IMMUNE ENCEPHALITIS: CLINICAL, PARACLINICAL AND THERAPEUTIC ASPECTS (A CLINICAL CASE)

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Abstract: *Immune encephalopathies are determined by an abnormal immune response and may be caused by infection or tumor. Classical onconeuronal antibodies are revealed, which act against intracellular neuronal agents. The discovery of a new group of antibodies to the surface and synaptic neuronal antigens that mediate autoimmune encephalitis is an accomplishment of the last years and enlarges the spectrum of autoimmune disorders of the central nervous system (CNS) in encephalopathy. These disorders are clinically manifested with different symptoms of CNS injuries. Many of them are presented with signs of dysfunctions of the limbic system, may occur as a consequence of some infections, however, much of the cases have a paraneoplastic character. The symptoms may be milder without changes on clinical exams. In children, psychological disturbances or other types of neurological disorders can be diagnosed. Syndromes can be treated with immunotherapy. We are describing the case of a child with immune encephalopathy.*

INTRODUCTION

Association of encephalopathies with some antibodies was determined several decades ago. Autoimmune encephalitis (AIE) can be confirmed by detecting specific autoantibodies in the cerebrospinal fluid (CSF) or serum. AIE can be divided into two groups depending on the location of the target antigen. The classical paraneoplastic syndromes are currently well known, which are defined by antibodies targeting intracellular proteins. For the first time, paraneoplastic limbic encephalitis (PLE) was described in 1960.(1) In paraneoplastic processes, some antitumor immune reactions are triggered, resulting from a response of T cells CD8+, the antibodies being susceptible to appear secondary to the T cell with the damage of the intracellular molecules.(2) However, a new group of antibodies associated with AIE was revealed. These antibodies interact directly with the surface receptors of neurons or with synaptic proteins.(2-4) The new discovered antibody group, i. e., surface antigens, is directly involved in the pathogenesis of AIE by various ways, e. g., modifying the target structure or function of the cell, destroying tissues, affecting or blocking the receptors, redistributing from synaptic to extrasynaptic site, interferences with ligand-receptor connection. It is considered that there are various trigger mechanisms of the AIE, including infections, which affect the immune system by activating T and/or B cells against their own tissues.(2,5,6) This group is part of the Herpes simplex virus encephalitis associated with NMDA-R encephalitis.(7) Unlike the classic PLE, this condition responds to multimodal immunotherapy and appears to have a better general prognosis.(8) In the last 10 years, in patients with encephalitis, there have been found some new antibodies which act against proteins and receptors involved in synaptic transmission and neuronal plasticity.

These disorders differ from PLE in clinical response, may frequently occur in young people and children and may have a good response to immunotherapy.(1,2,9) In this review we will elucidate some ethiopathogenetic, clinical, diagnostic aspects, treatment options of the AIE caused by cellular surface antibodies.

AIM

The aim of the present study is to elucidate some etiopathogenetic and clinical aspects, as well as diagnosis and treatment aspects of AIE with surface antibodies.

CASE REPORT

We present the case of a young girl aged 2.6 years, admitted to the Neurology clinic, with the following complaints: Frequent myoclonic-tonico-clonic seizures, atonic seizures and automatisms, up to 8-10 times/day, with the deterioration of consciousness. Duration of the disease was 4 months, seizures were not controlled with antiepileptic medication using Valproic acid, and phenobarbital.

Diagnosis on referral: Unspecified paroxysmal syndrome, possible epileptic.

Diagnosis on admission: Unspecified epilepsy, polymorphic frequent epileptic seizures.

Diagnosis on discharge: Autoimmune encephalitis caused by EBV with unspecified antibodies. Epileptic encephalopathy, with polymorphic seizures resistant to antiepileptic medication.

Comorbidities: Unspecified immunodeficiency. Bilateral pneumonia. Respiratory insufficiency I grade. Status epilepticus.

History of disease: The disease onset was 2,2 years ago, when the first episode of epileptic tonic-clonic generalized seizure developed on the background of febrile status. Initially, seizures responded to Phenobarbital for a month. Mother ceased medication on her own decision, provoking recurrence of seizures with high frequency and become polymorph, 8-10 times a day. Subsequently, Phenobarbital was ineffective. The girl was admitted to the District hospital, with no effect after treatment. 4 months later, the child was hospitalized in the Neurology Clinic of Mother and Child Scientific Practical Institute.

