Anti-NMDA encephalitis

Nevzat Tarhan
Uskudar University, Turkey

Abstract

Anti-NMDA receptor encephalitis was firstly described in 2007. Up-to this date more than 400 cases have been described, making the syndrome rather un-rare. It is an autoimmune disorder where the NMDA receptors are targeted. The disease may affect anyone at any age and any gender. The patients usually have a viral-like prodrome of lethargy, upper respiratory symptoms, headache, nausea, fever etc. The presenting symptoms of the syndrome are mainly psychiatric. The patients manifest various psychotic symptoms like delusions, disorganized thoughts and behaviors, paranoid ideation, hallucinations, mood lability and cognitive deterioration. After 1-3 weeks of neuropsychiatric symptoms, the patient suffers from neurological complications such as global alterations in consciousness, catatonic-like states, dysautonomia and seizures. The patients may need to be hospitalized for 3-4 months. Aggressive treatment with corticosteroids and immunotherapy is needed. Most patients respond to this treatment. However, they may have significant cognitive and behavioral abnormalities like deficits in executive functions, impulsivity and behavioral dis-inhibition and sleep disturbances that need further follow-up. Psychiatric and neurological symptoms are treated with psychotropic drugs as in other neuropsychiatric syndromes. Some patients may need neuro-rehabilitation. The diagnosis requires Cerebrospinal Fluid (CSF) work-up. In CSF lymphocytic pleocytosis, elevated protein and oligoclonal bands are found. Demonstrating antibodies against NMDA receptors in CSF and/or serum gives a solid diagnosis of the disease. Cranial Magnetic Resonance Imaging (MRI) may be normal in half of the cases. Electroencephalography (EEG) is usually abnormal with slowed and disorganized activity. In this session a review of anti-NMDA encephalitis will be presented in light of a case that was diagnosed and followed-up in our clinic. This is an important neuropsychiatric syndrome that may go unnoticed unless the physician follows-up the patient closely, runs in-depth neuropsychiatric tests and collaborates with other physicians.

Anti-N-methyl D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis, caused by immunoreactivity against the NMDA receptor 1 (NR1) subunit of the NMDA receptor, is one of the most common autoimmune encephalitides, first described in 2007 by Dalmau and colleagues in which psychiatric and neurologic symptoms were found in women with ovarian teratomas. The condition was later confirmed to be not exclusively paraneoplastic. Later studies reported patients afflicted without tumor involvement. Although available data suggest the disease is more prevalent in adult women, and in the non-Caucasian population, the condition has been described in both genders, in multiple races, and throughout the lifespan. However, increasing case reports of anti-NMDAR encephalitis in the psychiatric literature have demonstrated the significant overlap between neurologic and psychiatric pathology associated with autoimmune encephalitis. The clinical progression of the encephalitis has also been more thoroughly defined, with a multiphase model currently in use. The prodromal phase is suggestive of a viral flu-like illness, in which fever, malaise, and fatigue may be prominent. This phase varies in duration and may also involve upper respiratory or gastrointestinal symptoms. The condition is often clinically recognized in the ensuing psychotic phase, in which delusions, hallucinations, paranoia, and agitation may be exhibited. During this phase, anti-NMDAR encephalitis is often misdiagnosed as a primary psychotic or substance-induced disorder. Following these psychotic symptoms is often the progression to a state in which catatonia, impaired attention, dyskinesias, and seizures may develop. In addition, significant autonomic instability, with wide-ranging fluctuations in body temperature, blood pressure, respiratory rate, and cardiac rhythm, may occur. It is important to note that anti-NMDAR cases may not follow a strict phasic progression as mentioned earlier and may not include all of the symptomatology mentioned earlier, thereby complicating diagnosis.

In 70% of patients, there is a prodromal period, averaging 5 days but up to 2 weeks, of a viral-like illness with symptoms of headache, fever, malaise, myalgia, upper respiratory symptoms, nausea, and diarrhea. They often then present to hospitals after they develop psychotic symptoms, such as delusions, hallucinations, and paranoia. Memory loss, as well as difficulty with sustained attention, may occur. Symptoms of hyper-religiosity and disorganization in both thought process and behavior may occur. They may become agitated or afraid to the point of combativeness. The initial presentation is suggestive of psychosis, and may be mistaken for being substance

Note: This work is partly presented at 12th World Congress on Virology and Infectious Diseases, March 18-19, 2020, Amsterdam, Netherlands

induced, or malingering. Treatment at this stage includes antipsychotics and sedatives due to psychotic symptom presentation. In our experience, individuals may respond poorly to antipsychotics when compared to typical patients on the schizophrenia spectrum. Patients may also differ from typical first break psychosis in that they may have insight that their thoughts are disorganized. As the disease progresses, its presentation begins to differ from that of typical psychosis with the onset of autonomic dysfunction (often hypertension, hyperthermia, tachycardia, and hypoventilation), seizures, and movement disorders. Within this same timeframe, the patient may develop catatonia. Speech and verbal abilities decline. There may be stereotypical automatisms such as lip smacking and teeth clenching. Patients may still become agitated and require pharmacological sedation between periods of catatonia. Diagnostic evaluation: There are many types of encephalitis, each with differing presenting symptoms and biomarkers, and it is important to be able to minimize delays in both assessment and treatment. If anti-NMDAR encephalitis is suspected, CSF studies should be obtained. CSF reveals lymphocytic pleocytosis or oligoclonal bands. CSF protein can be elevated or normal. Glucose is also normal. Laboratory tests are also available to test the CSF for anti-NMDAR antibodies for confirmation. Serum anti-NMDAR antibodies assays are not as sensitive as CSF studies. In one study, out of 250 patients that had anti-NMDAR antibodies in CSF, only 214 had antibodies in serum (sensitivity 100 versus 85.6%). Brain MRI studies are normal or show transient fluid-attenuated inversion recovery (FLAIR) or contrast-enhancing abnormalities.3 EEGs generally reveal nonspecific abnormalities such as diffuse slowing. They may reveal extreme versions of the 'delta brush pattern', which are transient patterns characterized by a slow delta wave with superimposed fast activity. The extreme delta brush that appears to be unique to anti-NMDAR encephalitis may suggest a more prolonged illness, but it was only seen in 7 of 23 patients in a study by Schmitt and colleagues. Conclusion: Anti-NMDAR encephalitis is a serious, potentially fatal condition that is often initially confused with schizophrenia spectrum mental illness. As a relatively newly understood condition, it is increasingly diagnosed in inpatient settings as more providers become aware of its presentation. This review contributes to the growing body of literature by presenting a case presentation and the timeline of symptoms seen over the course of the illness. Key findings in the literature about anti-NMDAR encephalitis are highlighted to facilitate diagnostic consideration and treatment.

Note: This work is partly presented at 12th World Congress on Virology and Infectious Diseases, March 18-19, 2020, Amsterdam, Netherlands