prognosis in children is generally more favorable; 75–85% of children and teenagers achieve a full or substantial recovery. We describe here a preadolescent female, whose course of NMDARE was complicated by a unilateral stroke, resulting in permanent deficits. The imaging characteristics suggest a vascular (thrombotic) etiology. To our knowledge, this is the first report of stroke in the setting of NMDARE.

Background

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is an autoimmune form of encephalitis, first described in 2005 as a paraneoplastic syndrome in young women with ovarian teratomas. It has since surpassed all individual viral etiologies to become one of the more common causes of encephalitis, second only to acute demyelinating encephalitis [1]. It is most common in young women with ovarian teratoma, but can also occur in adult males and children, in whom a tumor is uncommon [1, 2]. The clinical course is often preceded by a

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prodrome of viral-like symptoms, followed by a constellation of neuropsychiatric manifestations. Neurocognitive symptoms include seizures, motor dysfunction (e.g., orofacial dyskinesia, choreoathetosis), memory/speech dysfunction, altered level of consciousness, autonomic dysfunction, and central hypoventilation [2, 3]. Psychiatric symptoms include anxiety, irritability, insomnia, paranoia, aggression, auditory or visual hallucinations, sexual disinhibition, mania, cognitive disorders, and psychosis, although these are less common in pediatric patients [2].

While NMDARE can result in permanent neurologic deficits or even mortality, prognosis in children can be good. Neuropsychiatric changes can be reversible with prompt treatment, wherein up to 75–85% of children and teenagers achieve a full or substantial recovery [2]. We describe here a preadolescent female, whose course of NMDARE was complicated by a unilateral stroke, resulting in permanent deficits. To our knowledge, there have been no previous reports of stroke in the setting of NMDARE.

Case Presentation

A previously healthy 12-year-old girl presented to her local Emergency Department complaining of difficulty walking and muscle spasms of her legs following a recent diarrheal illness. She was discharged with outpatient psychiatric follow-up and later referred to a regional referral center for further evaluation. There, she was diagnosed with conversion disorder with waxing/waning altered mental status, urinary incontinence, and continuous leg kicking movements (right more than left). A week after discharge, she presented again to her local Emergency Department with worsening symptoms. She was found to be severely dehydrated, hypotensive, and febrile with Glasgow Coma Score of 3 and teeth-clenching movements that were thought to be seizures.

The patient was transferred to our institution and resuscitated. Initial labs were significant for white blood cell count 14.1 × 10^3 cells/μL, sodium 156 mEq/L, anion gap 21 mEq/L, pH 7.25, lactate 2.6 mmol/L, CPK >16,000 U/L, AST 134 U/L, ALT 50 U/L, and INR 1.46. She was given an intravenous bolus of levetiracetam, intubated, and initiated on acyclovir. Video EEG captured events that were non-epileptic. Brain MRI, however, revealed an acute infarct(s) in the left frontoparietal lobe in the distribution of the ACA and MCA territories with MRA evidence of two arterial occlusions (Fig. 1). MRA of the neck showed no carotid or vertebral artery abnormalities. Echocardiogram with bubble study showed no apparent inter-atrial communication.

CSF studies demonstrated white blood cell count of 33 cells/μL with 97% lymphocytes, 8+ oligoclonal bands and anti-NMDA receptor IgG of 1:160. The patient started 5 days of IVIg and methylprednisolone 1 g IV daily. Pelvic ultrasound was negative for ovarian teratoma. Evaluation for an underlying thrombophilia condition was negative, with normal levels of protein C, protein S and antithrombin III, and no evidence of antiphospholipid antibodies or Factor V Leiden mutation.

The patient's hospital course was complicated by *Clostridium difficile* colitis and *Streptococcus viridans* bacteremia. Over a few weeks, she showed gradual, limited neurologic improvement. She was able to make eye contact and follow commands but did not regain any movement of her right side. She was subsequently transferred to a children's rehabilitation facility 1 month after hospital admission for continued care.