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Figure no. 1A. Cerebral MRI. Enhanced image of temporal bilateral regions suggesting autoimmune encephalitis

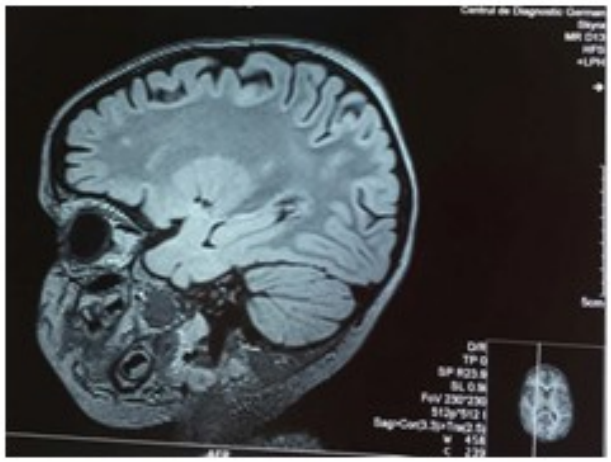
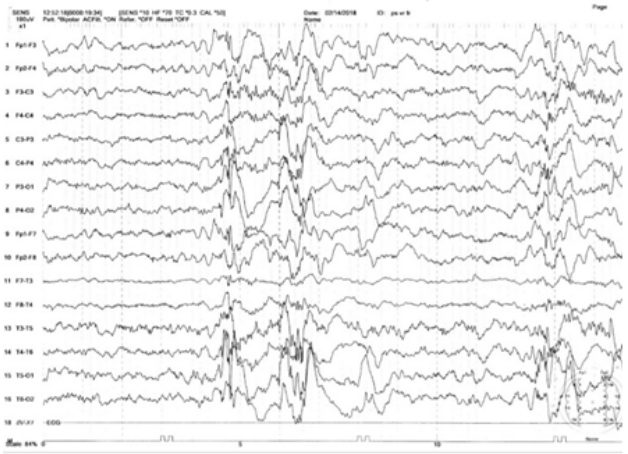


Figure no. 1B. Electroencephalographic recording reveal frequent generalized discharges of paroxysmal activity slow waves with epileptic-like features, complexes spike and polyspike and slow wave, sharp spikes, non-stable duration, interrupting on the background activity, hypsarrhythmia. Separately recorded complexes of spike and polyspike – slow wave, isolated, primary generalized, mainly in left hemisphere, and spike-wave isolated T-P in right



Personal history. A child born from pregnancy 3, the mother suffered from repeated respiratory infections at 3 and 6 months of gestation, full term pregnancy - 40 weeks, with an APGAR score of 8-9 points, weight – 3550g, head perimeter – 35 cm, neonatal period – physiological evolution. At the age of 1.8 years the child had purulent lymphadenitis. Physical and neuro-psychic development of the child before the onset of the disease corresponded to the age. Immunization conform schedule. During admission to the Neurology department the child was apathetic, restless sleep, periodically made fever, exhibited mastication seizures, head fall, frequent myoclonic seizures (up to 15 times) with loss of consciousness, in different periods of day and night, behavioral and cognitive disorders in progression. On the 5th day the condition worsened by the association of clonico-tonic afebrile frequent seizures, up to 20 times a day. The results of laboratory investigations were as follows: Lymphopenia (20% 1680 abs.); IgG – significantly increased (59.44 g/L); IgM CMV – suspected 0.278 g/L (N = 0,280 g/L), CMV IgG – positive 1.701 g/l (N = 0,290 g/L), EBV VCA IgM – positive, EBV EA Ig – positive, EBV VCA IgG – positive, EBV EBNA IgG – positive; Cellular immunity – CD3 1072 abs., CD4 – 640 abs., CD8 – 182.6 abs., CD16 – 267.9 abs., CD19 – 69.2 abs. Immunoregulator index (IIR) – 2.84. CSF clinical examination with increasing of proteins, lymphocytosis, IgG increased, immunological molecular tests with DNA EBV positive), hypoproteinemia (48 g/L), hypocalcaemia (1.7 g/L); IL-6 – 52.7 pg/mL.

