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Autoimmune Encephalitis in Children: A Retrospective Analysis of 13 Cases

Faruk Incecik* and Ozlem M. Herguner

Divisions of Pediatric Neurology, Cukurova University Faculty of Medicine, Adana, Turkey.

***Corresponding Author:** Faruk Incecik, Divisions of Pediatric Neurology, Cukurova University Faculty of Medicine, Adana, Turkey.

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Abstract:

Autoimmune encephalitis is a rapidly progressive encephalopathy caused by antibody-mediated neuro-inflammation that presents with a range of neuropsychiatric symptoms, seizures, focal neurologic deficits, abnormal movements, and/or dysautonomia. The aim of this study is to evaluate clinical findings, treatment and prognosis in children with autoimmune encephalitis. We retrospectively analyzed clinical records and data of 13 patients with autoimmune encephalitis. A total of 13 children had autoimmune encephalitis, 10 patients (%76.9) had anti-GAD encephalitis, two patients (%15.4) had anti-NMDAR encephalitis, and one patient (%7.7) had anti-LGI1 encephalitis. The median age at presentation was 9 years (range 5-17 years), and 7 of the patients (53.8) were female. The most common presenting symptoms were confusion, behavior change and seizures. Most of patients have a good response to first-line immunotherapy. In conclusion, autoimmune encephalitis may present with different clinical findings in children. As a result, autoimmune encephalitis may present with different clinical findings. Since early diagnosis and treatment are important, autoimmune encephalitis should be kept in mind in the diagnosis of children presenting with behavioral change, seizures and changes in consciousness.

Keywords: autoimmune encephalitis; prognosis; children

Introduction

Autoimmune encephalitis (AE) is emerging as an important and relatively common cause of encephalitis in the developed world. Crucially, early recognition and prompt initiation of a range of immunotherapies is likely to improve the outcomes of patients with AE. AE is characterized by an acute to subacute onset of neuropsychiatric symptoms, seizures, focal neurologic deficits, abnormal movements, and/or dysautonomia [1].

The pathophysiology of AE involves against specific neuronal molecular structures through various immune-mediated mechanisms. The major mechanisms are related to antibodies directed against extracellular and intracellular neuronal targets. Antibodies against the following cell surface targets are anti-glutamic acid decarboxylase (GAD), anti-N-methyl-d-aspartate-receptor (NMDAR), anti-voltage-gated potassium channels (VGKC) complex, anti-leucine-rich glioma-inactivated-1 protein (LGI1) and anti-γ-aminobutyric acid receptor [2].

Cerebrospinal fluid and serum antibody detection is crucial to determine the specific type of AE. However, some patients were diagnosed with AE clinically but autoantibodies were negative. Although there is much in the literature about AE, regarding specifically for children's AE it is still limited [3-5]. Therefore, we presented the clinical characteristics, treatment, and prognosis of children with AE herein.

Methods

Patients who were diagnosed with AE with antibody positivity between 2016 and 2020 were included in the study. The data were retrospectively collected from the clinic files and included age, sex, history of previous infection, type of infection, prodromal and presenting symptoms, time of onset of symptoms, electroencephalogram (EEG), cerebral magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) findings, antibody type, treatment, response to treatment, whether there is sequela and relapse existence.

Autoimmune encephalitis was diagnosed by pediatric neurologists in our hospital on the basis of clinical findings and the presence of specific antibodies in serum or CSF. All suspected reasons of central nervous system infection were excluded as well as encephalopathy secondary to sepsis or systemic inflammatory response syndrome.

Prodromal period findings are fever, headache, debility, loss of appetite, vomiting and weight loss. Onset of the disease was defined as acute when neurological symptoms appeared at onset of any symptoms or within 7 days of a prodrome. They were subacute when appearing 8-30 days after prodrome and chronic if the interval was longer than 30 days. Cerebral MRI findings were grouped as normal and abnormal ones. Locations of abnormal MRI findings were determined as basal ganglia, brainstem, cerebellum and cerebrum (frontal, temporal, temporo-occipital localization). EEG findings were grouped as normal, focal slowing, generalized slowing, epileptic discharge, and extreme delta brush. All CSF samples were examined using cytology, glucose and protein levels, and infection agent determination. All patients were screened for malignancy; no tumors were identified. First-line immunotherapy

included high-dose intravenous methylprednisolone (IVMP) or intravenous immunoglobulins (IVIg), or combination of these. All patients were followed for at least 2 years.

