NMDA receptor antibody encephalitis presenting with enhancing lesion and seizures

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We report an adult man presenting with sudden-onset epilepsy syndrome with evolution to refractory status epilepticus and an enhancing left frontal MRI lesion. The atypical nature of his presentation resulted in emergent epilepsy surgery. He was eventually diagnosed with NMDA receptor antibody (NMDAR AB) encephalitis based on positive CSF antibodies.

Practical Implications

In rare instances, NMDA receptor antibody encephalitis may present clinically with refractory seizures and radiologically as a focal enhancing lesion on brain MRI.

CASE REPORT

A 19-year-old African American man presented with a new-onset generalized seizure after watching a film followed by another event 3 days later. Brain MRI performed after the patient recovered revealed an 8-mm focus of increased fluid-attenuated inversion recovery signal intensity with gadolinium enhancement of the left middle frontal gyrus, suggestive of neoplasm (figure, A and B). Despite initiation of levetiracetam 500 mg bid, he continued to have breakthrough seizures that resulted in a hospitalization 2.5 weeks from symptom onset.

On examination, the patient had expressive aphasia without any other focal findings. Initial EEG showed continuous lateralized periodic discharges over the left frontal region, culminating in frequent left frontal seizures and 1 generalized convulsion (figure, C). Repeat brain MRI showed a stable left frontal lesion. Initial CSF analysis revealed a leukocyte count of 63 with 99% lymphocytosis, protein 52, and glucose 57, and no oligoclonal bands or immunoglobulin G (IgG) index elevation. Serum studies for HIV, Lyme antibodies, Bartonella antibodies, *Anaplasma* antibodies, and an autoimmune epilepsy panel were negative. He was treated empirically with methylprednisolone 1 g IV × 3 days without clinical response. A repeat lumbar puncture performed 1 week after the initial study showed 6 leukocytes and normal protein (37) and glucose (83). Again, there was no evidence for oligoclonal bands or elevated IgG index. CSF studies were normal or negative for herpes simplex virus 1, cryptococcus, varicella-zoster virus, viral/bacterial cultures, West Nile virus, enterovirus, Lyme, Whipple PCR, pyruvate/lactate, and venereal disease research laboratory. CSF for an autoimmune epilepsy panel was sent to the Mayo Clinic.

Throughout his hospitalization, the patient continued to have persistent seizures refractory to phenytoin 200 mg Q8, levetiracetam 2,500 mg Q12, phenobarbital 150 mg Q12, lacosamide 250 mg Q12, topiramate 150 mg Q12, and felbamate 600 mg TID. He required intubation and therapeutic coma to attempt to control refractory status. Seizures initially responded to propofol, but relapsed on taper. He continued to have breakthrough seizures during a second trial of propofol 120 μg/kg/min and midazolam 2.0 mg/kg/h. He was treated empirically without improved seizure control.

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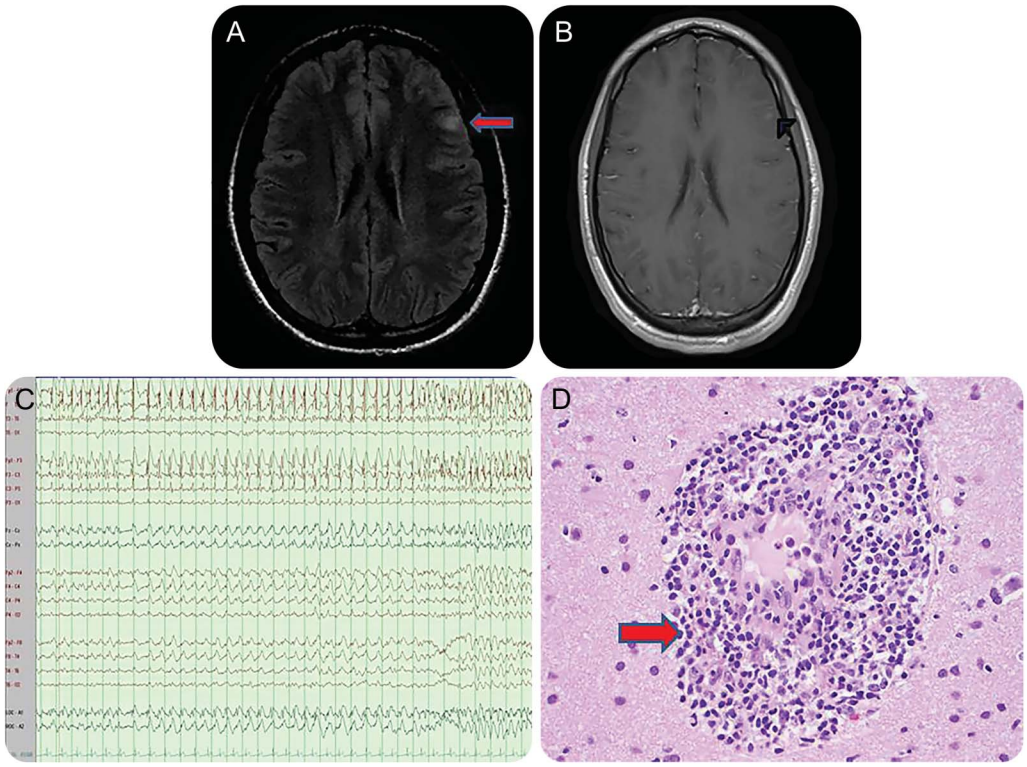
Figure **Clinical studies in a patient presenting with focal seizures and positive CSF NMDA receptor antibodies**



