CASE REPORT

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DIFFERENTIATION OF THE FIRST PSYCHOTIC EPISODE AND AUTOIMMUNE ENCEPHALITIS WITH ANTI-NMDA RECEPTOR ANTIBODIES, USING THE EEG FINDINGS – CASE REPORT AND LITERATURE REVIEW

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Abstract

Purpose: The first-time psychotic incident is a diagnostic challenge due to the lack of definite tests that initially verify the underlying cause. Differential diagnosis should include autoimmune encephalitis with anti-NMDA receptors antibodies (NMDARE). The waiting time for the antibodies determination, being the only method of confirmation, may exceed several days. The article presents the capability of electroencephalographic study (EEG) to strengthen the NMDARE suspicion.

Case description: In a 19-year-old healthy woman sudden behavioural changes occurred. Initially, psychotic episode was diagnosed. Severity of the symptoms and no reaction to the treatment determined further diagnostics. Based on clinical symptoms and EEG, NMDARE was diagnosed and adequate treatment initiated. Antibody assay confirmed this diagnosis.

Comment: The presence of extreme delta brush in the EEG with the clinical suspicion of NMDARE allows to accelerate therapy in anticipation of antibodies determination. The EEG can be a valuable diagnostic tool for differential diagnosis, especially in the first psychotic episode.

Key words: autoimmune encephalitis, NMDA, psychosis, EEG, extreme delta brush.

PURPOSE

The first-time psychosis incident may be a diagnostic challenge due to the lack of definite tests that initially verify the underlying cause and indicate further prognosis [1]. Considering that on average 70.56% [2] of patients with autoimmune encephalitis with antibodies against N-methyl-D-aspartate receptors have psychotic symptoms, the initial suspicion of "mental illness" in this group accounts for as much as 42-44% [3] of cases. Undoubtedly, therefore, this disease should be taken into account in the differential diagnosis.

Autoimmune encephalitis in some cases is provoked by a neoplastic lesion [4, 5] and its immediate removal is then the basis for treatment [4, 6]. The most common neoplastic change detected in 58% [7] of women with NMDARE is ovarian teratoma, constituting 90-98% [3, 8] of all diagnoses. In children and men, cancer is found only in 6% of cases [3]. Autoimmune encephalitis is defined as a set of symptoms resulting from the interaction of antibodies with surface antigens of nerve cells and synaptic connections. In contrast, paraneoplastic encephalitis is the effect of antibodies impact on specific intracellular onconeuronal proteins (e.g. Hu, Ma1, Yo, Ri). Thus, the accepted distinction is the result of the molecular pathomechanism which triggers the disease. NMDARE is therefore autoimmune encephalitis due to the fact that antibodies, both in the presence of and without neoplastic lesion, are directed to the surface subunit of the NMDA receptor. The same situation occurs in the cases of encephalitides with antibodies against the LGI1, Caspr2, AMPA, DPPX, GABA, mGluR5 and GlyR receptors [9, 10].

Over the past several years, we have been continually improving our understanding of NMDARE. We already know that shorter time of diagnosis with the inclusion of adequate treatment has an impact on the patient's future prognosis [11-13]. However, one should not stop searching for a proper diagnosis; cases of patients treated unsuccessfully for 1.5 years due to catatonic schizo-

phrenia are described, who were then diagnosed with NMDARE and a definite improvement was achieved with the use of targeted therapy [14]. Although we have a test confirming the presence of specific antibodies in the cerebrospinal fluid (CSF), we are still struggling with a few difficulties. First and foremost is the waiting time for the test results, which often exceeds a dozen days or so. Next, depending on the material used for the assay, antibodies in the serum may be absent, so the diagnosis may be further extended.

The article describes the possibility of accelerating the suspicion of NMDARE based on the evaluation of the EEG study. We also describe the case of the patient, where we managed to advance treatment in this way. We draw attention to the often difficult initial differential diagnosis with the first-time psychosis incident.

The most common symptoms in the course of NMDARE include behavioural disturbances, psychosis, quantitative disturbances of consciousness, memory deficits, often agitation, high level of anxiety, speech problems including mutism, and in some cases catatonia [15]. Movement disorders are also characteristic – in particular, oromandibular dyskinesias, but those may occur parallel to or in the form of dyskinesias of other body parts. Dystonias, increased muscle tone or myoclonus are also observed [16]. In the course of the disease, epileptic seizures may occur. In NMDARE, instability of the autonomic nervous system is often observed in the form of fluctuations in arterial pressure, tachy- or bradycardia, cardiac arrhythmias or excessive salivation. Occurring even in 66% [3] of patients central hypoventilation episodes are often the cause of transfer of the patient to the intensive care unit. NMDARE estimates 1% of total admissions of young adults to intensive care units [4]. Disturbances in consciousness during the course of the disease are an unfavourable prognostic factor [13]. Up to 82-86% of patients report that the disease was preceded by prodromal symptoms of a viral-like infection, i.e. fever and headache [17].