Visualization using cerebral MRI determined increased intensity of signal in temporal mesial lobes with hippocampus implication.

Ultrasound cardiography: Disorders of right ventricular conductivity, left ventricular hyperfunction. Ophthalmoscopy: Optic nerve with unclear temporal margin, pale pink color, moderately dilated veins. Infectionist: Epstein-Barr virus (EBV) infection, generalised form, autoimmune encephalitis with EBV, administered treatment: AE: phenobarbital, Depakin, lamotrigine, Clonazepam, Leviteracetam; Therapy with corticosteroids; Antibiotic therapy; Antiviral therapy (acyclovir); Human antiviral immunoglobulin (Cytotec). The condition of the child has improved after the administration of human immunoglobulin.

Conclusion of clinical case. The causes of autoimmune encephalopathies may be different, including viral infections, which occur especially in children with immunodeficiency. Specific antibodies can be revealed not in all cases. In this case we deal with autoimmune encephalitis, caused by EBV, with unspecified antibodies, on the background of an immunodeficiency, which led to the epileptic encephalopathy, with the involvement of inflammatory-immune mechanisms and the development of resistance to antiepileptic drugs. Immune therapy is usually effective in such cases.

DISCUSSIONS

IE can develop in children of different ages. Initially, the clinical features of different types of AIE can be similar. Symptoms include epileptic seizures, movement disorders, psychiatric and cognitive changes.(10) To date, the most well-known subtype of AIE associated with antibodies against neuronal surface antigens is the prototype of N-methyl D-aspartate-receptor encephalitis (NMDA-R). This type of AIE affects approximately 80% of young patients, and also can be diagnosed in children. Usually, symptoms appear in stages. Initially, patients develop virus-like prodromal symptoms with headaches, lethargy and fever, followed by progressive behavioral changes, memory deficits, confusion and psychosis within 2 weeks. After that a speech problems manifests, seizures, different motor disorders and, ultimately, global encephalopathy. Similarly, disorders of autonomic functions may occur, with severe complications such as hyperthermia, cardiac arrhythmias, instability of blood pressure or coma. The limbic system is the most vulnerable structure.

The clinical type varies depending on the affected protein, and additional clinical findings can allow for differentiation between these types.(11) In one third of all patients, tumors can be found.(12) These patients require treatment in intensive care units. Most patients require long-term hospitalization and rehabilitation. Full recovery lasts up to 18 months. There were described several clinical-immunological forms of AIE depending on the affected protein.

Table no. 1. Diagnostic criteria of autoimmune encephalitis (AIE) (13)

Criteria	Type		
	Possible AIE	Definite AIE	Possible AIE with negative auto-antibodies
Evolution	Sub-acute onset, usually in few weeks, but less than 3 months	Sub-acute onset, usually in few weeks, but less than 3 months	Rapid progression of clinical symptoms, less than 3 months
Manifesting symptoms	- disorders of personality or level of consciousness - symptoms which suggests implication of limbic system, i.e., operational memory deficit - psychiatric symptoms - seizures	- disorders of personality or level of consciousness - symptoms which suggests implication of limbic system, i.e., operational memory deficit - psychiatric symptoms - seizures	- operational memory deficit - psychiatric symptoms - altered mental status
At least one of the following symptoms is need for the diagnosis:	- new clinical focal CNS event - epileptic activity on EEG or slow wave - pleocytosis in CSF - MRI findings suggestive for encephalitis*	- epileptic activity on EEG or slow wave - pleocytosis in CSF	- MRI findings suggestive for encephalitis - brain biopsy suggests inflammation with infiltrate on, with exclusion of other causes - pleocytosis or oligoclonal bands in CSF and/or increased IgG index in CSF
Exclusion of well-defined symptoms		Typical MRI findings: bilateral increased T2 weighted/highly restricted FLAIR signal intensity in mesial temporal lobes	Auto-immune encephalitis, e.g., ADEM, Bickerstaff encephalitis
Reasonable exclusion of alternative cases **	**	**	**

