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Autoimmune encephalitis as a possible reason for psychiatric hospitalization in the teenage population

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Summary

Autoimmune encephalitis (AE) is a rare disease manifested by rapidly progressive short-term memory loss and other cognitive impairment accompanied by multiple disorders related to the limbic system involvement. The initial symptoms of autoimmune encephalitis may imitate other psychiatric disorders and delay the implementation of an appropriate treatment.

The case description of a 15-year-old patient with an initial diagnosis of psychotic disorder has been presented. Because of atypical course of an illness and an ineffective treatment with psychotropic drugs, additional tests were made including serological tests, a cerebrospinal fluid (CSF) analysis and magnetic resonance imaging. Due to the entire clinical picture an autoimmune encephalitis was suspected. The implemented treatment included steroid therapy, intravenous immunoglobulins (IVIG) and plasmapheresis. The treatment regimen was repeated until remission was achieved.

Key words: limbic encephalitis, anti-N-methyl-D-aspartate receptor encephalitis, psychiatric disorders

Introduction

Autoimmune encephalitis (AE) is a rare disease manifested by rapidly progressive short-term memory loss and other cognitive impairment that may be accompanied by multiple behavioral, motivation and emotional disorders related to the limbic system involvement [1]. Although the disease occurs with the frequency of 13.7 in 100,000 cases, in recent decade there has been a significant increase in the number of AE cases, especially among children and teenagers [2, 3]. The disease contributes to 10–20%

of all brain inflammations and is characterized by a higher rate of relapse and death rate at the level of 6% [3–5]. The mechanism of AE is based mostly on a pathological response of cytotoxic CD8+ lymphocytes against neuronal proteins with a secondary humoral reaction [6]. The clinical manifestation, as well as sex ratio and age of onset of symptoms depend mainly on the type of produced antibodies [7]. The most common antibodies detected among patients diagnosed with AE are extracellular ones, out of which in 80% of cases antibodies against N-methyl-D-aspartate receptors (anti-NMDA receptors) are produced [4]. The second important type of antibodies is a group of intracellular – onconeural antibodies, whose presence is often associated with a co-existing cancer, mainly small-cell lung carcinoma, ovarian cancer, breast cancer, testicular cancer or thymoma [8]. AE is typically characterized by a subacute course (up to 6 weeks), and in 50–70% of cases the fully-fledged clinical manifestation of the disease is preceded by prodromes such as fever, headache and fatigue [6–9]. In addition to the aforementioned symptoms related to short-memory loss, behavioral abnormalities and emotional disorders, there is a range of co-existing disorders that are related to type of produced antibodies, such as: psychotic, mood and anxiety disorders [4, 7]. AE can also be accompanied by disorientation, epileptic seizures, catatonia, dystonia, myoclonic seizures and gastrointestinal hyper-excitability [1].

The wide range of clinical manifestation of AE makes it difficult to properly interpret and classify the disease since there are no clear diagnostic criteria included in the International Classification of Diseases 10th Revision (ICD-10) [2].

We present a case of a 15-year-old male patient with symptoms of acute psychotic disorder and behavior change in the course of AE. It is an example of the need to extend a differential diagnosis of psychotic disorders, especially while dealing with a non-specific clinical picture and no response to standard pharmacological treatment.

Case study

A 15-year-old male patient without previous chronic diseases, as well as mental and neurological disorders in his family medical history was admitted to the child and adolescent psychiatry ward due to sudden changes in his behavior. The patient produced delusional spoken content and insisted he heard voices. He stated that “his skin is being torn” and „his bowels are cracking”. In addition, he was psychomotorically hyperactive and complained about persistent headaches and sleeping problems. The use of psychoactive substances by the patient was excluded. The initial diagnosis of acute psychotic disorders was made based on the clinical picture and the patient was treated with haloperidol and olanzapine. The treatment administered in appropriate doses and at appropriate intervals turned out to be ineffective. During hospitalization, attention was paid to the variable circadian intensity of the above-mentioned symp-

toms, accompanied by temporary disturbances in orientation and memory. During a basic neurological examination, he demonstrated low muscle strength of the upper limbs. No meningeal symptoms were found. The results of complete blood count and biochemical parameters (C-reactive protein level, procalcitonin level, hemoglobin level, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, a count of nucleated red blood cells, cytomegalovirus and Epstein-Barr virus antibodies) were normal. Due to the overall clinical picture, the patient was ordered to perform a magnetic resonance imaging (MRI) of his head. MRI revealed 8 hyperintensities on FLAIR and T2-weighted images in the basal ganglia and corona radiata regions. The largest lesion was up to 13 mm with the contrast enhancement in the central part. Therefore, a differential diagnosis with multiple sclerosis, acute disseminated encephalomyelitis and autoimmune encephalitis was made. The extended diagnostics was done via performing a cerebrospinal fluid (CSF) analysis. Considering an increased protein level and pleocytosis, the patient was diagnosed with suspected autoimmune encephalitis.

