

## Case Report

# The role of clinical diagnostic criteria for anti-N-methyl-D-aspartate receptor encephalitis in children: a case report

Irawan Mangunatmadja, Ricca Fauziyah, Achmad Rafli

**E**ncephalitis is a neurological disorder that develops rapidly into a progressive encephalopathy caused by inflammatory processes in the brain. The incidence of encephalitis in developed countries is 5-10 per 100,000 per year. Encephalitis can affect all ages and cause long-term effects on patients, their families, and society.<sup>1-3</sup> Autoimmune encephalitis, including anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, is increasingly recognized as a cause of encephalitis in children and has a considerable mortality rate of 5-7%.<sup>4</sup> Physicians should suspect anti-NMDAR encephalitis in patients with prominent neuropsychiatric symptoms and movement disorder.<sup>1-3</sup> We report here a case of anti-NMDAR encephalitis and discuss the role of clinical criteria in diagnosing anti-NMDAR encephalitis in children. [Paediatr Indones. 2022;62:66-71 ; DOI: 10.14238/pi62.1.2022.66-71 ].

**Keywords:** anti-N-methyl-D-aspartate receptor; encephalitis; anti-NMDAR encephalitis

## The case

An 8-year-old girl came to the Cipto Mangunkusumo General Hospital, a tertiary facility, with chief complaints of convulsions and restlessness. Three weeks before admission, the patient showed changes in behavior (decreased eye contact, self-talking, hand-wringing), which gradually led to decreased consciousness and increased daytime sleepiness accompanied by restlessness when awake. Two weeks before admission, the patient had a seizure with tonic stiffness of the left hand, blank stare,

and unresponsiveness. She was then brought to a healthcare facility where she underwent a spinal tap and cerebrospinal fluid (CSF) analysis, electroencephalography (EEG), and brain CT scan, with results within normal limits. She was discharged from the facility with a referral to a pediatric neurologist.

One day prior to admission, she refused to eat or drink and had seizures. She was then brought to our hospital. A repeat CSF analysis showed a cell count of 20 cells/mm<sup>3</sup>; other parameters were within normal limits. A CSF sample was sent for anti-NMDAR antibody testing. A second EEG was also performed, revealing moderate diffuse slowing and an excessive delta brush pattern in bilateral frontal regions (**Figure 1**). Based on the criteria by Graus *et al.*,<sup>1</sup> she was diagnosed with possible autoimmune encephalitis and given high-dose (10 mg/kg single daily dose) methylprednisolone injection for five days. Seizures, agitation, and involuntary movements were managed using phenytoin, haloperidol, and supportive therapy.

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Department of Child Health, Universitas Indonesia Medical School/Dr. Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.

Corresponding author: Irawan Mangunatmadja. Department of Child Health, Universitas Indonesia Medical School/Dr. Cipto Mangunkusumo National Hospital. Jl. Diponegoro 71, Jakarta, Indonesia. Phone: +6281314578483; Email: irawanma2802@gmail.com.

