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Case Report

Autoimmune Encephalitis: Report of Two Pediatric Cases

Azita Tavasoli [1], Mitra Hakim Shooshtari [2*], Behnaz Parvini [3]

1. Department of Pediatric Neurology, Ali Asghar Children's Hospital, Iran University of Medical Sciences, Tehran, Iran
2. Department of Pediatric Psychiatry, Ali Asghar Children's Hospital, Iran University of Medical Sciences, Tehran, Iran
3. Pediatrician, Iran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Autoimmune encephalitis (AIE) with neural cell autoantibodies is a treatable category of non-viral encephalitis in children and adolescents which presents with neuropsychiatric manifestations. Anti-N-methyl- D-aspartate receptor encephalitis, the most common identified type of AIE, is more frequent than individual viral encephalitis in young patients. Early diagnosis and treatment of the disease have been associated with improvement in the majority of patients.

Case Report: we report two pediatric cases with acute neuropsychiatric presentations in whom the diagnosis of AIE was proved based on the cerebrospinal fluid (CSF) antineuronal antibodies in one and on clinical and paraclinical grounds in another seronegative patient. Immunotherapy in both patients resulted in improvement. No underlying tumor was found in patients.

Pediatricians should be aware of manifestations, investigations, and treatment of AIE and consider it as the differential diagnosis of encephalitis.

Keywords: Autoimmune encephalitis, Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Pediatrics, Encephalitis, Immune-mediated encephalitis

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***Correspondence** Mitra Hakim Shooshtari; Email: Mitra.hakim@gmail.com

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Introduction

Encephalitis is a brain inflammatory disease that causes altered consciousness state, seizure and focal neurologic deficit, and usually is associated with cerebrospinal fluid (CSF) inflammation (1). Encephalitis is developed by various causes including primary central nervous system (CNS) infection or development of an immune-mediated response to vaccination, viral infection or occult tumor (2). Some tumors have neural tissue or express the neural proteins that result in immune reaction with antibodies. Some viral encephalitis such as herpes simplex encephalitis (HSE) can induce antibodies to neural cell surface antigens (3).

Auto immune encephalitis (AIE) that is associated with antibodies to neuronal proteins presents with primary neuropsychiatric complaints. It is the third most frequent form of acute encephalitis after viral infection and post-infectious encephalitis (2). Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, the most common identified type of AIE, is more frequent than individual viral encephalitis in young patients (3). Anti-neuronal antibodies that are detected in patient's serum and/or CSF are consisted of antibodies against cell surface proteins, which are involved in neural transmission, antibodies to synaptic antigens that are related to neurotransmitters release, and antibodies against intracellular antigens (4). According to the antibody type, clinical manifestations vary and contain psychological and behavioral complaints, amnesia and cognitive defects, dysautonomia, movement disorders, seizures, and encephalopathy (3,4). Some types of AIE predominantly occur in children and are more frequent in females and less associated with neoplasm (5). Immunomodulatory regimens that are used for the treatment include corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis (6). If a concurrent neoplasm is present, oncologic management also is necessary (4, 5). Early diagnosis and treatment of the disease have been associated with improvement in the majority of patients (3).

Here, we report two pediatric cases with acute neuropsychiatric presentations in whom the diagnosis of AIE was proved based on the CSF anti-neuronal antibodies in one and on clinical and paraclinical grounds in another seronegative patient.

Case reports

Patient 1

The patient was a previously healthy 4-year-old boy presented with acute episodes of seizure evolved to unilateral tonic-clonic status epilepticus. He had fever, headache, and abdominal pain from 3 days before the occurrence of seizures. His perinatal period was uneventful and developmental status was appropriate for age. The parents were genetically not related and family history of neurological disorders was negative. At first, he had fever, lethargy, and neck stiffness on examination. Laboratory tests showed leukocytosis with 62% predominancy of polymorphonuclears. CSF analysis showed white blood cell count (RBC) of 650/mm^3 with predominancy of lymphocytes and 60 red blood cells without xanthochromia. CSF protein was 47 mg/dl and its lactate and glucose level were normal. CSF and blood cultures and CSF PCRs for herpes simplex virus and enetroviruses were negative. Serum biochemistry tests were normal. Seizures were controlled with parenteral diazepam, phenobarbital, and phenytoin. Empiric therapy with antibiotics and acyclovir started with the probable diagnosis of meningoencephalitis. Brain MRI with and without contrast was normal but electroencephalography (EEG) showed generalized slowing. Four days after admission, the patient became afebrile but he developed severe agitation, restlessness, insomnia, and facial dyskinesia and choreiform movements in the extremities. He lost his eye contact and could not recognize his parents. His speech was slurred, and ultimately, evolved to aphasia. He could not sit independently and developed motor, speech, and cognitive regression during a few days later. Clonazepam and risperidone that were prescribed according to the psychologist consultation, were ineffective. He experienced two another seizure episodes. Antinuclear antibodies, lupus anticoagulants, anti-phospholipid antibodies and other investigations for vasculitis, thyroid function tests, serum ammonia, lactate, pyruvate and serum and urine amino acid chromatography, urine organic acid, and echocardiography were normal. As the diagnosis of AIE was suspected, serum and CSF specimens for antineuronal antibodies were sent to laboratory. IVIG at 400 mg/kg/day and methylprednisolone at 30 mg/kg/day were prescribed for 5 days, but the symptoms of the patient were not improved. The results of abdominal, pelvic and testicular ultrasound for