Note. * High intensity of T2 weighted signal / highly restricted FLAIR on one or both mesial temporal lobes or in zones of grey or white matter implicated in demyelination or inflammation;

** Infections of CNS, septic encephalopathy, toxicity caused by pharmaceuticals, cerebral vascular disease, neoplastic disorders, Creutzfeldt-Jakob disease, epileptic disorders, epilepsy, rheumatologic disorders, mitochondrial diseases. (13, 17, 18)

*** If meets all above criteria, definitive diagnosis can be established. (13)

Acute disseminated encephalomyelitis (ADEM) may be associated with neuronal antibodies and represent an important differential diagnosis, as clinical and/or imaging findings may be similar. Among the neuronal compounds with increased specificity are the MOG antibodies.(13) Differentiation between ADEM and other AIE can be carried out using MRI, especially 3 months after the onset of symptoms, as ADEM should not present new clinical or imaging results. Moreover, AIE may be associated with demyelinating disorders. Patients may have some atypical symptoms, e.g., optic neuritis, demyelinating changes and neuropsychiatric symptoms. In such cases, testing for concomitant disorders should be performed, i.e., AQP4 and MOG antibodies as well as NMDA-R antibodies. (14-16) Table no 1 presents the criteria for diagnosis (table no. 1).

Clinical diagnosis of the AIE is difficult. Initially, at the onset of the disease, the combination of symptoms such as headaches, mild hyperthermia and pleocytosis in the CSF may mislead the diagnosis and treatment, until the obtaining the results suggestive of infectious encephalitis or psychiatric disorders. Psychological disorders can be associated, among which the most common in children are behavioral, sleep and mood disorders. These are the most common symptoms that occur at the onset of a AIE, and may change over time.(19) It is important to recognize the disease and not to administer some pharmaceuticals, which could be harmful.(20) Obtaining the data from the history of the disease is important to exclude some prodromal syndromes. In the course of the disease, other symptoms may be associated, including motor disorders, seizures etc. To confirm a diagnosis of AIE, it is important to detect the antibodies involved. Until this stage the diagnosis of AIE can be only "probable". Not always, at the early stage of diagnosis, we can find the antibodies involved, because the test can be negative in up to 50% of cases, (13,17) and it may take several days to obtain the results. Complications of AIE can include coma, hyperkinesis, autonomic dysfunction, respiratory insufficiency and long-term need of artificial ventilation as well as intensive care.(4) The diagnosis of exclusion should initially be done primarily with infectious encephalitis. If the result of DNA diagnosis was initially negative in a case of clinical suspicion for AIE, it should be repeated.(13) With the purpose of differential diagnosis, other pathologies should be tested, including metabolic encephalopathy, endocrine encephalopathy, psychiatric disorders, neuroleptic malignant syndrome and rheumatic diseases, i.e., Sjögren's syndrome or lupus erythematosus.(2,4) The prognosis can be severe and directly correlated with the comorbidities, malignancies and persistence of autoantibodies.(13)

To confirm the diagnosis of AIE it is important to perform several examinations, which are mandatory. A lumbar puncture is required at the onset of symptoms with CSF analysis. Only in 60-80% of patients, there is a mild to moderate lymphocycosis (< 100 cells/μl); in one third of cases there is mild to moderately elevated concentrations of protein; in 50% of cases there is oligoclonal bands.(1-3,13) The lack of changes in the CSF will not exclude the diagnosis.(13) Similarly, it is important to test specific antibodies in serum and CSF. Sometimes antibodies can only be found in CSF, in particular, in NMDA-R encephalitis. Correlations between the clinical severity of the disease and concentrations of antibody have been found. However, the authors do not recommend determining the clinical relevance based on the antibody titer.(13) IgA and IgM antibodies do not have a clear significance in AIE since they have been found in many other psychiatric disorders and in healthy controls. However, the subtype of IgG antibodies is described in the majority syndromes of AIE.(8) Thus, the detection of antibodies in the serum and in the CSF contributes to the establishment of the diagnosis of AIE.(13,19) Brain