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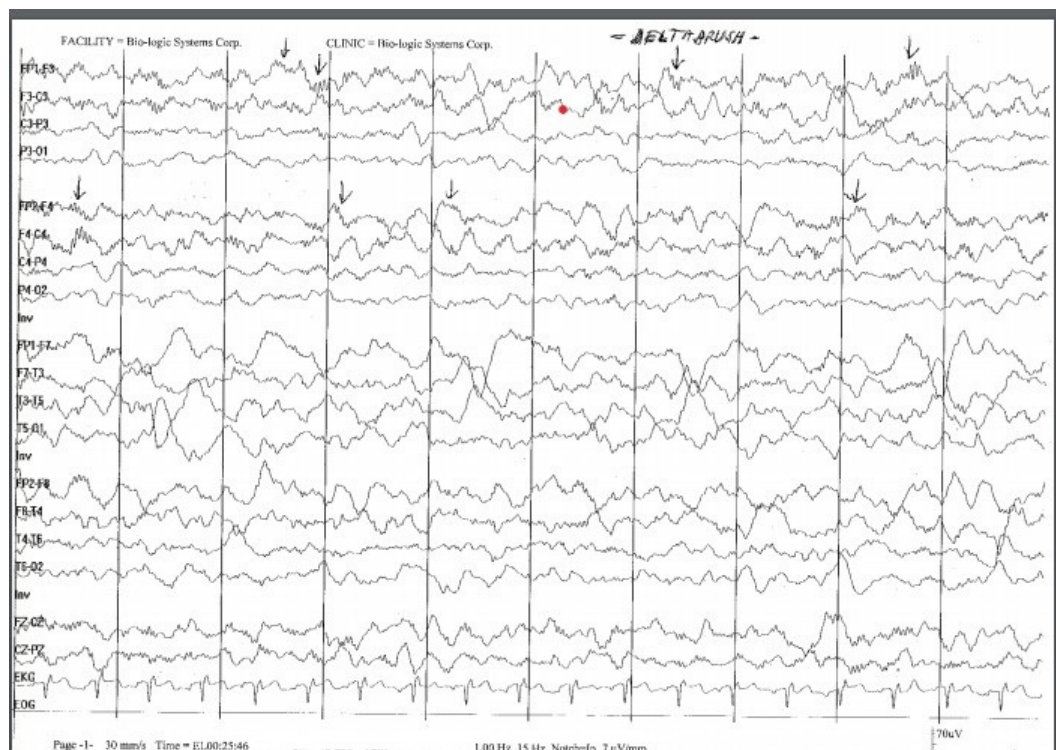
There was no significant improvement in clinical symptoms following completion of the five-day course of high-dose methylprednisolone. On the seventh day of admission, results of CSF testing showed positive anti-NMDAR antibodies. Intravenous immunoglobulin (IVIG) was started on the eighth day of admission with a dose of 2 g/kg given over five days in once-daily infusions. On the 12<sup>th</sup> day of admission, the patient had shown clinical improvement in the form of reduced agitation and involuntary movement and slightly improved interaction. She was then discharged for further follow-up on an outpatient basis.

## Discussion

In children presenting with acute or subacute onset of psychiatric symptoms, anti-NMDAR encephalitis must be suspected and EEG must be done as a supporting investigation.<sup>5</sup> The electroencephalogram may show (1) normal background rhythm and absent epileptiform activity, as seen in general psychiatric disorders such as excessive anxiety, fear, tantrums,

and restlessness (**Figure 2**);<sup>6</sup> (2) normal background rhythm with epileptiform discharges in the temporal regions suspicious of temporal lobe epilepsy (**Figure 3**); (3) diffuse background slowing accompanied by asymmetry and/or epileptiform discharges in the temporal region suspicious of herpes simplex virus (HSV) encephalitis (**Figure 4**); or (4) diffuse background slowing that accompanied by an "excessive delta brush" pattern suspicious of anti-NMDAR encephalitis (**Figure 1**).<sup>5</sup> The "excessive delta brush" pattern is defined as rhythmic, 1-3 Hz delta activity with superimposed bursts of 20-30 Hz beta activity, occurring diffusely or frontally predominant.

Psychiatric symptoms in children with temporal lobe epilepsy may include anxiety, excessive fear, and déjà-vu, sometimes followed by a stupefied, sudden silence, as well as oral-motor and hand automatisms, dilated pupils, hyperventilation, or tachycardia.<sup>7</sup> Interictal EEGs in mesial temporal lobe epilepsies show spikes or sharp waves in the anterior temporal (F7/F8), midtemporal (T3/T4), or posterior temporal (T5/T6) regions originating from regional abnormalities in the neocortex region of the temporal lobe.<sup>7</sup>



