Dear Editor,

The encephalitis associated with anti-N-methyl-D-aspartate receptor (NMDAR) antibodies is a recently identified autoimmune disorder that associates with antibodies against NR1 heteromers (1,2).

The disorder predominantly affects children and young adults (3). The incidence in pediatrics is indeterminate, although recent studies suggest that it is the second most common immune-mediated encephalitis, after acute disseminated encephalomyelitis (4). It occurs with or without tumor association (3). In young adult females, the encephalitis is often accompanied with the ovarian teratoma, but that is uncommon in children (4).

Clinically, the presentation is similar in pediatric patients and adults, although there are differences in the frequency and manifestation of some symptoms (5). After prodromal viral-like symptoms including headache, fever, nausea, vomiting, diarrhea or upper-respiratory-tract symptoms (1,2,3), patients manifest psychiatric disorders consisting of anxiety, insomnia, paranoia, agitation, and visual or auditory hallucinations (4,5). In young children, psychiatric symptoms can be difficult to detect because they often present with temper tantrums, hyperactivity, aggression or irritability (3,5). These behaviors can be overlooked, which may mislead the diagnosis. Psychiatric manifestations are commonly accompanied by seizures, memory loss, language dysfunctions, and dyskinesia (1). Oro-lingual-facial dyskinesia is one of the most characteristic symptoms (3). Other movement disorders have been reported such as limb and trunk choreoathetosis, dystonia, and rigidity (4). The autonomic instability can be seen in children, but it appears to be less severe than adults (4,5). Unrecognized, the condition may progress to a pseudo-vegetative state (4).

Cerebral magnetic resonance imaging (MRI) is normal in the majority of patients, although nonspecific T2 signal hyperintensity may be seen in white matter (4). These abnormalities appear to have minimal or no correlation with neurologic symptoms (4).

Electroencephalogram (EEG) is abnormal in most patients (1,3), usually showing focal or generalized slow activity with or without epileptic discharges (1).

The cerebrospinal fluid (CSF) is initially abnormal in 80% of patients and becomes abnormal later in the disease in most other patients (3). Findings include moderate lymphocytic pleocytosis, mild increase of the protein concentration, and CSF specific oligoclonal bands (1,3). Anti-NMDAR antibodies can be detected in both serum and CSF (4). CSF titers have been correlated with severity of the disease. There is an association between high levels of antibody and teratoma and/or poor outcome (1).

The treatment is based on immunotherapy and removal of neoplasm, if present (1). First-line immunotherapy includes immunoglobulins, methylprednisolone, and plasma exchange (1,3). The second-line therapy with rituximab or cyclophosphamide can be performed when first-line therapy has failed (3). The recovery is slow, frequently over months (5). One year of immunosuppression with mycophenolate or azathioprine is recommended because relapses occur in 15-25% of children (1,4).

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To sum up, anti-NMDAR encephalitis should be suspected in any child or a teenager who develops psychiatric and neurologic symptoms (3). Supportive findings include results of laboratory and imaging as well as EEG examinations (1,3). The diagnosis is based on the detection of IgG antibodies against NMDAR in CSF and/or serum (1,5). Patients should be examined for a tumor and treated with immunotherapy (5).

Herein, we report the case of a child with chiefly psychiatric and behavioral symptoms to highlight the need for increased awareness and high diagnostic suspicion when physicians approach children with psychiatric symptoms.

A 5-year-old previously healthy girl, born from non-consanguineous Moroccan parents, was admitted to the Unit of Neuropediatrics and Metabolic Diseases with a fifteen-day history of disorientation, agitation, and visual hallucinations, without fever. Her symptoms were preceded by headaches. On admission, the examination revealed that the patient was confused with no verbal contact, she did not follow orders, could follow objects with her eyes and uttered incorrect words. Liver function tests, serum ammonia, and lactate were within normal limits. Brain computed tomography and MRI were normal. CSF examination was normal. EEG showed diffuse slowing. Diagnosis of viral encephalitis was presumed, and treatment with acyclovir was started. While in hospital, symptoms progressed, and the patient experienced insomnia, orofacial dyskinesia, and self-mutilation (impulsive hair pulling and teeth tearing). Suspicion of autoimmune encephalitis led to a test for CSF anti-NMDA-R antibodies that confirmed the diagnosis. Imaging of the thorax, abdomen, and pelvis failed to detect malignancy. The patient was treated with intravenous pulse methylprednisolone followed by intravenous immunoglobulins (2 g/kg divided over five days). The clinical state of the patient gradually improved within two weeks after immunomodulation therapy. She started to utter simple words, followed commands, and was auto-oriented. Psychiatric symptoms, agitation, and dyskinesia resolved. At the last follow-up, seven months after onset, she had recovered completely.

Ethics
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Authorship Contributions

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