

Psychiatric Symptoms and Electroencephalograms in Anti-NMDAR Encephalitis

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Abstract

The awareness of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been increasing throughout the world. Typically, psychiatric symptoms (PS) initially occur, followed by the development of seizures, involuntary movements, autonomic instability, or central hypoventilation.

Keywords:

Anti-NMDAR Encephalitis, Epileptic seizures, Cognitive disorders, Memory disorders, Central hypoventilation

Discussion

When symptoms of anti-NMDA receptor encephalitis are classified into 8 categories of behavior cognitive disorders, memory disorders, speech disorders, epileptic seizures, dyskinesia, consciousness disorders, autonomic nervous symptom, and central hypoventilation, within 1 month of onset 87% of patients present with symptoms of more than 4 categories [1]. During the initial psychiatric presentations, neurological involvement such as memory problems is often minor. If a patient has only PS, the diagnosis can be delayed. The diagnosis is sometimes difficult because brain magnetic resonance imaging in most patients shows normal findings or non-specific lesions, especially when other types of neurological involvement, such as oropharyngeal dyskinesia, are absent. Electroencephalography (EEG) shows some abnormalities, such as background slowing, even when only PS was evident [2,3]. I focus on PS in this disorder and electroencephalographic (EEG) findings during psychiatric presentations.

Typically, patients with anti-NMDAR encephalitis initially present with PS, followed

by the development of florid neurological deterioration. Two-thirds of patients with NMDAR antibody encephalitis have prominent PS [4]. During the initial psychiatric presentations, mild neurological abnormalities such as orofacial dyskinesias and memory problems are often observed [5]. PS include various combinations of symptoms, such as delusions, delusional thinking, auditory or visual hallucinations, paranoid thoughts, aggression, irritability, confusion, bizarre behavior, paranoid thoughts, mania, anxiety, insomnia, or depressed mood. Non-specific common-cold-like prodrome (subfebrile temperature, headache, fatigue) precedes the psychiatric presentations. PS rarely persists without neurological involvement, and this prevalence is 4% [5]. Among 23 patients with the isolated PS, 74% patients had delusional thinking, 43% had auditory or visual hallucinations, 57% showed aggressive behavior, and 70% had a documented mood component [5]. A case report showed that PS without neurological involvement can persist for 14 years [6]. PS with or without mild neurological presentations do not necessarily progress to severer multisymptom disease, even

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if the period without treatment is prolonged [5]. Psychiatrists have reported that anterograde amnesia independently of PS or alteration of the perception of time is particularly evident in anti-NMDA receptor encephalitis [7]. For example, it sounds as if a song is being played in the reverse direction, or one day feels like 48 hours, and the surrounding people appear to be moving in slow motion. The author mentions that these symptoms are likely not to be evident in patients with schizophrenia. Psychological studies in healthy volunteers who received ketamine, which decreases the function of NMDA receptors, showed alteration of the perception of time [8]. Moreover, transient and sudden emotional changes that were not derived from personal experience occurred within several minutes to several periods of ten minutes [7]. For example, the patient was in a good mood and suddenly said "I want to die" and cried. PS often become prominent, and sedative medication is required for their management [5,9,10]. Eighty-three percent of patients with isolated psychiatric episodes of anti-NMDAR encephalitis had good outcomes in response to immunotherapy and tumor removal [5].

