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Case Reports

Psychiatric Manifestations of Anti-NMDA Receptor Encephalitis in a Man without Tumor

Doris Hichi Kung, D.O., Cuie Qiu, M.D., Joseph Shimon Kass, M.D.

Limbic encephalitis, whether paraneoplastic or autoimmune, is a well-recognized but rare neurological disorder. Patients are often initially referred to psychiatrists because the initial clinical presentation of this disease mimics a primary thought or mood disorder. Many different forms of limbic encephalitis have been described, with a number of anti-neuronal antibodies. Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has recently emerged in the literature with distinct clinical characteristics, including personality changes, anxiety, bizarre behavior, delusions, paranoia, and catatonia.[1,2] In Dalmau's study, greater than 90% of reported patients with anti-NMDA receptor encephalitis were female and were found to have an ovarian teratoma.[2] Here, we report clinical features, extensive diagnostic investigations, and the treatment response to immunotherapy in a man with anti-NMDA receptor encephalitis without evidence of any tumors.

Case Report

Mr. A, a 24-year-old Hispanic man who immigrated from El Salvador was brought to our county hospital in Houston, Texas after being found by the police banging his head on the concrete. He was admitted to the psychiatric service for aggressive behavior, agitation, pressured speech, and paranoid delusions. He also exhibited hyperreligiosity and grandiose delusions. His mental status examination was otherwise intact.

On admission, a noncontrast computed tomography (CT) of his head revealed only a midline parietal scalp hematoma near the vertex. Antipsychotic treatment was initiated including use of oral aripiprazole and intramuscular haloperidol. He was also started on lithium for manic symptoms. Three weeks later, the neurology service was consulted for deteriorating mental status and possible seizure activity. On examination, Mr. A was noncommunicative and seemed to respond to internal stimuli. He also exhibited orofacial dyskinesias (e.g., grimacing and masticatory-like movements), upper extremity rigidity, and had episodes of dystonia with diaphoresis. His lithium level was elevated at 1.5 mmol/L. Electroencephalography (EEG) showed absence of an occipital dominant rhythm, with both slow and excess fast activities in the frontal regions without electrographic seizures.

Mr. A was then transferred to the neurology service for the management of possible neuroleptic malignant syndrome (NMS) caused by antipsychotic treatment.[3] He had a creatinine kinase (CK) level of 1590 Units/L, leukocytosis of 13,500 cells/μL, and fever up to 102.2° F. All antipsychotics were discontinued and bromocriptine therapy was initiated. An initial cerebrospinal fluid (CSF) study showed normal protein levels and no pleocytosis. All bacterial, fungal, and viral studies in the CSF were negative. Herpes simplex virus (HSV) polymerase chain reaction (PCR) from the CSF was also negative. Carbamazepine was initiated for possible seizures. A noncontrast magnetic resonance imaging (MRI) of the brain revealed no intracranial abnormalities, although the study was limited due to motion. His clinical symptoms did not improve over the next 2 weeks. He continued to be agitated, did not follow commands, and mumbled unintelligible words. His agitation was managed with scheduled oral clonazepam and intravenous (IV) lorazepam as needed. On telemetry,

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From the Dept. of Neurology, Baylor College of Medicine, Houston, TX. Send correspondence and reprint requests to Joseph Shimon Kass, M.D., Dept. of Neurology, Baylor College of Medicine, One Baylor Plaza, MS NB302, Houston, TX 77030. e-mail: kass@bcm.edu

Mr. A had frequent episodes of tachycardia and bradycardia. A percutaneous endoscopic gastrostomy (PEG) was placed because of poor oral intake. A CSF study was repeated and showed a very mild lymphocytic pleocytosis with a white blood cell (WBC) count of 8 WBC/mm^3. He was given a course of antibiotic treatment for possible bacterial meningitis and acyclovir for possible herpes encephalitis although bacterial, fungal, viral studies, and HSV. PCR in the CSF were again negative.

