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Anti–*N*-methyl-D-aspartate (NMDA) Receptor Encephalitis in a Young Lebanese Girl

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Abstract

Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a recently recognized autoimmune neurologic disorder that presents with severe neuropsychiatric symptoms in previously healthy children. A 4-year-old Lebanese girl presented with new-onset behavioral changes, orofacial dyskinesias, fluctuation in consciousness, inability to walk, and mutism. Antibodies directed against NMDA receptors were detected in the patient's serum and cerebrospinal fluid. Prompt treatment with a single course of intravenous immunoglobulin resulted in early complete recovery. This is the first case report of a Middle Eastern child affected with this condition.

Keywords

anti–*N*-methyl-D-aspartate receptor encephalitis, Middle East, early recovery, NMDA

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Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a newly recognized, treatable, and potentially reversible disorder. The disease is characterized by prominent psychiatric symptoms, dyskinesias, seizures, and cognitive deterioration. Although it has initially been described in young women with ovarian teratoma, it is relatively common in children, often without associated tumor. The diagnosis is based on the detection of autoantibodies directed against the NMDA-type glutamate receptors in serum or cerebrospinal fluid.[1] Prompt recognition of this entity is crucial for the institution of proper therapy, leading to improved outcomes.[2] The early suspicion of anti–NMDA receptor encephalitis in our patient prompted initiation of intravenous immunoglobulin, resulting in complete recovery.

Case Report

A 4-year-old girl of Lebanese origin presented to the emergency department for evaluation of behavioral disturbances, abnormal movements, and acute deterioration of mental status. Three weeks before presentation, she had a febrile illness with tonsillitis that was successfully treated with antibiotics. She was growing and developing appropriately. Five days before presentation, her mother reported that her daughter had episodic temper tantrums and unexplained crying at school. She also had bizarre and inappropriate smiling and became increasingly aggressive. Subsequently, her neurologic condition worsened, as she started to show difficulties in walking and in speech, progressing into mutism, daytime incontinence, mood lability with episodic uncontrollable laughter, alternating with irritability and withdrawal. One day before presentation, her motor skills and eye contact declined and she developed intermittent orofacial dyskinesias and stereotypical hand movements. The neurologic examination in emergency department demonstrated impaired cognition, poor social interaction, absence of speech, orofacial dyskinesias, vocal tics, hand washing movements, and inability to walk. She was afebrile and normotensive.

Initial workup consisted of the following: both brain computed tomographic scan and magnetic resonance imaging (MRI) were unremarkable. Basic blood tests, anti–streptolysin O antibodies, double-stranded DNA virus antibody, and toxicology screening were normal. The electroencephalogram (EEG) showed diffuse generalized slowing with bifrontal, left more than right, sharply contoured theta activity. Cerebrospinal fluid analysis showed 4 white blood cells/μL (36% lymphocytes), 1 red blood cell/μL, a total protein of 0.17 g/L (reference value 0.1-0.5 g/L), glucose of 95 mg/dL (reference value 35-80 mg/dL), and weakly positive polymerase chain reaction for DNA of herpes simplex virus 1. A polymerase

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chain reaction for enterovirus was negative. At this point, phenytoin and a 21-day course of acyclovir were initiated.

Over the following 2 days, the patient quickly deteriorated, exhibiting episodes of inappropriate nocturnal laughter, extreme agitation, and hyperkinetic state characterized by upper extremity choreiform movements. These conditions transiently responded to diazepam and haloperidol. In view of both the clinical picture and the EEG features suggestive of an active ongoing encephalitic process, a tentative diagnosis of autoimmune encephalitis was entertained. On the third day of her hospitalization, a repeat lumbar puncture revealed a negative polymerase chain reaction for DNA of herpes simplex virus 1. Cerebrospinal fluid and serum were sent for NMDA receptor and voltage-gated potassium channel antibody analysis. Oligoclonal band testing was not performed. In view of ongoing neurologic deterioration, intravenous immunoglobulin (1 g/kg for 2 days) was administered 1 week after symptom onset.