**Figure 1.** EEG showing slow background activity with excessive delta brush pattern seen in bilateral frontal regions

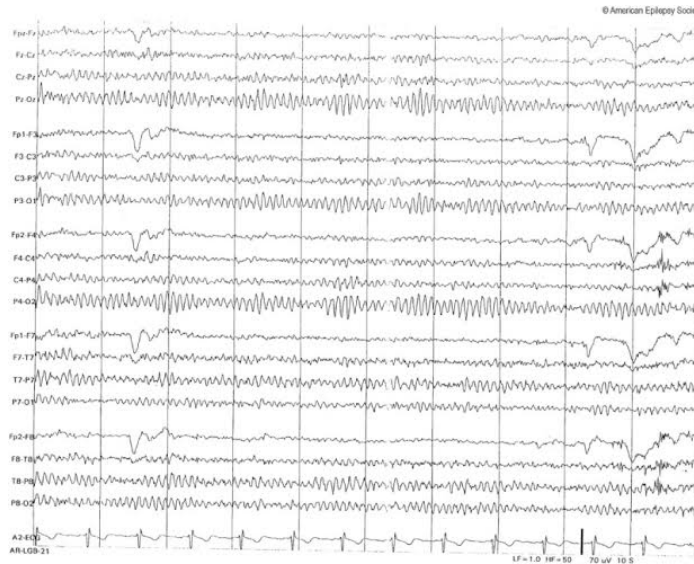
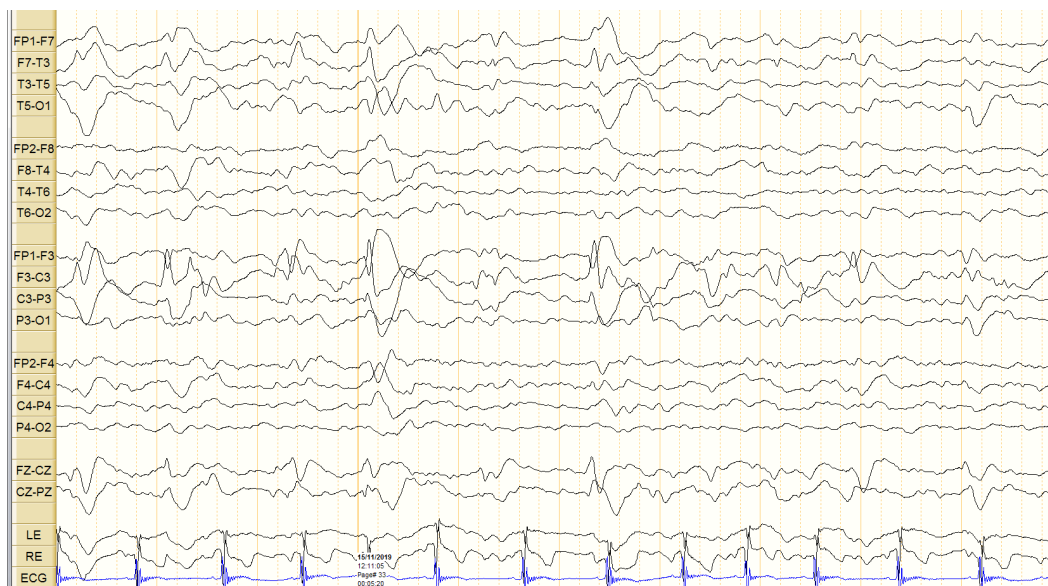


Figure 2. Normal EEG (normal background activity and no epileptiform activity)<sup>5</sup>



Figure 3. EEG suggestive of temporal lobe epilepsy with slow background activity and epileptiform activity in the left frontotemporal region (F7; arrows)



**Figure 4.** Asymmetric EEG in herpes simplex encephalitis showing slow background activity with periodic lateralized epileptiform discharges in the left frontal region<sup>5</sup>

The classic clinical manifestations of HSV encephalitis in the initial state are behavioral changes, fever, and headache. Approximately 80% of cases show focal neurological abnormalities such as hemiparesis, cranial nerve deficits, visual disturbances, aphasia, focal seizures, and impairment of consciousness.<sup>8-10</sup> The electroencephalogram shows diffuse slowing accompanied by asymmetry with epileptiform waves of periodic lateralized epileptiform discharges (PLEDs) (Figure 4).<sup>8,10,11</sup>

Anti-NMDAR encephalitis is an acute form of encephalitis caused by autoimmune responses associated with antibodies in the serum and CSF against the GluN1 subunit of the N-methyl-D-aspartate receptor. It comprises 4% of all encephalitis events and is the most common type of autoimmune encephalitis. The first neurological symptom in pediatric patients is seizures (72%), of which 42% are focal, preceding other encephalitis symptoms by up to 15 days. Many patients show behavioral abnormalities (26%) and movement disorders. Seizures are often difficult to diagnose because they may take the form of unilateral tonic posturing or sudden unilateral pain without clonic movements. Post-ictal motor deficits are common. Other symptoms include disorders of memory, cognition, and speech, as well as loss of consciousness, central hypoventilation, and autonomic dysfunction.<sup>11-14</sup> EEG findings in

autoimmune encephalitis show generalized moderate hypofunction accompanied by excessive delta brush (Figure 1).<sup>5</sup>