searching occult neoplasm were negative. Plasmaphresis was started, and after the third session, the patient demonstrated a significant improvement in behavior, sleep, motor, and language. After that, he could sit and walk independently and choreic movements reduced markedly. He discharged 2 weeks later with anticonvulsant drug while all the symptoms were recovered completely. The results of anti-neuronal antibodies in the serum and CSF were negative. At 6-month follow-up, the patient was good and by the time of writing this paper, the symptoms have not been recurred.

Patient 2

He was a previously healthy 11-year-old boy presented with lethargy and psychiatric symptoms such as delusions, aggression, and bizarre behavior from one week ago, after a few days of fever and upper respiratory tract infection. He refused to go to school and had low appetite and decreased level of activity and speech. The previous history of neuropsychological diseases was negative. Physical examination of the patient showed no abnormal organic findings. He admitted with the primary diagnosis of encephalitis. In the paraclinical investigations, serum biochemistry, transaminases, complete blood count (CBC), sedimentation rate, and the results of lumbar puncture, brain MRI, and EEG were normal. CSF and blood cultures and PCRs for herpes simplex virus (HSV), Epstein-Barr virus (EBV), and enteroviruses were negative. Based on the clinical history, presumptive diagnosis of AIE was made. Serum and CSF specimens for anti-neuronal antibodies were sent to laboratory and IVIG at 400 mg/kg/day was started for 5 days. Then, the patient was discharged with relative improvement while risperidone was prescribed for him. One month later, he referred with the previous psychiatric symptoms and admitted again. The results of CSF antibodies against voltage-gated potassium channel complex (VGKC) was 294.6 pM, which is significantly higher than the normal value (<85 PM). The results of other antibodies in the CSF and serum were negative. The findings of abdominal, pelvic, and testicular ultrasound for occult neoplasm were negative. Methylprednisolon started for him at 30 mg/kg/day up to 1 gr/day for 5 days. Psychiatric symptoms diminished gradually and the patient was discharged with medications. One month later, the VGKC antibodies were decreased to 30.6 pM and the patient was symptom free while consuming risperidone.

Discussion

Recognition of AIE is progressively increased as an etiology for acute or subacute neuropsychiatric disorders that are sensitive to immunotherapy (7). Presentation of AIE in children is frequently subacute. A combination of various symptoms occurs that are related to the underlying antibodies indicative of the specific type of AIE (4). AIE in adults is usually associated with an occult neoplasm that triggers autoantibody synthesis. Although tumor association is less frequent in childhood, there are some reports about paraneoplastic or tumor-associated AIE in childhood. Hence, it is mandatory to look for the underlying neoplasm (1). Unilateral or bilateral teratomas occur in 30% of females under the age of 18 years and 9% of girls under the age of 14 years (8). Teratomas of testis in men is rare and it has not been found in young boys (1). As well, we could not find any underlying tumor in our patients. Anti-NMDA receptor encephalitis is the most common type of AIE in children, which was first recognized in 2007 (4). Approximately, 40% of all patients are younger than 18 years and young girls make up 80% of childhood cases (2). IgG subclass G1 antibodies bind the glu N1 subunits of the NMDA receptors and lead to their underexpression (9). NMDA receptors are ionic channels in the brain which have an essential effect in plasticity and synaptic function (2). The absence of the receptors induces the typical presentations of the disease. The syndrome evolves in stages consisting of a prodromal phase with a few days of fever, headache and/or upper respiratory tract infection symptoms. These complaints are followed by behavioral and neuropsychiatric problems including amnesia, speech disorder, bizarre behavior, Paranoia, anxiety, insomnia, delusions, agitation, seizure, ataxia, abnormal movements, and dysautonomia (1). A recent study has shown that seizures, abnormal movements, and behavioral problems are the most frequent symptoms in children (8). Movement disorder may present as dystonia, choreoathetosis dyskinesia, and tremor (2). Decreased speech and mutism, aggression, temper tantrum, and personality changes have been reported in the patients. We found all of these symptoms in our 22-month-old patient. Autonomic dysfunction in children is not as common as adults and include

gastroparesis, urinary incontinence, central hypoventilation syndrome and Paroxysmal tachycardia, fever or hypertension (1). These conditions develop in almost 40-50% of children and adolescents (6). Sleep disturbances particularly insomnia and less commonly lethargy develop in all patients (10). Cerebellar ataxia, hemiparesis, and memory dysfunction are the other manifestations (5). About one month after disease presentation, most patients have a combination of several symptoms, but in 5% of the patients, the disease may continue with only one dominant symptom such as psychiatric complaints (6). We observed these psychological symptoms in our 11-year-old patient.