In view of the above, the patient was transferred to a child neurology ward in September 2019. Laboratory tests excluded both encephalitis with bacterial and viral etiology. Extended diagnostic procedure gave a positive result for antiganglioside M1 IgM (GM1 IgM) antibodies and a borderline result for antiganglioside M2 IgM (GM2 IgM) and IgG (GM2 IgG) antibodies. Antinuclear antibodies (ANA) in the titre of 1/80 were present. Anti-neutrophil cytoplasmic antibodies (ANCA) were found in the titre of 1/10 with perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) fluorescence. The test for the presence of onconeuronal antibodies was negative.

MRI was performed again and showed multiple hyperintense lesions on T2-weighted and FLAIR images in both hemispheres, mainly in the basal ganglia regions, both periventricular and subventricular white matter, as well as in the left side, in the posterior limb of internal capsule on the border with left thalamus. Comparing to the previous MRI, the largest lesion in the right hemisphere slightly shrank.

In the next neurological examination, the patient additionally presented slow speech, tongue fasciculations, reduced knee-jerk, facial droop to the left side, loss of forehead wrinkles. In further days of hospitalization in a neurology ward, the patient kept complaining about symptoms related to somatic delusional content, problems with sleeping and short-term memory loss, as well as about muscle soreness and shortness of breath. The aforementioned symptoms were not somatic.

The patient was initially treated empirically with cefotaxime and aciclovir. Antipsychotic treatment with olanzapine and then risperidone was continued. On the third day of hospitalization, the patient started to be treated with pulses of methylprednisolone. Another lumbar puncture revealed lower levels of leucocytes and proteins. Immunoglobulins in the dose of 2 g per kilogram of body weight were included into

the treatment. As a result, a remission was achieved. The patient was discharged home with the recommended dose of 0.5–1 mg of risperidone per day.

After having remained in remission for a month, symptoms returned. During the re-admission, most important was the weakened muscle strength of the limbs and slurred speech of the patient. Another head MRI revealed chronic inflammatory lesions. The treatment included steroids, plasmapheresis and intravenous immunoglobulin (IVIG – 150 g per day). The patient was transferred for a few days to a child and adolescents psychiatry ward due to autoagression episodes, suicidal ideation and overall difficult communication. During the hospitalization, he was psychomotorically hyperactive, his behavior was unpredictable and the use of force in the form of immobilization was necessary. As a result of administered treatment (risperidone up to 5 mg, clonazepam up to 4.5 mg, lorazepam up to 2.5 mg), the clinical improvement was observed and the patient was transferred to a neurology ward for further treatment, which included pulses of methylprednisolone, plasmapheresis (5 procedures) and receiving IVIG in the dose of 2 g per kilogram of body weight.

After 2 months, the patient was discharged home with the overall good status with the recommendation of next admission to the clinic after a month in order to continue the treatment. As a result of next hospitalization, complete remission of signs was obtained and the patient was discharged home in a general good condition.

Discussion

An extended neurological diagnosis towards AE should be especially taken when noticing non-specific course of psychiatric illness that does not respond to administered treatment with accompanying neurological symptoms. Basic symptoms that should prompt broaden differential diagnosis are epileptic seizures. AE maybe also accompanied by speech disorders, focal neurological signs, as well as dyskinesias [10]. Acute psychotic disorders with co-occurring headaches, fluctuations of consciousness and memory loss may also contribute to a non-specific clinical picture of A [10]. Other symptoms that may be present are related to activation of the autonomic nervous system (ANS) and include, i.a., tachycardia and hyperthermia. Excluding other possible causes of psychiatric symptoms thoroughly is vital especially among patients without psychiatric disorder manifestations in their medical histories [11].

So far, no unambiguous official criteria for the diagnosis of AE have been developed. In many cases, it is still a diagnosis of exclusion. In *The Lancet Neurology* in 2016, Graus et al. [8] presented criteria for AE clinical assessment. The diagnosis can be made when all of the following criteria are met:

1. Subacute onset (rapid progression of less than 3 months): short-term memory deficits and/or limited consciousness, lethargy, symptoms of mental disorders.

2. At least one of the following:
   – new focal central nervous system (CNS) findings;
   – seizures not explained by a previously known seizure disorder;
   – CSF pleocytosis (white blood cell count of more than 5 cells per mm^3);
   – MRI features suggestive of encephalitis.
3. Reasonable exclusion of alternative causes of the presented disorders.

