Anti-NMDA Receptor Encephalitis

BY MICHELLE L. DOUGHERTY, MD

Originally described in 2005, Anti-NMDA Receptor encephalitis is a syndrome characterized clinically by viral prodrome, followed by the onset of psychiatric symptoms, memory complaints, seizures, autonomic dysfunction, dyskinesia, and central hypoventillation.[1,2] This syndrome is increasingly recognized and now thought to be the second most common etiology of autoimmune encephalitis.[1] The disease course can be severe but with prompt diagnosis, appropriate intensive care support and aggressive immunotherapy, good outcomes can be achieved.

CLINICAL HISTORY

The most typical patient is a young female in her late teens to twenties, but reported cases include both males and females ages eight months to 85 years.[1] Patients will often complain of a viral prodrome including headache, low grade fever, gastrointestinal symptoms, and upper respiratory symptoms a few days to two weeks prior to presentation for evaluation.[2,3] Frequently, patients seek out or are brought to medical attention for prominent psychiatric symptoms including behavior change and psychosis; therefore, patients are often initially evaluated by psychiatrists.[1,2] During the first four weeks of the disease course most patients develop additional symptoms that can include: memory problems, seizure, autonomic dysfunction, dyskinesia, altered mental status and central hypoventilation.[1] Seizures are reported in approximately 76 percent of cases and can be generalized or focal.[4,3] Recent data suggest that initial presentation in men is commonly partial seizure followed by psychiatric symptoms.[3] Conversely in women presentation is more commonly psychiatric and less commonly seizure. Seizures in female patients are more commonly generalized.[3] Dyskinesias are commonly orofacial.[2] Autonomic findings can include bradycardia, tachycardia, and hypersalivation.[2] Central hypoventilation will often require ventilator support which can be prolonged.[2] Memory complaints are more common at presentation for adult patients than children, but amnesia for the disease course is often reported.[1,2]

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PATHOPHYSIOLOGY

NMDA receptors play a crucial role in memory, learning, and cognition.[2,5] Antagonists to the NMDA receptor such as ketamine and phencyclidine produce symptoms observed in Anti-NMDA receptor encephalitis such as psychosis, autonomic instability, dystonia hypertension and cardiac dysrhythmia.[2] In Anti-NMDA receptor encephalitis antibodies localize to target regions on the NR1, glycine binding, and NR2, glutamate binding, subunits.[2] More specifically the target regions appear to be located on extra cellular regions of the NR1/NR2 receptors.[2] The presence of these antibodies has been demonstrated to cause decrease in NMDA receptor density by internalization of the receptor.[2,5] More severe loss of receptors has been shown to be correlated with higher antibody titers.[2,5]

DIAGNOSIS

Diagnosis should be suspected based upon clinical presentation and can be confirmed with CSF and antibody testing for antibodies against the NMDA receptor. Less specific CSF findings include lymphocytic pleocytosis, increased protein concentration and the presence of oligoclonal bands.[2] Diagnosis can also be supported by MRI, EEG and in some cases, biopsy findings. MRI findings include increased FLAIR signal, faint enhancement of cortex or meninges or basal ganglia; alternatively MRI can be normal.[2] In cases where biopsy was obtained, pathologic description includes mild perivascular lymphocyte cuffing and microglial activation.[2] Most commonly, EEG findings are generalized slowing or generalized rhythmic slowing.[4,2] Focal slowing appears to

be less common.[4] Additionally, a novel EEG pattern termed "extreme delta brush" has been identified.[4] This pattern consists of 1-3 Hz rhythmic delta with 20-30Hz beta at the crest of each wave similar in appearance to beta-delta patterns seen in premature infants.[4] The appearance of this extreme delta brush pattern seems to be correlated with patients with more severe disease, and its presence should prompt further investigation for anti-NMDA receptor antibodies.[4]

Once diagnosis is suspected, the patient should be evaluated for underlying tumor.[1,2,6] Titularer, et al. reported 38 percent of patients studied had an underlying neoplasm.[1] The most frequently associated tumor in women is ovarian teratoma containing nervous tissue that is positive for expression of NMDA receptors on pathological evaluation.[2] Uncommonly, other tumors have been associated with the disorder including: testicular teratoma, small cell lung cancer, breast cancer, thymic cancer and pancreatic cancer.[1]

TREATMENT

Treatment should begin as soon as possible with tumor resection if possible and initiation of immunotherapy such as steroids, plasma pheresis and IVG as early initiation of therapy has been associated with good outcomes.[1] About half of patients treated in this manner will have symptom improvement in four weeks.[1] Should initial therapy fail, treatment with additional immunosuppressive agents such as cytoxan and rituimab is recommened.[1] Once clinical recovery is achieved the patient should be monitored for relapse.[1] ■

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