Brain MRI abnormalities in anti-NMDAR encephalitis are noted in less than 50% of children (6). In a study on 32 patients, abnormal MRI was seen in 31% of the patients (8). These findings include hyperintensities on T2-weighted images in cerebral cortex and subcortical areas, basal ganglia, brain stem, and cerebellum. According to the report of Kelley et al. (2017), in 80% of patients with anti-NMDAR encephalitis, the results of neuroimaging have been normal (11). Based on the studies, MRI abnormalities in AIE are not sensitive or specific (5). In both our patients, brain MRI was normal. It has been suggested to use 18-fluorodeoxyglucose positron emission tomography (FDG/PET) for diagnosis in the cases with strong clinical suspicion of AIE, as it is more sensitive than MRI in the early recognition of the disease (12). The CSF in AIE may be normal (5). In the study of Florance et al. (2009), lumbar puncture showed abnormalities in 94% of the patients that were pleocytosis with lymphocyte dominancy, elevated protein or oligoclonal bands (8). Electroencephalographic abnormality including focal or generalized slowing and/or epileptic discharges is seen in 90-100% of the patients (1, 2). A typical EEG finding, named "extreme delta brush" may be seen as a diagnostic support (5). Similarly, diffuse slowing in EEG was found in our patient. The diagnosis was confirmed by detecting anti-NMDA receptor antibodies in the serum and/or CSF (1, 2, 5). The antibody presence in the CSF is more sensitive and its level is correlated with the disease course (5). In some patients with clinical manifestations of AIE, no antibodies have been found (13). Many children with suspected immune-mediated encephalitis have undetectable antibodies (13). Besides, due to technical limitations in many laboratories, AIE do not be excluded by negative antibody results (5). Triggers of NMDA antibodies are ovarian teratomas, CNS infections especially HSV encephalitis, systemic infections, and sometimes, idiopathic (13). In our patient, despite of clinical presentation of anti-NMDA receptor encephalitis and abnormal EEG and CSF findings, the antibodies results were negative.

Randomized clinical trials have not yet assessed the standard treatment in AIE and plans are based on the retrospective studies (1, 5, 7, 13). The first line of treatment consists of high dose corticosteroids, IVIG, and plasma exchange. The second line of treatment, rituximab and/or cyclophosphamide, are used for patients without improvement after 10 days of the first line treatments (5, 7). Mycophenolate mofetil and azathioprine are used as chronic immunotherapy in patients with relapse probability (5, 7). Although it is a serious disease with 5% mortality, the clinical outcome is favorable in children, as up to 80% of whom have full improvement (2, 13). Dysautonomia, movement disorder, state of consciousness, and seizures are first improved. Psychiatric complaints can reoccur later at home (1). There is therapeutic differences between various syndromes of AIE. In anti-NMDA receptor encephalitis, the response to treatment is slow and usually the second line drugs are necessary for full improvement. In some other forms, patients respond rapidly to the first line immunotherapy (13). Early treatment is one of the factors that predicts good prognosis (6). In our series, the first line therapy resulted in improvement in both patients. Clinical relapses occur in 15-25% of the patients (1, 2, 5). At 12-month follow-up, relapses did not occur in our patients.

Two other forms of AIE are encephalitis with leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (Caspr2) antibodies. These syndromes have previously been considered to be related to antibodies to voltage-gated potassium channels (VGKC), but in fact, target antigens are composed of proteins LGI1 and Caspr2 (5). Many of the reported anti-VGKC-antibodies are indeed antibodies to one of these specific antigens that may not be identified (2). Although, positive results of VGKC-antibodies assessed by radioimmunoassay are nonspecific, high levels could be diagnostic in patients with suspected

AIE (14). Confusion, memory loss, cognitive defects, mood disturbances, and seizures are manifestations of this type of AIE. CSF is usually normal and brain MRI may show hyperintensities on T2/FLAIR images of the medial temporal lobe (2). Association with neoplasm is common in adults but there is not any report of this association in children (2, 5). Response to immunotherapy is good. We detected a very high CSF level of VGKC antibodies in our patient that in the context of clinical manifestations and good response to immunotherapy was indicative of AIE.

Conclusion

Autoimmune encephalitis with neural cell autoantibodies is a treatable type of non-viral encephalitis in children and adolescents, which presents with neuropsychiatric manifestations. Although, the diagnosis of AIE has been increased in recent years, pediatricians should be still aware of its manifestations, investigations and treatment, and consider AIE as the differential diagnosis of encephalitis. Early diagnosis and treatment are important, as the patients usually respond to immunotherapy. Paraneoplastic mechanism in children is not common, however, searching for underlying neoplasm is mandatory.

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