In acute encephalitis, the most frequent EEG finding is the presence of diffuse slowing of background activity [11]. In patients with anti-NMDAR encephalitis, diffuse background slowing or focal slow waves on EEG are usually seen, especially in the frontotemporal regions. Epileptic seizures were reported in 76% of adults [4] and 77% of children [4,12], and epileptic characteristics are not always evident during the initial psychiatric presentations. Extreme delta brush is a wave peak of 1-3 Hz delta waves superimposed on a large amount of 20-30 Hz beta waves. Extreme delta brush is a specific EEG finding in this disorder, but the sensitivity of 30% of the patients is low relative to the specificity [13]. Extreme delta brush is not present from the onset of disease, and indicates a more severe disease course, a prolonged disease course, or poorer outcomes at discharge [2,13]. The EEG abnormalities in anti-NMDA receptor encephalitis resolve along with clinical improvement [14]. In a previous study, 4 of 10 patients showed diffuse slowing and 1 patient showed focal slowing within 14 days of the first presentation of anti-NMDAR encephalitis [10]. Epileptic forms or extreme delta brush was seen in 2 patients and 1 patient, respectively. EEG was normal in 2 patients. One study performed by means of Fast Fourier

transformation (FFT) analysis in 10 patients with anti-NMDAR encephalitis showed that beta activity was increased relative to delta activity in contrast to patients with other types of encephalitis [3]. This finding was observed at the earliest phase of the disease, especially in 4 patients in whom EEG was performed at the time of presenting with only PS. The 4 patients had diffuse slowing without an epileptic form. The authors suggested that the evidence of the increased beta activity as compared with delta activity might be a useful marker for the differential diagnosis of this encephalitis from other types of encephalitis. These patients did not have extreme delta brush. Another study of 16 patients, including 4 patients who presented with only behavioral changes and PS without neurological involvement, reported general delta activity in 7 patients, focal delta activity in 7 patients, and increased beta activity in 8 patients [2]. Low-voltage EEG activity associated with lower levels of consciousness during the acute phase predicts unfavorable neurological outcomes in acute encephalitis [15]. In a patient with anti-NMDAR encephalitis who presented with the initial PS, EEG voltages of alpha bands were decreased in all brain areas as compared with those of the healthy controls [16]. In our two patients in whom EEGs were performed at the initial PS (**Table 1**) [17,18], FFT analysis with the use of a frequency analyzer as described previously [16] showed increased voltage of beta activity or delta activity (**Figure 1**). During the initial psychiatric presentations, some alterations of EEG including delta or beta activity, low-voltage EEG activity, or background slowing are often seen.

Conclusion

The reported prevalence of seropositive anti-NMDAR antibodies in psychiatric patients is 12 of 121 patients with schizophrenia (9.8%), 2 of 70 patients with major depression (2.8%), and none of 38 patients with borderline personality disorder [19]. Other studies detected the presence of anti-NMDAR antibodies in serum in 3 of 46 patients with first-onset schizophrenia (6%) [20] and in none of 80 patients who met the DSM-IV-TR criteria for schizophrenia-spectrum illness [21]. Patients with a history of psychosis associated with bipolar disorder or schizophrenia tend to display persistent EEG abnormalities even when not actively psychotic [22]. These facts should be kept in mind. During the initial psychiatric presentations, the presence