Results

Thirteen patients diagnosed and treated with AE were included in the study. In all of them 10 patients (%76.9) had anti-GAD encephalitis, two patients (%15.4) had anti-NMDAR encephalitis, and one patient (%7.7) had anti-LGI1 encephalitis. The median age at presentation was 9 years (range 5-17 years), and 7 of the patients (53.8) were female.

Onset of the disease was defined as acute in 9 patients (69.2%), subacute in 3 patients (23.1%) and chronic in 1 patient (7.7%). Prodromal period findings were seen in 8 (61.5%) patients. Common prodromal symptoms included fever alone in 3 patients (37.5%) and fever with associated symptoms in 5 patients (62.5%). The most common presenting symptoms were confusion (5/13 patients), behavior change (7/13 patients) and seizures (8/13 patients). Other common symptoms were speech difficulties, movement disorder, confusion, headache and neck stiffness.

Cranial MRI was performed in all patients and it was found to be normal in 5 (%38.5). The most common abnormal locations of findings in 3 (42.8%), 2 (25.5%), and 2 (28.5%) patients were found in the frontal lobe, temporal lobe, and basal ganglia, respectively. EEG was performed in all patients, and in 8 (61.5%) patients abnormal findings were found, 4 (50.0%) patients had epileptic discharge, 1 (12.5%) patient had generalized slow wave, 2 (25.0%) patients had focal slow-wave, and 1 (12.5%) patient had exhibited extreme delta brush.

In treatment, intravenous immunoglobulin (IVIg) plus IVMP therapy was performed in 8 patients (61.5%), IVIg plus plasmapheresis (PE) therapy was performed in 2 patients (15.4%), and IVIg plus plasmapheresis plus IVMP therapy was performed in 3 patients (23.1%). In prognosis, 9 patients (69.2%) had complete recovery, 3 (60.0%) patients had behavior disorder, and one (20.0%) patient had epilepsy. No relapse was observed in any patient during at least two years follow-up. The characteristics of the patients are shown in (Table 1).

Discussion

Autoimmune encephalitis is an increasingly recognized cause of encephalitis in which one's own antibodies target neuronal antigens, leading to an inflammatory central nervous system disease that presents with a range of neuropsychiatric symptoms, seizures, focal neurologic deficits, abnormal movements, and/or dysautonomia. Different forms of AE have been increasingly identified in the last 10-15 years, largely based on the identification of autoantibodies [1].

Autoimmune encephalitis associated with cell surface antigens is more common in children, encephalitis associated with antibodies against NMDAR, γ-aminobutyric acid A receptor (GABAAR), and GAD65 are the most frequent in literature [6]. The common clinical findings of AE include behavior change, seizure, abnormal memory and cognitive function, movement disorders, and change in consciousness.

To date, a very limited number of pediatric case series and reports have been published [3,5]. Rutatangwa et al. reported that they detected anti-NMDAR encephalitis in 11 patients, steroid-responsive encephalopathy associated with thyroiditis in two patients, and glial fibrillary acidic protein (GFAP) associated encephalitis in one patient [3]. Boesen et al. detected that they found anti-NMDAR encephalitis in four patients and anti-GAD65 encephalitis in 2 patients in their study [4]. In another study, Zhang et al. described a total of 103 children with AE, including 89 with anti-NMDAR encephalitis, two with anti-LGI1 encephalitis, one with anti-CASPR2 encephalitis, and 10 autoantibody-negative encephalitis [5]. In our study, we found anti-GAD encephalitis in 10 of 13 patients, anti-NMDAR encephalitis in two, and anti-LGI1 encephalitis in one.

Anti-NMDAR encephalitis is the most common type of AE in childhood. The most common clinical features of anti-NMDAR encephalitis were seizures, behavior change, language, movement, and sleep disorders [7,8]. Ho et al. identified 15 patients with anti-NMDAR encephalitis, and their median age of presentation was 12 years. The most common symptoms were abnormal psychiatric behavior or cognitive dysfunction (93%) and seizures (93%), followed by speech dysfunction (87%), movement disorders (80%), decreased level of consciousness (10/15, 67%) and autonomic dysfunction or central hypoventilation (33%) [9]. Another study, Zhang et al. reported that the most common symptoms were psychiatric symptoms in 72 (80.9%) patients, seizures in 65 (73.0%) patients, movement disorders in 65 (73.0%) patients, language disorders in 60 (67.4%) patients, memory disorders in 57 (64.0%) patients, and sleep disorders in 43 (48.3%) patients [5]. The common symptoms seen in our patients were behavioral change, seizure, headache and movement disorder.

