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Anti-*N*-methyl-D-aspartate receptor encephalitis in a 17-year-old girl – a case report

Przebieg autoimmunologicznego zapalenia mózgu z przeciwciałami przeciwko receptorowi *N*-metylo-D-asparaginowemu u 17-letniej dziewczynki – opis przypadku

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Abstract

Autoimmune encephalitis is rare in children and develops as a manifestation of a parainfectious or paraneoplastic syndrome. The disease is characterised by a sudden or subacute onset and a broad spectrum of neurological and/or psychiatric disorders. We present a case of a 17-year-old girl with anti-*N*-methyl-D-aspartate receptor encephalitis. The patient was admitted to hospital in a severe condition, unconscious, with injuries indicating a recent status epilepticus. Previous infection was found to be the most likely causative factor. Antiviral, antibacterial, immunosuppressive and anticonvulsant treatments were used with good outcomes. The aim of the paper is to point out the need to include autoimmune processes in the differential diagnosis of neuroinfections in children, which will allow for prompt implementation of appropriate treatment and improve prognosis.

Keywords: autoimmune encephalitis, NMDA receptor, status epilepticus, children

Streszczenie

Zapalenie mózgu o etiologii autoimmunologicznej u dzieci występuje rzadko, jest objawem zespołu parainfekcyjnego lub paranowotworowego. Choroba cechuje się nagłym lub podostrym początkiem oraz szerokim spektrum zaburzeń neurologicznych i/lub psychiatrycznych. W pracy przedstawiono przypadek 17-letniej dziewczynki z autoimmunologicznym zapaleniem mózgu z obecnością przeciwciał przeciwko receptorowi *N*-metylo-D-asparaginowemu. Pacjentka została przyjęta do szpitala nieprzytomna, w stanie ciężkim, z obrażeniami wskazującymi na przebyty stan padaczkowy. Ustalono, że najbardziej prawdopodobnym czynnikiem indukującym wystąpienie choroby była przebyta wcześniej infekcja. Zastosowano leczenie przeciwwirusowe, przeciwbakteryjne, immunosupresyjne i przeciwdrgawkowe z dobrym efektem. Celem pracy jest zwrócenie uwagi na konieczność uwzględnienia w diagnostyce różnicowej neuroinfekcji u dzieci procesów autoimmunologicznych, co przyczyni się do szybkiego wdrożenia u nich odpowiedniego leczenia i poprawi rokowanie.

Słowa kluczowe: autoimmunologiczne zapalenie mózgu, receptor NMDA, stan padaczkowy, dzieci

INTRODUCTION

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first described by Dalmau et al. in 2007[1]. Initially, the authors' observations related to a sudden onset of neurological and/or psychiatric symptoms in women with ovarian cancer. However, later studies have shown that the condition is not always a component of the paraneoplastic syndrome, and that it may be also triggered by infection. It occurs mainly in young people, women in particular (women are 4 times more likely to be affected than men). About 37% of patients are under the age of 18 years. The estimated incidence is 1.5 per million population per year[2].

CASE REPORT

A 17-year-old, unconscious girl was admitted to the department of paediatrics. The girl had complained of headaches, fatigue, and fever of 38.5°C two weeks earlier. After a short period of improvement, the symptoms recurred and low-grade fever persisted. Outpatient laboratory workup showed minor leukocytosis with lymphocytosis and elevated ESR – erythrocyte sedimentation rate (41 mm/h). On the day of admission, the girl did not attend school due to general malaise. In the afternoon the same day she was found on the floor with no logical contact and with a fever of up to 39°C.

On admission, the patient was in a serious condition, unconscious. Physical examination revealed extensive haematomas on the skin around the hips, knees and forearms, and a bitten lower lip, indicative of status epilepticus. The liver was palpable 2–3 cm below the costal arch, and the spleen was found to be enlarged. Neurological examination revealed poor pupil response to light, increased muscle tension, increased tendon-periosteal reflexes in the upper and lower extremities, stiff neck, Kernig's and lower Brudziński signs.