(A) Brain MRI reveals a focal left middle frontal gyrus hyperintensity on fluid-attenuated inversion recovery sequences corresponding to the location of ictal discharges (red arrow). (B) T1-weighted MRI sequence demonstrates trace enhancement of the left middle frontal gyrus lesion (arrowhead). (C) Initial EEG shows continuous lateralized periodic discharges over the left frontal region that developed into focal left frontal seizures. (D) Pathology (hematoxylin & eosin, original magnification ×400) reveals chronic inflammation of the cerebral cortex without evidence for cortical dysplasia or neoplasm (red arrow).

Due to the patient's refractory seizures, focal lesion on structural MRI, and seizures on continuous EEG, the patient underwent resection of the left middle frontal gyrus. The electrographic seizures persisted postoperatively. Pathology revealed chronic perivascular/parenchymal inflammation and reactive astrocytosis without evidence for cortical dysplasia or neoplasm (figure, D).

A CSF autoimmune epilepsy panel eventually revealed positive NMDAR AB. Body CT scan and testicular ultrasound were negative for malignancy. The patient was started on methylprednisolone 1 g IV and plasma exchange × 5 days, immediately followed by IV immunoglobulin × 5 days due to initial minimal response. Furthermore, he received rituximab × 2 doses, separated by 1 week. With immunosuppression, the patient's refractory status resolved, and he was discharged from the hospital with a normal neurologic examination 6 weeks from admission.

DISCUSSION

NMDAR encephalitis is the most common cause of autoimmune encephalitis after acute demyelinating encephalomyelitis and is characterized by psychiatric symptoms, seizures, extrapyramidal signs, decreased level of consciousness, and autonomic instability. The disorder affects individuals of all ages, with a high predilection for young women with or without teratomas.[1,2]

The most common presenting symptom in our patient's age group is behavior changes followed by seizures,[3] which may be focal, but are most commonly generalized.[2] In addition, routine structural brain MRI is often normal in this patient population.[4]

Although our patient's CSF autoantibodies and neuropathology were consistent with NMDAR AB encephalitis, this case was unusual based on (1) symptoms confined to a focal epilepsy syndrome and (2) enhancing focal lesion suggesting CNS neoplasm. A case series described focal seizures in 8 patients with NMDAR antibodies, but all the patients presented with accompanying cognitive, behavioral, or motor symptoms.[5] Furthermore, none of the described patients were found to have a focal, enhancing brain MRI lesion. Thus, NMDAR AB encephalitis presenting with isolated seizures and a clinical syndrome mimicking a focal CNS neoplasm is relatively rare.

Diagnosis was delayed due to the unique clinical presentation as well as the fact that the serum studies were negative for NMDAR AB. Our patient emphasizes the importance of investigating NMDAR antibodies in CSF[6] as recently suggested by most investigators in the field of autoimmune encephalitis.[7]

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AUTHOR CONTRIBUTIONS

M. Rosenbloom: manuscript preparation and figure design. M. Samuelsson: manuscript review and figure design. M. Brogan: manuscript review and editing. T. Tran-Lim: manuscript review, editing, and figure design.

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