imaging is essential for the exclusion of other causes than AIE. It is important to use MRI every time there is suspicion of AIE, though, the picture may be normal or with only mild changes. The findings are not specific, but typically there are enhanced unilateral or bilateral T2 weighted / FLAIR signals, especially in the mesial temporal lobe with extra-hippocampal cortical or subcortical lesions, without volume or hemorrhagic process (table no. 1).(11) Infectious encephalitis, especially provoked by herpes simplex virus, HSV, and tuberculosis meningitis are an important for differential diagnosis, but the differentiation cannot be performed solely on the basis of MRI data.(2,13) EEG is not a specific investigation since there are no changes which are specific for AIE.(2,8) Electrophysiological changes include the general slowing of activity, epileptic changes or status epilepticus, periodic lateralized epileptiform discharges (PLEDs). The exclusion of a tumor process is essential for differential diagnosis.(17)

Taking into account that infections are possible triggers of AIE, it is necessary to exclude some of them, including Herpes simplex encephalitis (HSE), which has monophase evolution. Usually, cases of HSE treated with antiviral drugs tend to relapse after a few weeks in less than 25% of cases. Viral reactivation may be one of the causes, and in the cases with new symptoms it may be a case with NMDA-R antibodies without viral reactivation. Thus, patients with HSE that worsens after the first onset of disease should be tested for HSE reactivated or AIE.(12,21) Immunotherapy is effective in such cases. Another infection to be excluded is the one with Campylobacter jejuni, which determines some syndromes, e. g., Guillain-Barré, Miller-Fisher and Bickerstaff encephalitis.(5,7,22)

Treatment is difficult since there are no studies based on standard protocols of immunotherapy with intravenous immunoglobulins (IVIG). The effectiveness of immunomodulatory therapy is argued in many retrospective studies and in some prospective ones. 70% of patients respond to progressive administration of immunotherapy, especially children and young people.(7,23-25) The first line of therapy in AIE consists in the administration of common corticosteroids with IVIG and/or plasmapheresis. Previous studies have shown that corticosteroid use, initially with high doses, is associated with good clinical results, but their effect is limited, therefore additional treatment may be required.(24,25) In cases where there is a reasonable suspicion of AIE, multimodal immunological treatment can be initiated until the results of the CSF antibodies are received, especially when the imaging findings supports the diagnosis.(2,4,8) To date, there is no strong evidence of the difference in the efficacy of IVIG and plasmapheresis, which is not recommended immediately after IVIG therapy.(2) Another method of depleting of the extra-corporal antibodies is selective immunoadsorption, being effective as part of multimodal immunotherapy in AIE, what is, determine a clinically significant improvement. Immunoadsorption allows for a release of proteins and avoids the disadvantages of plasma substitution, e. g., risk of infection or allergic reactions, as well as coagulation disorders.(2,25) The efficacy and tolerability of IVIG for the patient is indisputable for the elimination of antibodies, being readily available for immediate therapy. Whether there has been a moderate clinical improvement or not, second line therapy with Rituximab or cyclophosphamide is recommended.(8,18) Data about the optimum duration of these treatments is not known. The clinical manifestations and relapse phenomena, which must be treated with the same scheme as in the first clinical presentation, will certainly be taken into account.(9) Usually, seizures in AIE are very difficult to control and frequently require pharmacological induction of the coma until the regression of autoimmune disease.(6) It is recommended to select AE with minimal side effects, which appear to have a stronger impact on cognitive function, such as lamotrigine, benzodiazepines and lacosamide.(13) In general, cases of encephalitis associated with surface antibodies, as in the presented case, have a better prognosis than those associated with intracellular antibodies. However, in all cases, the treatment on early stage is crucial.(1-3,9)

CONCLUSIONS

The wide spectrum of symptoms in AIE are a great challenge for the diagnosis of this disease and for initiating appropriate treatment, which is the most important step in the management of these patients. It is extremely important to take into account acute psychological damage or mental state, for the exclusion of AIE at the initial stage. Cerebral MRI should be performed in all patients with suspected encephalitis. If there are determined criteria supporting the diagnosis of the possible AIE, treatment may be initiated early, until severe complications occur. After the results of the testing of antibodies are available, the treatment can be revised and adapted. However, the mechanisms underlying the activation of the autoimmune response of the CNS are still unclear. Further investigations are needed to obtain sufficient information about how immune mechanisms affect the functions of the nervous system.

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