Despite treatment, there was still no improvement in his clinical course, and investigation for an autoimmune limbic encephalitis ensued. A paraneoplastic panel was ordered, including serum anti-Hu, anti-Ma2, anti-VGKC, anti-MaTa, and anti-amphiphysin. Anti-N-methyl D-aspartate (NMDA) receptor antibodies from the serum and CSF were also sent. An enhanced CT of the chest, abdomen, and pelvis showed no evidence for neoplasm. A scrotal ultrasonography revealed no evidence of a testicular tumor. All tumor markers including PSA, beta-HCG, alpha-AFP, CEA, and CA19-9 were negative. A full body positron emission tomography (PET) scan was negative for neoplasm. Screening for heavy metal poisoning, ceruloplasmin, urinary copper levels for Wilson's disease, anti-measles antibody for subacute sclerosing panencephalitis (SSPE), and Treponema Whipplei PCR for Whipple's disease were all negative. Other investigations including thyroglobulin antibody, anti-thyroid peroxidase (TPO) antibody, anti myeloperoxidase (MPO) antibody, and anti-proteinase 3 (PR3) were also negative. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were mildly elevated.

Mr. A received a course of IV methylprednisolone 1000 mg daily for 5 days for presumed autoimmune limbic encephalitis but there was no improvement. He was then given a course of IV immunoglobulin (IVIg), 2 g/kg over 5 days. One week after IVIg treatment, he was able to follow a few simple one-step commands and engaged in brief episodes of intelligible conversation. At this time, the serum and CSF studies previously sent out were reported positive for NMDA-receptor antibody. He received a course of rituximab 375 mg/m^2 weekly for 4 weeks and was gradually able to respond to simple questions with brief sentences. He slowly regained the ability to walk and was able to feed himself. His agitation improved, and he was able to engage in basic conversation. However, he remained relatively amnestic about his 4-month hospitalization and became very agitated at times. The neurology service continued to follow him on an outpatient basis to monitor his progress and further investigate for possible neoplasm. Mr. A also continued to follow-up with the psychiatry service and was stable on olanzapine without further psychotic symptoms.

Discussion

Limbic encephalitis is often associated with a paraneoplastic process, and several anti-neuronal antibodies have been implicated in this condition. Recent research has identified a group of disorders that are immune mediated and not necessarily associated with tumors, including anti-NMDA receptor encephalitis. Patients with this disorder have antibodies in the serum and CSF to the NR1/NR2 heteromers of the NMDA receptor.[4]

Our patient had a typical clinical presentation of anti-NMDA receptor encephalitis with psychiatric, neurologic, and autonomic abnormalities. His initial psychosis was thought to be due to presenting symptoms of schizophrenia, and the patient was transferred to a psychiatric ward. In a study of 100 patients with anti-NMDA receptor encephalitis, 77% of the patients were first evaluated by a psychiatrist.[2] Anti-NMDA receptor encephalitis presents with prominent psychotic behavior including delusions, paranoia, hallucinations, and a catatonic-like state. Dyskinesias, seizures, autonomic instability, and central hypoventilation are also key features of this disorder.[2] Orofacial dyskinesias are reported to be most common, and this was noted in our patient as well, who exhibited peculiar tongue movements, lip twitching, bruxism, and frequent inappropriate smiling. These were initially thought to be automatisms associated with seizure activity but several repeat EEGs were negative.