The characteristic clinical manifestation of the syndrome is probably related to the dysfunction in fronto-striatal connections and prefrontal circuits [18]. It is suggested that this particular set of symptoms may be partly a result of over-representation of the NMDA receptor NR2B component in the prefrontal cortex [19]. It is also worth mentioning that the reports suggest participation, among others NR2C form of the NMDA receptor in the development of schizophrenia [20-22].

CASE DESCRIPTION

In their 19-year-old daughter, who was in good health until this point, the parents observed sudden growing behavioural changes. The first one was growing social withdrawal, strong feelings of anxiety, long periods of silence and frequent sleep problems. There were no mental illnesses in the family. Since the beginning of symptoms occurred during preparations for the secondary school certificate, the parents associated them with stress.

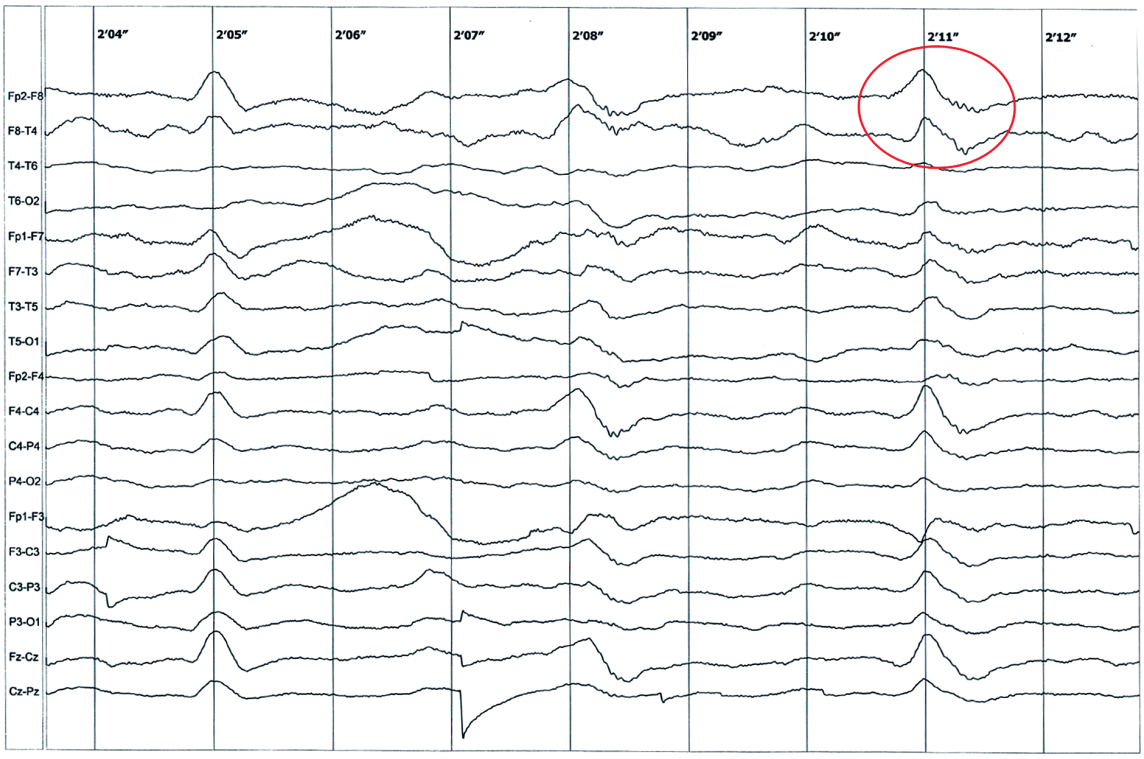
About a week after the manifestation of symptoms, the patient went to a psychiatrist who prescribed her olanzapine (20 mg/day). Due to the lack of treatment effect and further worsening of her condition after the next two weeks, she was admitted to the psychiatric ward with the suspicion of the first-time psychosis incident. Performed imaging studies of the central nervous system (CT and MRI with administration of contrast agent) showed only a 10 mm vascular change of the right frontal lobe. Despite the modification of antipsychotic treatment, the patient's condition deteriorated. After 15 days, she was transferred to the intensive care unit due to breathing and swallowing problems and decline in contact – mutism.