Glutamic acid decarboxylase, another antigen of interest, is dissimilar to the intracellular onco-neural antigens as anti-GAD antibody associated neurological syndromes are usually non-paraneoplastic and immune responsive [1,6]. This entity is mainly recognized in adults and very few cases were reported in children [4,10-12]. Anti-GAD65 encephalitis is characterized by limbic involvement with refractory seizures, cognitive impairment and behavioral disturbances. Extralimbic involvement is rarely reported. It is a rare condition in children and to the best of our knowledge, there have been only few paediatric cases [4,12]. Boesen et al. reported four children with anti-GAD65 associated AE [4]. Achour et al. presented a 9-year-old girl with refractory seizures, behavioral disturbances, and uncontrollable dysautonomia [10]. In another case, Korff et al. reported a 6-year-old patient who had developed refractory epilepsy, developmental regression associated with anti-GAD65 encephalitis [11]. We had 10 patients and the most common symptoms were altered consciousness, seizures, and behavioral change.

LGI1 is one of the synaptic autoantigens targeted in VGKC. LE associated with anti-LGI1 antibody is a rare inflammatory brain disease characterized by acute or subacute onset of confusion, cognitive impairment, facio-brachial dystonic seizures (FBDS), and behavioral and psychiatric disturbances [13,14]. To date, there have been only few pediatric cases associated with anti-LGI1 encephalitis. Zhang et al. described reported on two boys aged 8 and 15 years. The complaints of the patients were insomnia and seizures [5]. Our patient was an eight-year-old girl who was suffering from behavioral change, hallucinations, confusion, and seizures.

Brain MRI in patients with AE related antibodies may be normal or show increased T2 signal, especially in the medial temporal lobes [1,6]. Boesen et al. reported that brain MRI of all patients were normal in their study of 5 patients with anti-NMDAR encephalitis and 4 patients with anti-GAD65 encephalitis [4]. Zhang et al. found abnormal findings in brain MRI in 29 of 89 patients with anti-NMDAR encephalitis and 1 of 2 patients with anti-LGI1 encephalitis. Brain MRI findings of the patient with 2 anti-CASPR2 encephalitis were normal in their study [5]. We found abnormal findings in the brain MRI in 8 of 13 patients. Locations where the most frequent abnormalities were seen in brain MRI examination were the temporal lobe, frontal lobe and basal ganglia region.

EEG investigations besides brain MRI are widely used in the evaluation of AE. The EEG is non-specific and typically shows slowing or disappearing of background activities, focal or generalized slow waves, interictal epileptic discharge or extreme delta brush activity [15-17]. In our study, we found abnormal findings on EEG examination in 8 of 13 patients, these were epileptic discharge in four patients, focal slow-wave in two patients, generalized slow wave in one patient, and exhibited extreme delta brush in one patient. Certain EEG findings can provide support to an early diagnosis and appropriate treatment only in a small number of patients with AE.

Autoimmune encephalitis therapy mainly includes first-line and the second-line immunotherapy. Most clinicians use first-line therapy (steroids, intravenous immunoglobulin, plasma exchange) and, if severe or refractory, second-line therapy (rituximab, cyclophosphamide) [1,6]. The response of antibody-related AE to immune therapy varies. There is a consensus that early immune treatment of cases with suspected and confirmed AE has better outcomes. Rutatangwa et al. described that of 11 AE patients, two recovered spontaneously, all of the others received first-line therapy (IVIg plus IVMP) and 50% of them were given second-line therapy. They reported that most of their patients respond well to treatment [3]. We applied IVIg plus IVMP therapy to 8 patients, IVIg plus PE therapy to two patients, and combined therapy to three patients. After treatment, complete recovery was observed in 9 patients but 3 patients had behavior disorder, and one patient had epilepsy.

In conclusion, the AE associated with antibody are an important and rapidly emerging group of antibody-associated neurological diseases. It is less common in children than adults, and it presents with different clinical findings. Therefore, recognition of these conditions is crucial as with prompt diagnosis and treatment the majority have favorable outcomes.

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