An extensive workup to exclude inflammatory, infectious, endocrine, metabolic, and other autoimmune etiologies was performed. This included testing for thyroid function, antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, vitamin B_{12} level, copper, ceruloplasmin, cerebrospinal fluid, and blood polymerase chain reaction for DNA of *Mycoplasma pneumoniae*, arterial lactate, pyruvate, ammonia, plasma amino acids, and urine gas chromatography/mass spectroscopy. All results were normal.

Twenty-four hours after finishing the intravenous immunoglobulin cycle, the patient showed an improvement of her behavior as she became less combative and agitated. In view of her impaired swallowing ability and unstable mental status, a nasogastric tube was inserted. She also suffered from significant sleep circadian rhythm instability, requiring the initiation of melatonin.

Over the subsequent 2 weeks, more improvement in her neurologic condition was noted. She became more responsive and cooperative, could follow simple commands, and was able to walk unassisted and to say few single words. With the disappearance of hyperkinetic movements, her fine motor skills returned to baseline and subsequently she was able to resume full oral feeding. By that time, the NMDA receptor antibodies were found to be positive in both serum and cerebrospinal fluid. The voltage-gated potassium channel antibodies were negative. Magnetic resonance imaging of the pelvis was unremarkable.

Six weeks after onset of symptoms, an outpatient follow-up evaluation revealed significant improvement of her communication and language skills, including expression and comprehension. Her cognitive abilities and sleep circadian rhythm had normalized. All medications (phenytoin, melatonin, and haloperidol) were gradually discontinued. A month later, her neurologic function had returned to baseline. She went back to school with no reported academic difficulties.

Discussion

N-Methyl-D-aspartate receptors are ligand-gated cation channels with major roles in synaptic transmission and neuronal plasticity. These receptors, which are heteromers composed of glycine-binding NR1 subunits and glutamate-binding NR2 subunits, are highly expressed in the limbic system, forebrain, and hypothalamus. Overactivity of NMDA receptors causing excitotoxicity is a proposed underlying mechanism for epilepsy, dementia, and stroke, whereas underactivity produces symptoms of schizophrenia. Autoantibodies in the serum or cerebrospinal fluid of patients with anti–NMDA receptor encephalitis were shown to bind specifically to an epitope located in the extracellular domain of the NR1 subunits.[1] In anti–NMDA receptor encephalitis, antibodies decrease the number of postsynaptic NMDA receptor clusters that can be reversed after antibody removal.[1,3]

The characteristic clinical picture in childhood, which develops in several predictable phases, includes prodromal viral-like symptoms, followed a few days later by behavior and personality changes with cognitive regression. Parents often describe temper tantrums, agitation, aggression, and language disintegration with severe speech deterioration up to frank mutism as early manifestations of the disorder. Additional symptoms, seen in the majority of children, are movement disorders characterized by orofacial dyskinesias, choreoathetosis and dystonia, rigidity, and also seizures. An altered level of consciousness and sleep disturbance can occur, followed by gradual partial or complete recovery.[4,5] Unlike adults, children developed less severe autonomic manifestations such as hypoventilation, tachycardia, hypertension, hyperthermia, and diaphoresis. Although our patient did not show these manifestations, she had other signs of autonomic instability such as daytime enuresis and insomnia that are more commonly seen in children with anti–NMDA receptor encephalitis.[4]

Although there was an initial behavioral improvement, substantial cognitive and sleep dysregulation recovery took much longer. The early behavior improvement in our patient after intravenous immunoglobulin therapy is somewhat atypical. Poloni et al reported the following recovery sequence: gradual resolution of dyskinesias followed by improvement in motor, then comprehension and expressive functions.[6]

In most reports, the brain MRI is often normal or shows transient fluid attenuation inversion recovery or contrast-enhancing abnormalities involving the medial temporal lobes, basal ganglia, corpus callosum, and brainstem. The electroencephalogram reveals diffuse slowing without epileptiform discharges or disorganized activity that does not correlate with most abnormal movements.[1,4] Cerebrospinal fluid analysis can reveal lymphocytic pleocytosis, elevated protein levels, and the presence of oligoclonal bands, suggesting an inflammatory or immune-mediated neurologic process.[5,7] The diagnosis relies on testing for anti–NMDA receptor antibodies in serum and/or cerebrospinal fluid.[2] Most patients have higher levels of antibodies in cerebrospinal fluid than in sera, indicating intrathecal synthesis of antibodies.[1]