The definitive diagnosis of anti-NMDAR encephalitis can be established when anti-NMDAR antibodies are detected in the CSF of a patient with suggestive clinical features. However, there is often a delay in NMDAR antibody testing in our settings due to sample pooling and accessibility issues. To avoid delays in treatment, clinical criteria may help in the initial diagnostic process to identify patients with a high index of suspicion of anti-NMDAR encephalitis.<sup>15-17</sup> Existing clinical diagnostic criteria for anti-NMDAR encephalitis have been reported to have a sensitivity of 87-90% and a specificity of 96-98%.<sup>12,18</sup> The clinical diagnostic criteria we used has high sensitivity and specificity and can be applied in areas where anti-NMDAR antibody testing is not readily available. The criteria can be used to guide the initiation of immunotherapy before antibody results are available.<sup>12,18</sup>

We employed the diagnostic criteria of Graus *et al.* based on clinical-neurological assessment.<sup>1</sup> Through this approach, we were able to make a “possible” diagnosis immediately, thus allowing the initiation of immunotherapy while waiting for definitive antibody testing results, with the hope of achieving a better clinical outcome (Table 1).<sup>1,15,17,19</sup>

**Table 1.** Diagnostic criteria for possible autoimmune encephalitis<sup>1</sup>

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status\*, or psychiatric symptoms
2. At least one of the following:
  - a. New focal central nervous system (CNS) findings
  - b. Seizures not explained by a previously known seizure disorder
  - c. CSF pleocytosis (white blood cell count >5 cells/mm<sup>3</sup>)
  - d. MRI features suggestive of encephalitis<sup>†</sup>
3. Reasonable exclusion of alternative causes (diagnosis can be made when all three of the above criteria have been met)

\*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change.

<sup>†</sup>Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

A previous study reported Graus' diagnostic criteria to have very high sensitivity (90%) and specificity (96%).<sup>16</sup> However, clinicians must be aware that not meeting the criteria does not rule out the possibility of anti-NMDAR encephalitis, as shown by the presence of patients who tested positive for anti-NMDAR antibodies but did not meet the criteria. In addition, anti-NMDAR encephalitis is characterized by a gradual evolution of symptoms, and most patients do not meet the criteria during the first week of symptoms. A study in China reported that the sensitivity of Graus' criteria for probable anti-NMDAR encephalitis upon hospital admission was only 49%, with a specificity of 98%; sensitivity and specificity rise as patients advance further along the disease course to a maximum of 87% and 100%, respectively, in one to three months.<sup>18</sup> The average time to meet the criteria is 2 weeks from the onset of the first symptoms (range 1-6 weeks).<sup>16</sup> As it has been demonstrated that early initiation of immunotherapy is an independent predictor of good outcome, early diagnosis using diagnostic criteria may contribute to achieving better outcomes for patients.<sup>12,16</sup>

In our patient, we initiated high-dose corticosteroids as first-line immunotherapy on the first day of admission on the basis of a probable diagnosis of anti-NMDAR encephalitis according to Graus' criteria. Since response to steroids was deemed inadequate, she was subsequently given a five-day course of IVIG, following which her consciousness gradually improved, psychiatric manifestations and involuntary movement decreased, and communication improved. Reports have shown better results when immunotherapy is given as a combination of steroids and IVIG.<sup>17,19-22</sup>

Half of anti-NMDAR encephalitis patients respond well to steroids as the first-line treatment.

Other options include IVIG, plasma exchange, and second-line immunotherapy (rituximab and cyclophosphamide).<sup>15,17</sup> Anti-NMDAR encephalitis is known to occur as part of a paraneoplastic syndrome. The prevalence of tumors in pediatric patients with anti-NMDAR encephalitis varies, with reported percentages of up to 25-30% in girls under the age of 18 years. A percentage of less than 10% has been reported in girls less than 10 years old, with ovarian teratoma as the most common type of tumor.<sup>2,4</sup> In male patients, testicular teratoma has not been shown to be associated with anti-NMDAR encephalitis. In the absence of a malignancy, most children with autoimmune encephalitis have good prognoses.<sup>20-22</sup>

In conclusion, the clinical diagnostic criteria for anti-NMDAR encephalitis used in this study have high sensitivity and specificity and can be applied in limited-resource settings to identify patients with probable anti-NMDAR encephalitis and guide the initiation of immunotherapy before antibody testing results are available. Conversely, in patients who do not meet the criteria, other differential diagnoses, such as herpes simplex encephalitis, should be considered.

## Conflict of Interest

None declared.

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