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Anti–*N*-Methyl-D-Aspartate (NMDA) Receptor Encephalitis: An Unusual Cause of Autistic Regression in a Toddler

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Abstract

Anti *N*-methyl-D-aspartate (NMDA) receptor encephalitis in children is associated with psychiatric changes, seizures, and dyskinesias. We present the first report of autistic regression in a toddler caused by this entity. A 33-month-old boy presented with decreased appetite, irritability, and insomnia following an upper respiratory tract infection. Over the next few weeks he lost language and social skills, and abnormal movements of his hand developed. Within a month, this patient came to fit the diagnostic criteria for autistic spectrum disorder. Upon investigation, anti-NMDA receptor antibodies were found in the boy's cerebrospinal fluid. He was treated with intravenous immunoglobulins and steroids, resulting in reacquisition of language and social skills and resolution of movements. Our case emphasizes the significance of suspecting anti-NMDA receptor encephalitis as the cause of autistic regression, even in an age group where the diagnosis of autistic spectrum disorder is typically made, and especially when presentation follows a febrile illness.

Keywords

Autistic spectrum disorder, anti-NMDA receptor encephalitis, autoimmune autistic regression

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Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a relatively new entity, described for the first time in 2005 in association with ovarian teratomas in adults.[1] Initially described as an acute psychiatric syndrome, anti-NMDA receptor encephalitis is characterized by an array of psychiatric manifestations, including psychosis, paranoia, and catatonia, often following flulike prodrome. Other characteristic symptoms include decreased level of consciousness, memory deficits, and autonomic instability.[1-7] This condition has since been described in children and adolescents as a nonparaneoplastic condition, with clinical manifestations including personality and behavioral changes, aggression, seizures, language dysfunction, dystonia, or dyskinesias.[8,9]

Definitive diagnosis of anti-NMDA receptor encephalitis is based on the presence of anti-NR1 antibodies in the patient's cerebrospinal fluid or serum, and the mainstay of treatment includes corticosteroids, intravenous immunoglobulins, or plasma exchange, with most patients demonstrating good recovery following treatment.[7-9] Owing to the variability in presentation of this entity, identification of children with this condition can present a challenge to clinicians. We describe the first report of autistic regression in a toddler caused by anti-NMDA receptor encephalitis.

Case Report

A previously healthy 33-month-old boy was admitted to the hospital because of acute developmental regression starting a month prior to his admission. His perinatal history, as well as his past medical history and family history, was unremarkable. A month prior to admission, the parents had noticed a decrease in appetite and restless sleep, followed by significant behavioral changes that were progressive in nature, including

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irritability and temper tantrums. He later developed a mild febrile upper respiratory tract infection, which was treated with antibiotics. Despite resolution of the infection, the patient continued to regress, losing previously acquired language skills, finally becoming mute and noncommunicative. Interest in social interaction and eye contact were also subsequently diminished. The patient was reported to have facial grimacing that presented with twitching of the corners of his mouth, as well as repetitive left hand movements.

On examination, the patient was irritable, nonverbal, and did not make eye contact. No dysmorphic features, skin stigmata, midline lesions, or organomegaly was present. Cranial nerve exam was unremarkable. Cerebellar function tests were all normal, with neither ataxia nor tremor. He had normal muscle tone and strength and normal and symmetric deep tendon reflexes, with no pathologic reflexes. The patient's gait was narrow-based, and he toe-walked on occasion. Left arm posturing and occasional wringing movements of the left wrist were noted, as well as decreased spontaneous usage of the left hand. Based on examination, the patient met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for autistic spectrum disorder.[10]

Laboratory investigations were initiated, which included complete blood count, sedimentation rate, C-reactive protein, prothrombin time, partial thromboplastin time, electrolytes, urea, creatinine, iron, lactate, urate, catecholamines, amino acids in plasma and urine, organic acids in urine, very-long-chain fatty acids, beta-hydroxybutyrate, copper, ceruloplasmin, carnitine, and acyl carnitine, all of which were normal. There were mild elevations of alanine aminotransferase and aspartate aminotransferase (66 U/L and 76 U/L, respectively; normal < 50 U/L). Blood, urine, and cerebrospinal fluid bacterial cultures were negative. Serology for Lyme disease, Epstein-Barr virus, cytomegalovirus, parechoviruses, enteroviruses, herpes simplex types I and II, varicella zoster, West Nile virus, mycoplasma, and Bartonella were all negative. Antistreptolysin antibody was negative.