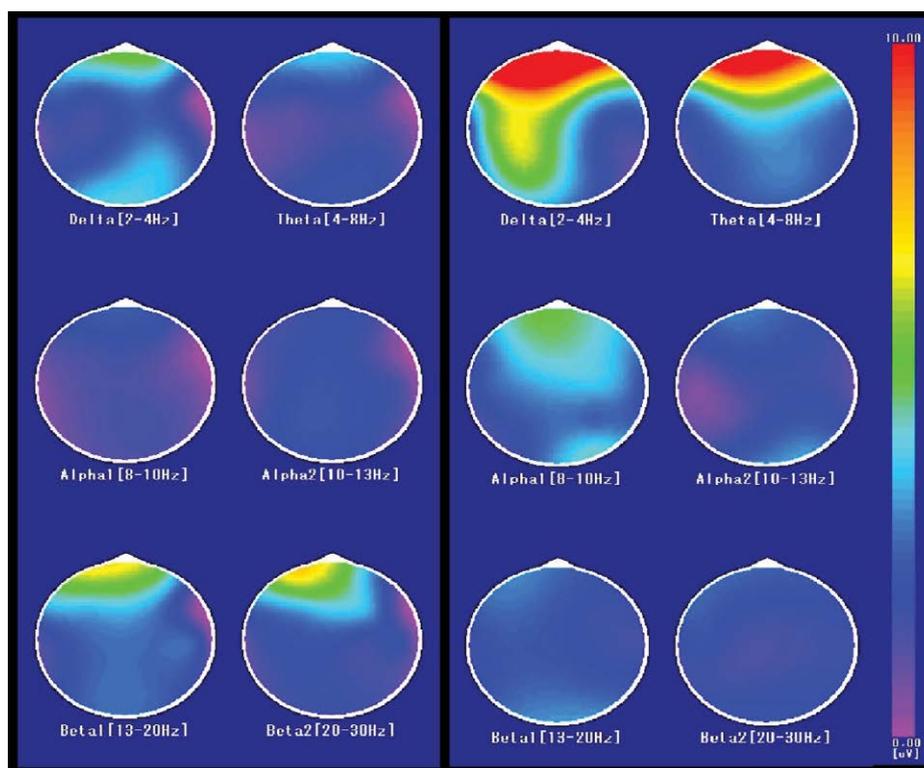


Figure 1: Fourier transformation (FFT) analysis in the two patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis who presented with psychiatric symptoms without neurological involvement.

The EEG voltages of beta (13-20 Hz) in Patient 1 (left panel) or delta (2-4 Hz) bands in Patient 2 (right panel) was increased. On the other hand, the EEG voltages of alpha bands in both patients were decreased.

Table 1: Characteristics of two patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis who presented with psychiatric symptoms without neurological involvement, and their EEGs were performed during the psychotic symptoms.

	Patient 1 [20]	Patient 2 [18]
Age/sex at admission	40 / M	18 / M
psychiatric symptoms	delusions, delusional thinking, hallucinations, aggression, irritability, confusion, bizarre behavior, paranoid thoughts, manic	delusions, delusional thinking, paranoid thoughts, hallucinations, aggression, irritability, confusion, bizarre behavior, cataplexy,
prodromal symptoms	fatigue	subfebrile temperature, headache
followed neurological features	seizure**	Kluver Bucy syndrome
duration from psychiatric symptoms to first neurological feature [days]	12	-
WBC in CSF [/mm ³]	1	100
first MRI abnormality	-	-
Treatments and outcomes		
immuno-treatments	ST, IVIG	ST
surgery	-	-
Duration follow-up [months]	72	3
Outcome	under medications	complete recovery
EEG examination during psychotic stage		
interval from EEG to neurological onset [days]	6	-
sedative drugs*	low dose midazolam	low dose midazolam
anticonvulsant drugs*	-	-
background diffuse slowing	+	-
epileptiform discharge	-	-
extreme delta blush	-	-
periodic complexities	-	-

WBC: white blood cells, CSF: cerebrospinal fluid, MRI: magnetic resonance imaging, EEG: electroencephalogram

ST: steroids, IVIG: intravenous immunoglobulin, *during EEG examination

** : short periods and one attack of tonic seizures 12 days after the initial psychiatric presentation, and partial seizures were evident 6 year later.

of neurological involvement, such as involuntary movement or seizures, is useful for diagnosis. A prodrome of fever or headache is also helpful for diagnosis. If the psychiatric presentations are confirmed to be caused by anti-NMDA receptor antibodies, the psychiatric symptoms are treatable.

Acknowledgement

We are extremely grateful to Professor Josep Dalmau (University of Pennsylvania, Philadelphia; and Institució Catalana de Recerca i Estudis Avançats (ICREA) (JD), Barcelona,

Spain) and Professor Keiko Tanaka (Kanazawa Medical University, Kanazawa, Japan) for measuring the anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibodies.

Disclosure

The authors report no conflicts of interest related with our paper.

Funding Statement

H.K received JSPS KAKENHI Grant Number (15K9356).

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