Laboratory workup showed leukocytosis – 11.87 × 10^3/μL (reference: 4.00–10.00 × 10^3/μL), anaemia – 11.0 g/dL (reference: 12.0–16.0 g/dL), increased transaminase activity: alanine transaminase – 174 U/L (reference: <35 U/L), aspartic transaminase – 86 U/L (reference: <35 U/L) and the total IgM of 401 mg/dL (reference: 40–230 mg/dL), with normal values in other immunoglobulin classes. Head computed tomography (CT) showed no significant abnormalities. Abdominal ultrasound showed an enlarged liver with increased echogenicity, and splenomegaly. Transocular ultrasound showed an increased optic nerve sheath thickness and a slight elevation of optic nerve discs. An analysis of the cerebrospinal fluid (CSF) revealed cytosis of 27/μL (reference: 0–5/μL) with lymphocytic smear (74% lymphocytes, 26% segs), protein level of 148 mg/dL (reference: 15–45 mg/dL), glucose level of 60 mg/dL (reference: 50–80 mg/dL), and IgG index of 0.57 (reference: 0.3–0.7). Additionally, oligoclonal bands were found in CSF, but they were identical to the serum ones, which indicates their passive diffusion from the blood. A suspicion of neuroinfection was raised. Empiric antiviral (acyclovir) and antibacterial (cefotaxime) treatment was initiated, and anti-oedema agents (dexamethasone, mannitol) were included. Due to the possible recent status epilepticus, IV levetiracetam was included. Magnetic resonance imaging (MRI) of the brain showed a generalised enhancement of the dura mater and the pia mater of the right brain hemisphere and the cerebellum. In electroencephalography (EEG), all leads were dominated by irregular theta and alpha activity with a frequency of 7.5–8.4 Hz and the highest amplitude of 40 μV in the forebrain. No paroxysmal or focal abnormalities were found. No genetic material of neurotrophic viruses, i.e. type 1/2 herpes simplex virus (HSV1/HSV2), varicella-zoster, Epstein–Barr virus (EBV), cytomegalovirus, human herpes virus 6 and 7, parvovirus B19, parechovirus, enteroviruses, adenoviruses, or bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*) was found in CSF.

Serological tests revealed the presence of IgM antibodies against HSV1, IgM antibodies against EBV – 29.94 S/CO (negative: <0.5, positive: >1.0) and IgG – 4.36 S/CO (negative: <0.75, positive: >1.0), against enteroviruses in the IgG class and against *Mycoplasma pneumoniae* in the IgA class – 19.29 VE (negative: <9, doubtful: 9–11, positive: >11) and IgG – 19.58 VE (negative: <9, doubtful: 9–11, positive: >11). No antibodies against HSV2, tick-borne encephalitis virus or Lyme disease were found. Furthermore, EBV DNA was detected in serum and *Mycoplasma pneumoniae* DNA was identified in upper respiratory aspirate.

On day 3 of hospital stay, consciousness returned, the patient was auto-and allopsychically oriented. Subsequent EEGs showed gradual improvement in the bioelectrical activity of the brain. A follow-up CSF analysis performed after one week showed cytosis (12/μL) and normal protein level. Blood, CSF and urine cultures were negative. Due to the lack of a clear aetiological factor, the diagnostics was extended to include tests for autoimmune diseases. Screening for anti-nuclear antibodies (ANAs) showed a titre of 1:640, speckled nuclear pattern and nuclear dots. Anti-NMDAR antibodies were found in serum and CSF. No other antibodies against neuronal surface antigens were found, including anti-AMPA GluR1/GluR2, anti-GABA B, anti-DPPX, as well as anti-voltage-gated potassium channel antibodies (anti-VGKC), including anti-CASPR2, and anti-LGl1. Gynaecological examination ruled out ovarian teratoma. Immunosuppressive therapy was used based on methylprednisolone at 30 mg/kg body weight per day for 5 days, followed by non-specific IV immunoglobulins at 0.4 g/kg body weight for 5 days. Follow-up brain MRI and EEG were normal. At week 3 of the disease, serum levels of anti-NMDAR antibodies were described as poorly positive. The patient was discharged home in good condition. She remained under outpatient neurological and gynaecological care.

DISCUSSION

Anti-*N*-methyl-D-aspartate receptor encephalitis (anti-NMDAR encephalitis) is an autoimmune disease, where the autoimmune response directed against the NMDAR

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GluN1 subunit in the hippocampus and the forebrain. By blocking the receptors, the patient's autoantibodies trigger inflammation and cause multi-level disorders of the nervous system[3]. Cancers (most often ovarian teratomas) and infections caused by herpes viruses are confirmed causative factors. Due to its histological structure (neuroglia), ovarian teratoma can induce the formation of specific antibodies. The pathomechanism underlying the autoimmune process arising from a past herpesvirus infection has not been fully understood[1,2,4,5]. In the presented case, diagnostic workup ruled out neoplastic processes, but indicated a possible involvement of herpesviruses (HSV1 or EBV). The role of *Mycoplasma pneumoniae* cannot be clearly defined either.