In CSF analysis, increased levels of protein and leucocytes are indicative of encephalitis. MRI may reveal hyperintense lesions visible on T2-weighted and FLAIR images, appearing mainly in the temporal lobes, or lesions present in the grey and white matter of the brain [8]. Electroencephalography (EEG) is used in the differential diagnosis of epileptic seizures and along with MRI is used to monitor the progress of convalescing patients [8, 12].

The patient whose case is presented in this paper met the aforementioned AE diagnostic criteria –CSF pleocytosis and characteristic lesions in MRI were present. However, it needs to be taken into consideration that these criteria have been developed mainly for adults and, in the opinion of researchers, there is a need to specify them also for the pediatric population [13].

Rapid development and accessibility of laboratory diagnostics allowed to identify numerous types of antibodies related to the particular autoimmune encephalitis subtypes. The patient was not found to have onco – and anti-neuronal antibodies. However, the identified borderline ANA and ANCA titers that accompany autoimmune diseases have directed the diagnosis to autoimmune encephalitis [6]. Despite having negative serologic tests for auto antibodies typical for AE, the diagnosis of autoimmune encephalitis in our patient is still possible. Because of ambiguous diagnostic criteria and lack of a sufficiently sensitive and specific marker, the role of careful psychiatric evaluation is emphasized in the diagnosis of AE along with examination of the cerebrospinal fluid and the analysis of imaging examinations of the central nervous system. Most likely, the complicity of GM1 antibodies was not related to the symptoms presented by the patient. Earlier scientific reports point to the correlation between the increased level of GM1 antibodies and the presence of Guillain-Barré syndrome and its variants – Miller Fisher syndrome and Bickerstaff encephalitis [6].

It should be emphasized that the course of AE in our patient is atypical, which is indicated by the lack of strongly expressed neurological symptoms and the lack of somatic symptoms in the prodromal phase. Also, the symptoms of mental disorders that prevailed at the time of admission to the hospital are not a characteristic manifestation of AE in children and adolescents. In the group of pediatric patients, in the course of AE, neurological symptoms such as epilepsy and dysfunction in the motor activity in the form of dystonia and chorea are more common [3, 13–15]

There are many subtypes of AE, however, considering psychiatric profile of our patient, the anti N-methyl-D-aspartate receptor autoimmune encephalitis (NMDAR-AE) entity proposed in 2008 seems to be the most relevant [16, 17]. It is the most common type of AE combined with psychiatric symptoms, which are present in 60–80% of cases [7, 12]. In children, the course of NMDAR-AE is usually exacerbated and rapid, resulting from the early onset of the disease, appearing during the development of the nervous system. That causes within 2 weeks gradual replacement of non-specific early symptoms described in the introduction with psychopathological symptoms such as psychomotor agitation, delusions, cognitive impairment, and memory loss [6, 12]. In the prodromal phase, the most common are somatic disorders such as autonomic dysregulation in the form of hyperthermia, arrhythmias and hemodynamic instability [6, 7]. The disease can also be accompanied by neurological symptoms. Acute epileptic seizures were described in over 80% of NMDAR-AE cases (mainly generalized seizures). Moreover, reduced basic transition (delta and theta waves) may be revealed in frontal and temporal areas. It is characteristic for NMDAR-AE [16].

Another subtype of AE considered for the presence of psychiatric symptoms is limbic encephalitis with antibodies to the L-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) activated glutamate receptor, where these disorders may be the only manifestation of the disease. If, on the other hand, the abnormalities are accompanied by gastrointestinal symptoms (especially diarrhea with significant weight loss), the diagnosis should be extended to the determination of antibodies directed against the subunit of voltage-gated potassium channel (dipeptidyl-peptidase-like protein 6 – DPPX), appearing in the course of disseminated AE [8, 18].

It should be remembered that in the early stage of autoimmune encephalitis psychiatric symptoms can be the only manifestation, and as a consequence, patients are often referred first to and initially diagnosed on psychiatric wards and only there the diagnosis is verified. This is especially true of NMDAR-AE, where such an image may concern 4% of patients [7, 11]. The clinical picture of the disease often impedes proper diagnosis, and in turn delays the administration of immunosuppressive therapy and leads to worse long-term prognosis [12].