The mechanisms that initiate this disorder are unknown. The frequent prodromal flulike symptoms in anti–NMDA receptor encephalitis suggests a viral infection–triggered immune response.[8] The occasional presence of an NMDA receptor

expressing ovarian teratoma might also trigger an immune response, hence the favorable outcome following tumor removal and immunosuppressive therapy.[7]

The clinical constellation in our patient of neuropsychiatric symptoms, social withdrawal, mutism, orofacial dyskinesias, and sleep disturbances was consistent with the known profile for anti–NMDA receptor encephalitis. In spite of the latter, viral encephalitis had to be excluded. Our patient initially had a weakly positive polymerase chain reaction for DNA of herpes simplex virus 1 that became negative after 48 hours of acyclovir therapy. However, herpes simplex virus 1 encephalitis is generally associated with a higher cerebrospinal fluid white blood cell count and protein concentration when compared to patients with anti–NMDA receptor encephalitis,[9] and will typically have a negative cerebrospinal fluid herpes simplex virus 1 polymerase chain reaction after 14 days of acyclovir treatment.[10,11] False-positive test results are rare and usually reflect accidental laboratory specimen contamination.[10] Although bizarre personality changes are well described in patients with herpes simplex virus type 1 encephalitis, a review by Gable et al suggested that severe neuropsychiatric manifestations, in addition to choreoathetosis and orofacial dyskinesias, are more prominent in patients with anti–NMDA receptor encephalitis.[9] Thus, we believe that our patient had a falsely positive polymerase chain reaction for DNA of herpes simplex virus type 1. Indeed, the presence of NMDA receptor antibodies in both serum and cerebrospinal fluid confirmed the diagnosis of anti–NMDA receptor encephalitis.

There is no specific treatment protocol for the management of anti–NMDA receptor encephalitis. Immune modulation through the use of immunoglobulin, corticosteroids, cyclophosphamide, plasmapheresis, and possibly rituximab are the mainstay of treatment in nonparaneoplastic encephalitis.[1,6,12,13] Individuals with ovarian teratoma are treated by tumor excision and with immunotherapy. About 75% of individuals have full or substantial regression of symptoms. However, 25% of cases suffer from severe neurologic deficits or die. Neurologic relapses occur in 25%.[6,12,13] The reported time to clinical recovery is variable, ranging from 2 weeks to 24 months.[1,4,6]

Our patient has no evidence of an ovarian tumor and has made a full recovery after immunotherapy. Periodic surveillance for at least 2 years using MRI of the pelvis has been recommended in females of all ages diagnosed with anti–NMDA receptor encephalitis.[3] Our patient is scheduled to undergo MRI of pelvis at 6-month intervals. Moreover, Florance et al reported that tumor detection is usually inversely proportional to patient's age (the frequency of ovarian teratomas was 56% in women >18 years old, 31% in girls <18 years old, and 9% in girls <14 years old).[4]

Most patients with anti–NMDA receptor encephalitis described in the literature were of non-Caucasian (Asian or Pacific Islander), Caucasian European, and African American origin.[5,9] To our knowledge, this is the first case report from the Middle East. The underlying genetic predisposition for anti–NMDA receptor encephalitis is unknown. Verhelst et al reported on a 3-year-old male patient with anti–NMDA receptor encephalitis in whom an inherited microdeletion on chromosome 6, including the human leukocyte antigen cluster, was detected.[14] These observations raise many questions regarding the pathology of this disease and suggest that there can be human leukocyte antigen or other genetic factors involved in disease susceptibility.

In conclusion, anti–NMDA receptor encephalitis should be considered in the differential diagnosis of acute encephalitis with neuropsychiatric features in children. Microarray comparative genomic hybridization and human leukocyte antigen studies in future patients with anti–NMDA receptor encephalitis might help in elucidating the genetic as well as possible ethnic variability for this condition. Early diagnosis and therapy are crucial to achieve the best possible outcome.

Author Contributions

LS wrote the manuscript drafts. OD revised the draft writing, mentored LS, and edited subsequent manuscript drafts.

Declaration of Conflicting Interests

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Ethical Approval

The local policy at the American University of Beirut Medical Center does not require approval from the Institutional Review Board for case reports. None of the presented data carries patient identifiers.

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