Typical EEG findings show frontotemporal slowing or diffuse delta activity without epileptic discharges.[2,4] Typical MRI findings in limbic encephalitis show hyperintensity in the medial temporal lobes on fluid attenuated inversion recovery (FLAIR) and T2 sequences, which is associated with intracellular antigens, such as anti-Hu, Ma2, and CV2/CRMP5[5]. However, patients with anti-NMDA receptor antibodies, a cell membrane antigen, may show meningeal enhancement or even a normal MRI.[5,6] In our patient, CSF studies showed lymphocytic pleocytosis as is frequently described in other case reports and a normal brain MRI.[1,6]

Our patient's Parkinsonian symptoms, including rigidity and bradykinesia, elevated CK, and fever led to an alternative diagnosis of possible NMS that resulted in a delay in

his diagnosis. NMS is a rare complication of antipsychotic treatment and has been reported in association with typical and atypical antipsychotics.[3,7] Our patient received aripiprazole, haloperidol, and lithium for 3 weeks while on the inpatient psychiatric ward. NMS and anti-NMDA receptor encephalitis share many common features including fever, autonomic disturbances, extrapyramidal symptoms, elevated CK, and altered mental status. In the study by Dalmau et al., only seven out of 100 patients with anti-NMDA receptor encephalitis had elevated CK levels.[2]

Both NMS and anti-NMDA receptor encephalitis are rare diseases and other more common differential diagnoses to consider include viral encephalitis, viral or bacterial meningitis, drug toxicity, serotonin syndrome, nonconvulsive status epilepticus, malignant catatonia, and other autoimmune disorders.[8] The extensive differential often requires a comprehensive workup that can lead to inappropriate treatments with significant side effects.

It is important to recognize this disorder since early immunotherapy with or without tumor resection can be curative. A multidisciplinary approach is beneficial because of the neuropsychiatric manifestations, the risk of respiratory decompensation, and possible surgical intervention if a neoplasm is identified. Once the diagnosis of anti-NMDA receptor encephalitis is suspected, a prompt thorough investigation for neoplasm is obligatory. Anti-NMDA receptor encephalitis has been associated with neoplasms, specifically, ovarian teratomas. Patients with tumor resection within 4 months after the onset of symptoms are reported to have the best prognosis.[2] Tumors are not detected in about 40% of patients with anti-NMDA receptor encephalitis, although tumors can be detected 4 to 30 years after recovery.[2]

The treatment for patients with anti-NMDA receptor encephalitis without tumors can be quite challengining. Ishiura and colleagues reported that a combined treatment strategy with corticosteroids, plasmapheresis, and rituximab was effective for a woman without an associated tumor.[9] They speculated that rituximab treatment may result in a faster recovery, although its efficacy was difficult to evaluate given the multiple therapy regimen and the possibility of spontaneous resolution. Our patient demonstrated a similar clinical response to corticosteroids, IVIg, and rituximab treatment. IVIg contains pooled IgG immunoglobulins extracted from the plasma of many blood donors. In treating autoimmune disorders, one plausible mechanism is that IVIg neutralizes the host's auto-antibodies by binding to them and facilitating their removal. In contrast, rituximab is a monoclonal antibody, which binds to CD20+ proteins that are widely expressed on B cells, leading to the elimination of B cells from the body and subsequently reducing auto-antibody production. Rituximab has been efficacious in the treatment of multiple autoimmune diseases.[10] Rituximab has also significantly improved clinical symptoms in patients with positive anti-Hu or anti-Yo paraneoplastic encephalitis.[11] Moreover, combination treatment with rituximab and IVIg has produced excellent clinical responses with minimal adverse events due to their synergistic effects and long-term remission.[12] Since recurrence is possible in patients with anti-NMDA-receptor encephalitis, especially in those without tumors or without tumor resection,[2] it is possible that combined IVIg and rituximab might produce long-term remission. Since rituximab does not cross the blood-brain barrier, intraventricular infusion has been considered to increase its efficacy.[13]

Anti-NMDA receptor encephalitis is an autoimmune encephalitis with a reversible clinical course and a favorable prognosis especially with early recognition and treatment.[2] The clinical presentation of patients with anti-NMDA receptor encephalitis leads to a broad differential diagnosis as in our patient. Awareness and recognition of this unique disorder is paramount since a prompt diagnosis can lead to early treatment and a better prognosis.

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