It is worth emphasizing that within the clinical course of AE paraneoplastic syndromes may appear, thus cancer screening tests using particular diagnostic imaging techniques (ultrasonography, computed tomography, magnetic resonance imaging) need to be performed. The whole diagnostic process and performed tests depend mainly on the class of antibodies accompanying the particular case [1, 11]. The highest risk is attributed to onconeural antibodies, therefore their identification is a strong indication to focus on secondary prevention. The symptoms of AE often precede the appearance of clinical symptoms of the tumor, thus it is necessary to perform proper tests again, after obtaining remission. For instance, in the case of NMDA-AE, that is associated

with ovarian teratoma, screening of this organ is repeated in the period of 2 years since the diagnosis [1]. In the case of the patient discussed in the following paper, the disease is unlikely to be cancer-related due to the negative result for onconeuronal antibodies, as well as his sex and young age. It is suggested that AE in patients who are under 18 years of age is usually not related to a paraneoplastic syndrome [19]. Among male patients with positive anti-NDMA antibodies accompanying tumors include, i.a., small-cell lung carcinoma, testicular teratoma, hepatocellular carcinoma, and clear cell renal carcinoma, however, they are very rare [8, 16, 19, 20]

The most common differential diagnoses are viral CNS infections, especially herpes simplex virus encephalitis as well as infection with enteroviruses, chickenpox virus or West Nile virus. The similar clinical picture is characteristic for bacterial infections (e.g., listeriosis) and fungal infections (e.g., cryptococcosis). Streptococcal infection, Lyme disease, syphilis and tuberculosis should also be excluded, while the latter are often related to immunosuppression due to human immunodeficiency virus (HIV) infection or immunosuppressive therapy. Excluding metabolic encephalopathy, drug-induced encephalopathy, as well as encephalopathy due to proliferative diseases of the CNS or rheumatic diseases such as systemic lupus and vasculitic diseases is also vital. Among the neurological diseases, early manifestation of multiple sclerosis ought to be excluded at first [1, 6, 8, 21]. Due to age, in the described case, metabolic disorders were less likely, however, this diagnosis should always be considered in younger patients.

So far, no risk factors have been identified that would allow the identification of patients particularly at risk of developing AE. Systemic manifestation of herpes infection increases the risk of developing AE [21, 22]. It was shown that in the pediatric population with the NMDAR-AE subtype, 15% of patients experienced systemic viral infection most often involving the central nervous system and the respiratory system. Herpes virus was the major predisposing risk factor among these patients. Presence of IgG4 subclass antibodies that are characteristic of autoimmune hepatitis, thrombotic thrombocytopenic purpura or membranous nephropathy may predispose to the development of AE [23]. The coexistence of systemic autoimmune diseases has been reported rarely [17].

There are no clear and specific recommendations concerning AE treatment. Data on the discussed topic are mainly taken from retrospective studies [5]. The basis of treatment is immunotherapy. First-line medicines include steroids, plasmapheresis and IVIG [2, 11, 24]. Recommended doses are as follows: methylprednisolone – 1 g per day for 3–5 days, intravenous immunoglobulin – 2g per kilogram of body weight per day for 5 days, 5–7 daily treatment cycles of plasmapheresis. In the discussed patient's case, the symptoms disappeared after the first-line treatment was applied. If patient's condition does not improve after a week of the therapy, it is recommended

to administer second-line treatment including cyclophosphamide or rituximab or both simultaneously [24].

Based on an example of a 13-year-old patient diagnosed with AE with extrapyramidal symptoms, the treatment combined with levodopa was found relevant since it can ease muscle stiffness [13]. It has also been shown that extending the IVIG therapy by 3 months helps recover language and communication skills [13].

The course of autoimmune encephalitis has a tendency to relapse frequently. From 577 cases analyzed by Titulaer et al. [15] the relapse occurred in 45 patients, which gives 12% probability of the relapse within 2 years. In some forms of AE, the risk of recurrence is estimated to be as high as 25–32% [3, 9]. It has been shown that patients treated with the second-line treatment have a lower risk of disease recurrence [1]. Delay in the implementation of treatment, young age of the first disease flare, coexisted consciousness and memory disorders, and high antibody titers are associated with a worse prognosis [23]. It should also be remembered that the recurrence rate is higher in patients with autoimmune disease [3].

Conclusions

Diagnosing autoimmune encephalitis constitutes a great challenge due to a rare occurrence of the disease and a non-specific disorder profile. Cases such as the one presented in the following paper emphasize the need to be vigilant in the differentiation of acute psychotic disorders, as misdiagnosis delays the treatment of AE, contributing to a deterioration of the prognosis [12]. Clinicians should remain vigilant, especially when there is no psychiatric disorder manifestation in patient's medical history, an atypical clinical picture and a failure to respond to pharmacotherapy. Accompanying symptoms such as memory loss, neurological disorders and psychotic symptoms that do not respond properly to treatment should be the reason for performing extended AE diagnosis [10]. Moreover, if a patient has been diagnosed with autoimmune encephalitis, it is necessary to exclude paraneoplastic syndromes [1].

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