Cerebrospinal fluid biochemistry and neurotransmitter analysis were both normal; however, protein electrophoresis of cerebrospinal fluid revealed a mild elevation of IgG index 0.97 (normal < 0.85). Cerebrospinal fluid IgG index is a nonspecific indicator of autoimmune pathology,[10] described to be elevated in disorders such as multiple sclerosis[11] and anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis.[12] Hence, the increase in this index has raised our suspicion of an autoimmune condition. Brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy were both normal. Video electroencephalography (EEG) performed overnight revealed a nonspecific generalized background slowing with no seizures. As anti-NMDA receptor encephalitis was suspected because of the elevated cerebrospinal fluid IgG index, cerebrospinal fluid was sent to test for anti-NR1 antibodies, which came back positive, confirming our clinical suspicion.

The patient was treated with a 5-day course of intravenous immunoglobulins 0.4 g/kg/d, as described previously in the literature for treatment of anti-NMDA receptor encephalitis,[13] and as is also used in other autoimmune conditions such as Guillain-Barré syndrome.[14] Reacquisition of language and social skills were noted since the third day of treatment. He began using single words in the appropriate context again, started showing more interest in social interaction with his parents, and demonstrated an increment in eye contact. After termination of this treatment course, he was prescribed high-dose steroids (2 mg/kg/d) for 2 weeks, with slow tapering over 6 weeks. During that period, the patient made significant improvement, as behavior and personality were restored to their pre-illness state. He regained more linguistic skills and demonstrated the ability to use multiple short phrases. The facial grimacing and left hand posturing were resolved, and he started using his left hand as he previously had.

Discussion

Autistic spectrum disorder is characterized by impairment in communication and social behavior, as well as repetitive or stereotypical behavior, with onset before 3 years of age.[15]

Although most children diagnosed with autistic spectrum disorder fail to attain communication and/or social skills in their first 2 years of life, up to one third of cases are characterized by loss of previously acquired skills during toddlerhood.[16-18]

The great heterogeneity in presentations of autistic spectrum disorder suggests that its etiology is complex and can involve an underlying autoimmune process, as previously suggested by Singh.[19] This hypothesis is plausible given the higher rate of autoimmune conditions in families of patients with autistic spectrum disorder as compared to healthy controls, such as type 1 diabetes mellitus, systemic lupus erythematosus, ankylosing spondylitis, and thyroid disorders.[20-23] Further studies supporting the autoimmune hypothesis have shown that 30% to 70% of autistic patients have circulating anti-brain antibodies, a rate that is significantly higher than that found in healthy controls, but their significance in the pathogenesis of autistic spectrum disorder is unknown.[24-30]

With regard to the role of NMDA in autism, emerging genetic data suggests that some autistic spectrum disorder–linked mutations disrupt the NMDA-receptor transsynaptic signaling; moreover, in murine models of autism, partial NMDA-receptor agonists were able to correct social and communication deficits, as well as repetitive behaviors.[31-38] A partial explanation for the link between NMDA and autism could lie in the hormone oxytocin shown to be involved in social cognition, the action of which is mediated by the NMDA receptor.[39,40] However, further studies will be needed to elucidate the exact pathophysiology of glutamatergic dysfunction in autistic spectrum disorder.

Our case emphasizes the significance of suspecting anti-NMDA receptor encephalitis as the cause of autistic regression. We caution physicians to maintain a high index of suspicion even in an age group where the diagnosis of autistic spectrum disorder is typically made, and especially when presentation follows a febrile illness.

Author Contributions

OS and ME performed the literature search and cowrote the initial draft. LR, KF, LS, AC, and HG were all a part of the clinical team who diagnosed and treated the patient. They all made contributions to the final draft. All authors reviewed and approved the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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