During the stay in the intensive care unit, determination of anti-NMDAR antibodies from serum was ordered (waiting time 11 days). Within 3 days after symptomatic treatment, the patient's general condition improved and she was transferred back to the psychiatric ward. After the neurological consultation, it was decided to transfer the patient to the neurological department. At the time of admission to the ward, the patient was conscious, lying still in a state of catatonia, with generalised increased muscle tone and pronounced oromandibular dyskinesias; she was unresponsive. Tachycardia and a tendency to fluctuate arterial pressure persisted. In addition, no other deviations in the neurological assessment were found. Immediate EEG and lumbar puncture were performed. In the general assessment of CSF, no clinically relevant deviations were detected and anti-NMDAR antibodies were determined (11 days waiting period). The EEG recording revealed the pathology of extreme delta brush (Figure 1A). On this basis, awaiting the results of NMDA receptor antibody determination, it was decided to initiate NMDARE treatment.

The patient was treated simultaneously with immunoglobulins (0.4 g/kg/day) and steroids (methylprednisolone 500 mg/day) in the intravenous form. After 5 days of infusions, immunosuppression was continued in the form of oral steroid therapy (methylprednisolone 32 mg/day). The day after completing the infusions cycle, we also received a positive result of the determination of anti-NMDA receptor antibodies tire from blood serum ordered in the intensive care unit (Table 1), which confirmed the diagnosis. At the same time, a gynaecological consultation took place; the pelvic ultrasound and pelvic MRI showed no pathology. We have also performed a number of additional tests to detect another potential trigger for antibody production (Table 2), but unfortunately we could not find it.

One week after the end of the infusions, the first signs of neurological improvement were observed – initially