Anti-NMDAR encephalitis usually has a subacute onset. It is preceded by prodromal symptoms, such as fever, headache, nausea or fatigue, in about 70% of cases. After this period, psychiatric symptoms develop. Cognitive and anxiety disorders, speech and consciousness disorders, agitation, mania, hallucinations and insomnia can be observed. Autonomic disturbances can manifest as blood pressure and heart rhythm fluctuations, hyperthermia, excessive salivation or urinary incontinence. About 70% of patients develop seizures or even status epilepticus. In our patient, neurological symptoms were preceded by a febrile condition followed by a short period of improvement, after which the symptoms recurred, and the patient developed status epilepticus with prolonged loss of consciousness. Dyskinesias occur in 75% of adults and 95% of children with anti-NMDAR encephalitis. Due to the sudden onset of symptoms and wide clinical manifestation, approximately 70% of patients are admitted to intensive care units[1–3].

The diagnosis is based on the presence of characteristic clinical symptoms and anti-NMDAR antibodies in CSF (Tab. 1). Antibodies are simultaneously detected in the serum in 75% of patients. In the presented case, anti-NMDAR antibodies were found both in the serum and the CSF. The studies conducted so far indicate that the initial levels and dynamics of antibodies do not correlate with the clinical condition of patients and may persist long after treatment completion. General CSF analysis reveals slight lymphocytic pleocytosis, increased protein levels and, less frequently, oligoclonal bands in most cases[2,3]. Detection of anti-NMDAR antibodies requires search for possible neoplastic process. Brain CT and MRI show no significant abnormalities in most cases. EEG, which is usually abnormal, proves helpful. In the described case, the CSF analysis and other diagnostic findings were typical of anti-NMDAR encephalitis. Differential diagnosis of anti-NMDAR encephalitis should rule out infectious encephalitis, neurodegenerative and demyelinating diseases, poisoning, central nervous system neoplasms, and primary psychiatric disorders, as was done in the presented case.

No clear therapeutic regimen for anti-NMDAR encephalitis has been developed so far. Removal of any potential tumours is crucial. First-line treatment includes steroid pulses with methylprednisolone, IV non-specific immunoglobulins and plasmapheresis. If this fails, second-line treatment with rituximab (a chimeric anti-CD20 monoclonal antibody) and cyclophosphamide is used. In the case of resistance to these therapies (seen in about 10% of patients), treatment based on bortezomib (proteasome inhibitor) or tocilizumab (interleukin-6 antagonist) is suggested[2,3,6]. The variety of clinical manifestations of anti-NMDAR encephalitis requires multi-specialist patient care and rehabilitation after treatment completion. Mild symptoms in the initial stage of the disease, prompt treatment and no need for hospitalisation in the intensive care unit improve the prognosis. Full recovery or minor neurological deficits are observed in 75% of patients, whereas fatal outcomes are reported in 7% of cases[6,7]. The first-line therapy led to an improvement in our patient. No neurological deficits were observed in the girl.

Probable diagnosis
All 3 criteria should be fulfilled: 1. Rapid onset (<3 months) of at least 4 out of 6 major groups of clinical symptoms, including: • abnormal behaviour or cognitive dysfunction • speech dysfunction (mutism, verbal reduction) • seizures • movement disorders, dyskinesias, or rigidity/abnormal postures • impaired consciousness • autonomic dysfunction or central hypoventilation 2. The presence of at least one of the following laboratory results: • EEG – either abnormal (focal or diffuse slow activity, epileptic activity, or delta brush) • CSF – pleocytosis >5/μL or oligoclonal bands 3. Exclusion of other causes The presence of the 3 main symptoms listed under Criterion 1 and confirmed teratoma.
Definitive diagnosis
1. Meeting at least 1 of the major symptoms listed under Criterion 1 and the presence of anti-NMDAR antibodies in CSF 2. Exclusion of other causes
anti-NMDAR – antibodies against the *N*-methyl-D-aspartate receptor; **EEG** – electroencephalography; **CSF** – cerebrospinal fluid.

*Tab. 1. Diagnostic criteria for anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis[2]*

CONCLUSIONS

Due to non-specific prodromal symptoms, subacute onset, and common psychiatric manifestations, anti-NMDAR encephalitis poses a great diagnostic and therapeutic challenge for clinicians. Therefore, particular attention should be paid to cases of young patients admitted to hospital with sudden consciousness disturbances and psychotic symptoms.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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