Anti-*N*-Methyl-D-Aspartate-Receptor Encephalitis Complicated With Antiphospholipid Syndrome and Cerebral Venous Thrombosis

To the Editor:

Encephalitis, which can be caused by various viral infections or an autoimmune reaction, may present with behavioral and consciousness changes, neck pain, stiffness, photophobia, lethargy, seizures, acute confusion or amnesia, and flaccid paresis.[1] In the autoimmune disease anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis,[2] anti-NMDAR antibody binding triggers NMDAR internalization, disrupting neurological function.[3] It occurs predominantly from childhood to young adulthood and may be comorbid with teratomas.[4]

Antiphospholipid syndrome (APS) is a primary or secondary autoimmune disease that renders patients prone to vascular thrombosis, spontaneous miscarriage, thrombocytopenia, and hemolytic anemia. It may develop in patients exposed to infectious agents or with rheumatic diseases.[5] Antiphospholipid (aPL) antibodies detected in APS include lupus anticoagulant (LA) and anti-cardiolipin antibodies.

A 20-year-old man sought treatment for severe anxiety, insomnia, confusion, delusion, hallucinations, and bizarre behaviors that had begun 2 weeks prior. He exhibited agitation, slurred speech, limb convulsion, and cognitive impairment. He had no history of systemic disease or potential toxin exposure. Brain magnetic resonance imaging (MRI) with contrast revealed diffuse vascular enhancement along the cerebral sulci in T1-weighted images (Fig. 1). We admitted him for suspected brain infection, and given antibiotic/antiviral therapy.

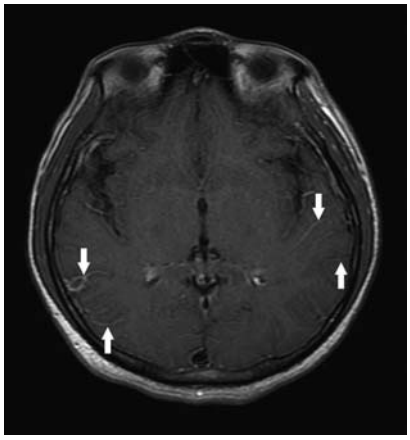

FIGURE 1. First brain MRI scan of the patient. T1-weighted MRI image with contrast showing diffuse enhancement of vascularities (arrows) along cerebral sulci.

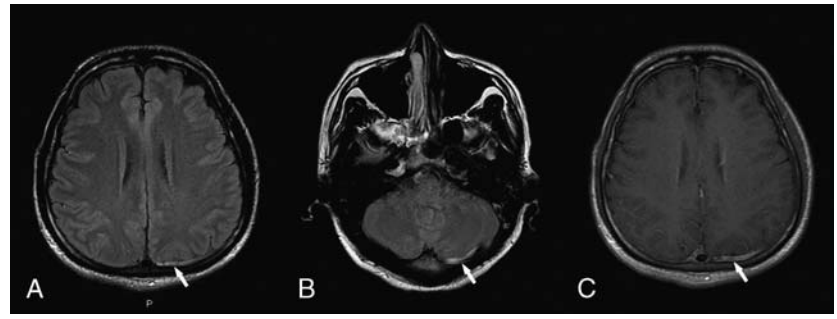

FIGURE 2. Postadmission follow-up brain MRI. FLAIR T2-weighted MRI images showing hyperintense cortical veins (A) and left transverse sinus (B). (C) Evidence of a cortical-vein filling defect in a contrast-enhanced T1-weighted image.

Cerebrospinal fluid (CSF) analysis results were normal. An awake electroencephalogram revealed intermittent nonspecific slow waves. Over the next 3 days, the patient's condition deteriorated into catatonia with seizures, and he was prescribed antiepileptic agents. When signs of rhabdomyolysis developed (status epilepticus and creatine kinase elevation), he was transferred to the intensive care unit, where he required endotracheal intubation with mechanical ventilation.

A second brain MRI scan with contrast showed hyperintensity of the cortical veins and left transverse sinus (FLAIR T2-weighted images). Cortical-vein filling defects were evident in contrast-enhanced T1-weighted images (Fig. 2), raising concerns of cerebral venous thrombosis (CVT). Coagulation disorder and autoantibody screening[6] revealed anti-NMDAR immunopositive CSF consistent with NMDAR encephalitis as well as elevated beta2-glycoprotein antibody, LA, and D-dimer levels consistent with APS.[7] Serologic evaluation was negative for anti-nuclear antibodies, anti-double-stranded DNA antibodies, anti-Ro/SSA, and anti-La/SSB antibodies, thus ruling out other autoimmune disorders such as SLE.

The patient became comatose with bradycardia and a long pulse indicative of autonomic dysfunction. The patient's seizure frequency decreased after he was given ten plasma exchanges. Subsequently, he was weaned off ventilation. He regained consciousness, although temporary neurological abnormalities remained. The patient was given rivaroxaban (5 mg/day) for thrombosis prophylaxis and the innate immune response inhibitor hydroxychloroquine (200 mg, twice daily). Within 3 weeks, the patient's serum D-dimer levels normalized, he regained full consciousness, and was transferred to a standard ward. Follow-up tests 12 weeks after admission showed sustained beta2-glycoprotein antibody and LA elevation, confirming APS. He was maintained on rivaroxaban-hydroxychloroquine pharmacotherapy, and was free of thromboses and neurological sequelae at a 1-year follow-up.

During the overt onset of anti-NMDAR encephalitis, patients may experience headache, fever, gastrointestinal malaise, or upper respiratory-tract symptoms. In the early stages of the disease, patients may exhibit psychiatric symptoms, including anxiety, insomnia, fear, delusions, hyper-religiosity, mania, paranoia, social withdrawal, and stereotypical behaviors. Thereafter, patients may experience rapid disintegration of cognitive function, autonomic instability, hypoventilation, and seizures. Mild or transient multifarious MRI hyperintensities are evident in approximately half of anti-NMDAR encephalitis cases.[8] Periodic immunological screening is useful to assess progression and treatment efficacy. The symptoms are often reversible.

In the present case, APS with CVT was comorbid with anti-NMDAR encephalitis without a systemic disease history, suggesting that APS can be a sequela of anti-NMDAR encephalitis. Therefore, patients with anti-NMDAR encephalitis and a thrombosis event should be screened for APS. In the present case, CVT was evident in MRI, but not computed tomography scans.

We prescribed the recently approved non-vitamin-K antagonist oral anticoagulant rivaroxaban to avoid dosage and monitoring concerns, and observed no subsequent venous thromboembolism (VTE) events.

The safety/efficacy profile of rivaroxaban is similar to that of warfarin for VTE,[9,10] though the aPL statuses of patients in these trials were unknown. The present case demonstrates that anti-NMDAR encephalitis may be associated with APS and demonstrates rivaroxaban efficacy for secondary thromboprophylaxis in an APS patient with VTE.

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The authors declare no conflict of interest.

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