A



B

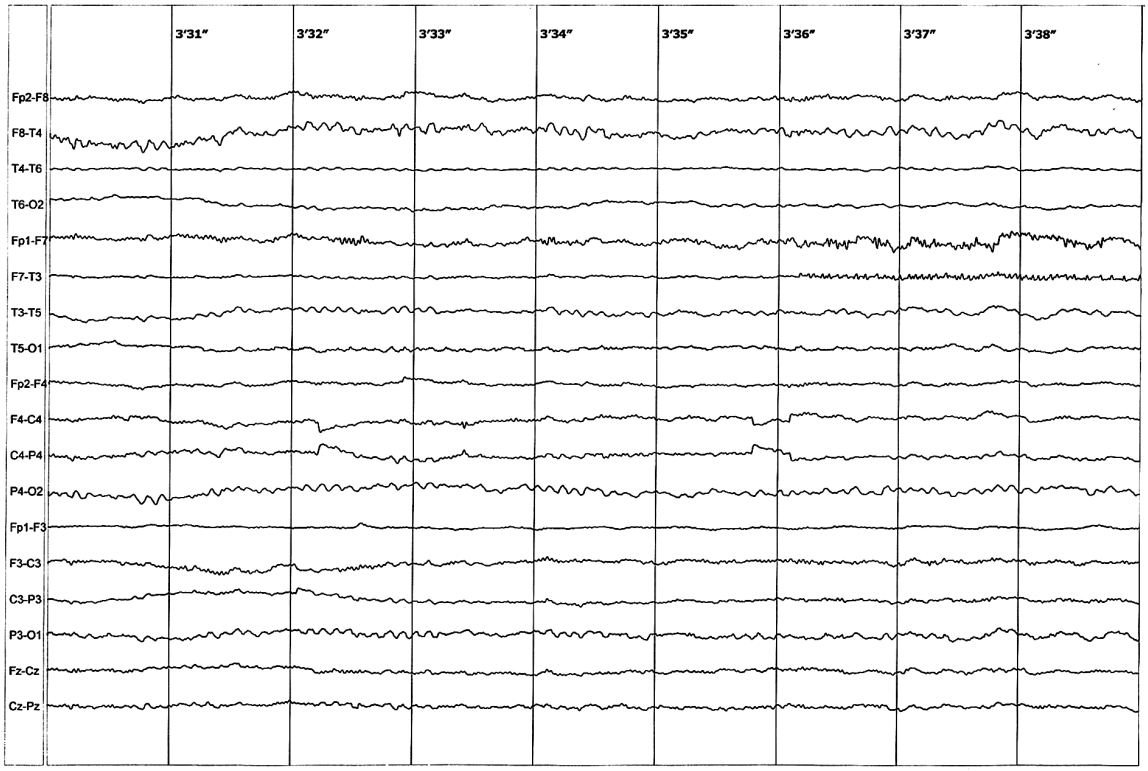


Figure 1. A) EEG made on the first day of stay at the Neurological Department (22 day of hospitalization). The extreme delta brush visible in the frontal leads is marked in red. **B)** EEG made on the 26th day of stay at the Neurological Department (48 day of hospitalization). Abnormal record – changes in the fronto-temporal leads in the form of single or groups of slow waves, on the background of the poorly spatially differentiated basic activity. Extreme delta brush changes are absent

Table 1. Results of specific antibodies determinations

CSF tests			
anti-NMDA receptor antibodies: **1 : 32** (1: < 1) (D23)	anti-CASPR2 receptor antibodies: **1: < 1** (1: < 10) (D23)	anti-GABA receptor antibodies: **1: < 1** (1: < 1) (D23)	anti-LGI-1 receptor antibodies: **1: < 1** (1: < 10) (D23)
Serum tests			
anti-NMDA receptor antibodies: **1 : 5120** (1: < 1) (D16)	anti-NMDA receptor antibodies: **1 : 2560** (1: < 1) (D23)	anti-NMDA receptor antibodies: **1 : 1280** (1: < 1) (D48)	

Table 2. Other CSF tests and serum tests

Other CSF tests	
Lyme borreliosis (IgG, IgM), Coxsackie (IgG, IgM), CMV DNA, EBV DNA, VZV DNA, HSV-I DNA, HSV-II DNA, HHV-6 DNA, HHV-7 DNA, B19 DNA, adenovirus DNA, parechovirus RNA, enterovirus RNA, HIV RNA, *N. meningitidis* DNA, *S. pneumoniae* DNA, *H. influenzae* DNA, S. group B DNA, *L. monocytogenes* DNA	Negative results
Other serum tests	
Picorna/echovirus (IgG, IgM), Lyme borreliosis (IgG, IgM), syphilis, creatine kinase, CA 15-3, CA 19-9, CA 125, onconeuronal proteins (Titin, SOX1, Recoverin, Hu, Yo, Ri, PNMA2, CV2, Amfifizin)	Negative results

the patient was trying to soundlessly speak the words, she was also following with her eyes after the examiner. With subsequent days, a gradual improvement in contact and speech was visible – from speaking singular words to complex sentences. At the same time, the physiological muscle tone of the limbs was restored. During the entire period of stay in the ward, neurologopedic treatment and physiotherapy was carried. On the 26th day of stay at the neurological ward, the EEG did not reveal the extreme delta brush (EDB), however, the features of the abnormal record persisted (Figure 1B). Also, the level of antibodies against NMDA receptors in blood serum gradually decreased with successive determinations (Table 1). Finally, the patient was transferred to a neurological rehabilitation ward – in a balanced mood, walking alone, eating meals, using the mobile phone efficiently, without memory deficits (except for time of the disease), while maintaining a mild decrease in cognitive functions and speech problems – mainly discrete dysphonia and troubles with efficient articulation of words. Currently, 2 months after discharge from the neurological ward, the patient almost completely returned to full fitness; no symptoms of disease recurrence were observed.

COMMENT

Currently, the only method that always confirms the clinical diagnosis of NMDARE remains the detection of specific antibodies against the NMDA receptor GluN1 subunit in the CSF study [7]. Although blood serum testing is technically more easily available, false-negative results are found in 14-40.6% [7, 23] cases, also in the acute phase of the disease [24]. Considering, for example, the potential irreversible effects of hippocampal damage in the course of the disease [25], the waiting time for a test result may be decisive for a response to treatment. At the same time, the difficulties caused by the diversity of NMDARE clinical manifestations may not encourage early treatment.