Discussion and Conclusions

While stroke is uncommon in the pediatric population, it can result in significant morbidity and mortality. Approximately 10–25% of pediatric stroke patients will die, and up to 25% will experience recurrence. Of those affected, up to 66% will have persistent seizures, or develop other neurological deficits such as developmental delays [4]. The prevalence of pediatric stroke in western countries is 8–13 per 100,000 children aged 5–14 years [5]. In the United States, the leading causes of pediatric stroke are as follows: arteriopathy (42%), cardiac disorders (32%), acute head and neck disorders (23%), chronic systemic disorders (21%), acute systemic disorders (21%), infection (18%), prothrombotic states (13%), and chronic head and neck disorders (10%) [6]. Of note, 89% of pediatric stroke patients have at least one identifiable risk factor [6].

Triggers for synthesis of anti-NMDAR antibodies include teratomas, viral infections (in particular, herpes simplex virus), and other unknown factors [2]. Both in vitro and in vivo models confirm the pathogenic role of anti-NMDAR antibodies. The binding of antibodies to NMDA receptors results in crosslinking and internalization of these NMDA receptors [7], leading to a reversible and titer-dependent decrease in NMDA receptors on the postsynaptic membrane [2]. While overactivity of NMDA receptors can result in excitotoxicity and acute neuronal injury through excessive presynaptic glutamate release and reversal of calcium uptake by astrocytes, [2, 8], our patient's imaging results suggest instead a vascular etiology for her stroke.

Byun et al. [9] reported elevation of interleukin-6 and interleukin-17A in the cerebrospinal fluid of NMDARE patients. Both cytokines promote inflammation via a variety of mechanisms [10–12]. Finally, regional inflammation can trigger arterial thrombosis, although the mechanisms are complex and incompletely understood [13].

Aside from encephalitis, our patient did not have apparent risk factors for pediatric stroke, and there was no apparent extracranial source for (multifocal) emboli. Her presentation is most consistent with in situ cerebral thrombosis and infarct secondary to parenchymal inflammation/ischemia. Based on our review of the literature, this is the first report of stroke as an apparent consequence of NMDARE.

Statement of Ethics

The subject's mother has given her written informed consent to publish this case, including images.

Disclosure Statement

The authors declare that they have no competing interests.

Author Contributions

J.M.J recognized the case as having potential for publication, advised in the hematologic workup, recruited Z.H.S. (at the time, a senior medical student) to prepare an initial draft report. Z.H.S. prepared the case description, researched NMDARE, and prepared a draft

discussion speculating as to the pathophysiology of the case. C.H.N. offered neurological perspective and advised the final version of the discussion. All authors read and approved the final manuscript.

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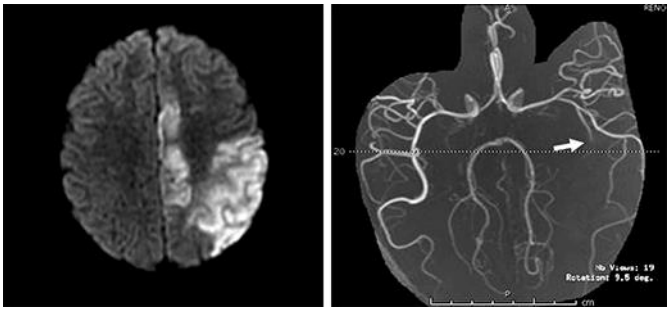

Fig. 1. Diffusion-weighted axial image (left) shows acute infarct in the left frontal and parietal lobes, in the distribution of both anterior and middle cerebral arteries. MRA (right) reveals truncation of a LEFT M2 branch artery (arrow) with nonvisualization of flow in the arteries to the precentral gyrus, postcentral gyrus, and anterior parietal artery peripheral to it. A left A2 branch artery along the longitudinal fissure was also occluded (not shown).