Considering that the high doses of steroids, immunoglobulins or plasmapheresis [11] used in the first round of treatment are not free of side effects, caution may be warranted given the uncertain clinical picture. The first psychotic episode with manifesting catatonia certainly belongs to such situations [26]. Therefore, objective tests which could strengthen the suspicion of NMDARE and accelerate the implementation of adequate treatment are being sought all the time. The test, which turns out to be useful in this area, while remaining quite accessible and without additional risk, is EEG. It is accepted that EEG in patients with NMDARE is almost always abnormal (90-100%) [18, 23, 27, 28]. Compared to the incorrect EEG record found in the first psychotic episode in 20.4% [29] of cases, this test seems to be a valuable element of differential diagnosis. It should also be emphasised that the term abnormal record is not synonymous with the registration of a seizure activity. Moreover, although the clinical manifestation of seizure episodes is observed on average in 81% [2] patients in the course of NMDARE, they rarely constitute the initial symptom – 18.8-30.6% [18, 22]. Also, a wide range of movement disorders observed in patients with NMDARE may or may not be associated with epilepsy aetiology.

However, in NMDARE patients, EEG changes are often recorded the most common is non-specific, general slowing in EEG profile [4, 30, 31]. It can be also seen

in patients with consciousness disturbances as an indicator of disorders of the ascending reticular activating system [23]. As a result of interaction of antibodies on NMDA receptors, the time of depolarisation of nerve cells is shortened and it comes to the occurrence of slow waves in EEG [23]. Also generalised rhythmic delta activity and excess beta activity are registered [32].

Since the association of EDB with NMDARE by Schmitt *et al.* in 2012 [33], the number of reports on the occurrence and very high specificity of this record pathology has been increasing [30, 34, 35]. It occurs in 16.1-30.4% [23, 33] people in the acute phase of NMDARE. EDB is the rhythmic delta activity at the frequency of 1-3 Hz with superimposed bursts of rhythmic 20-30 Hz beta activity [33]. As a result, a characteristic record is produced (Figure 1A). Similar EEG changes known as delta brush are seen in premature infants as a feature of the maturing nervous system [36]. EDB in the NMDARE course, however, distinguishes the lack of explicit influence of the sleep-wake cycle and that in most cases is synchronous. The registration of the EDB record is continuous and not related to movement symptoms, i.e. dystonias, dyskinesias or chorea movements [33].

The prognostic significance of EDB remains unclear. Some researchers consider EDB a specific, unfavourable prognostic factor [16, 18, 37]. However, there are studies suggesting a lack of correlation with the severity of the disease [25, 38]. Reports of rare cases of EDB without association with NMDARE, e.g. in critically ill patients monitored in the intensive care unit [39], and favourable course of the disease [34] should also be taken into account. Some note that the clinical improvement was achieved with the disappearance of EDB in the EEG record [37].

Moreover, one should remember about the influence of the antipsychotics drugs on the induction of abnormalities in the EEG record (clozapine 47.1%, olanzapine 38.5%, risperidone 28.0%) [40, 41] – none of these drugs was given in the neurological ward. In cases of clinical doubt, it is also suggested to use a continuous EEG record or its repetition, because a single 30-minute registration can be performed outside the period of characteristic changes [31].

It is also worth mentioning that MRI in patients with NMDARE shows abnormalities only in 30-46.8% of cases, which makes it overall a less sensitive test than EEG [7, 23]. However, it should be underlined that the highly specific for NMDARE extreme delta brush is less frequent than MRI changes. Changes in the CSF general examination present in up to 91% of patients remain non-specific [27]. Interestingly, 50% of patients have elevated levels of serum creatine kinase, which in certain situations may require differentiation with a neuroleptic malignant syndrome [34, 42].

In the context of abnormal brain bioelectrical activity, one should also remember about potential sleep disorders. In fact, in patients with autoimmune encephalitis, they occur relatively frequently. Up to 73% of them experience previously absent symptoms – from insomnia to somnambulism [43]. Our patient also experienced temporary insomnia. That is why this group of patients requires special care also during the night time.

The presence of EDB in the EEG study with the simultaneous clinical suspicion of NMDARE allows the acceleration of targeted therapy in anticipation of the determination of specific anti-NMDA receptor antibodies. The low cost, safety, relatively good availability and high specificity of EDB support the routine performance of the EEG. Despite the general high sensitivity of the EEG, the relatively low specificity of other changes that can be found in recordings is still its limitation. The EEG study can be a valuable diagnostic tool for differential diagnosis in particular if we consider the overall occurrence of an incorrect record in 90-100% of patients with NMDAR compared to 20.4% of patients with the first psychotic episode [27-29]. Some of EEG changes like diffuse slowing, extreme delta brush, and electroencephalographic seizures are not found early in primary psychiatric illness and are not caused by treatment with atypical antipsychotics or benzodiazepines, which can be helpful [44].

Conflict of interest

Absent.

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