Anti-NMDAR encephalitis: a rare cause of status epilepticus and chorea in children

Encefalite anti-NMDA: uma causa rara de estado de mal epiléptico e coréia em crianças

Angélica Lizcano¹, Daniela de Suza², Milena de Albuquerque¹, Kátia Schmutzler², Karine Teixeira², Laura Silveira², Maria Augusta Montenegro², Fernando Cendes¹, Marilisa Guerreiro²

ABSTRACT

Introduction: The anti-N-methyl-D-aspartate-receptor (NMDAR) encephalitis is a relatively rare auto-immune disease characterized by a severe encephalopathy with subacute onset of behavioral and neuropsychiatric symptoms. Methods: We discuss three cases of children with encephalitis in which we identified anti-NMDAR antibodies. Results: The three patients had similar onset symptoms: status epilepticus followed by behavioral changes and chorea. Conclusions: Encephalitis anti-NMDAR should be included in the differential diagnosis of acute and subacute encephalitis in children presenting status epilepticus and extrapyramidal movement disorder.

Keywords: anti-NMDAR encephalitis, status epilepticus, chorea

RESUMO

Introdução: a encefalite com anticorpos anti-receptor N-metil-D-aspartato (NMDAR) é uma doença autoimune relativamente rara, caracterizada por uma encefalopatia grave com aparecimento de sintomas comportamentais e neuropsiquiátricos de forma subaguda. Métodos: discutir três casos de crianças com encefalite em que identificamos anticorpos anti-NMDAR. Resultados: os três pacientes tiveram o início dos sintomas semelhantes: estado de mal epiléptico seguido de alterações comportamentais e coréia. Conclusões: encefalite anti-NMDAR deve ser incluído no diagnóstico diferencial de encefalite aguda e subaguda em crianças com estado de mal epiléptico e distúrbio de movimento.

Palavras-chave: Anticorpos anti-NMDA, encefalite, estado de mal epiléptic, coréia

1. Department of Neurology, Neuroimaging Laboratory, Epilepsy service
2. Department of Neurology, Pediatric Neurology service, Epilepsy service University of Campinas (Unicamp)
Autoantibodies against glutamate receptors (type NMDA) are specific markers for anti-glutamate receptor (type NMDA) encephalitis, an inflammatory encephalopathic autoimmune disease which was first described in 2007 and is currently a still widely underdiagnosed disease. This condition is observed in adults, often in young women with ovarian teratomas. It is characterized by a severe encephalopathy that follows some signs and symptoms in a particular order: seizures, decreased level of consciousness, dyskinesia, dysautonomia and hypoventilation. As the patients usually improve with immunotherapy, an immune-mediated pathogenesis has been suggested, even considering the severity of the neurological deficits and the removal of the tumor, if it was present. The improvement follows an inverse chronological presentation of symptoms. Also, the presence of an immune reaction among serum, CSF and the cell surface of the neuron contributed to this hypothesis.

A recent series demonstrated that this disease affects not only adults or patients with teratoma, showing an increase in cases diagnosed in the pediatric population.

In our hospital, we admitted three children between November 2011 and February 2012 with acute encephalitis. In all cases, the studies of autoimmune antibodies tested positive for anti-NMDAR, both in serum and CSF. But different clinical presentation as described by the original authors (Figure 1), and in absence of tumor, as will be described below.

**CASE REPORTS**

Case 1 - A girl previously healthy. At two years and six months of age, she presented fever, diarrhea and vomiting for three days, self-limited. After a week, she began psychomotor agitation, no sphincter control, ataxia, regression of spontaneous speech and insomnia. Then, she presented status epilepticus and later generalized choreoathetosis. Next, irritability, global aphasia, dysphagia, drooling, and worsening of choreic movements associated with oromandibular dyskinesia. She also presented hyperthermia refractory to medication during the acute phase. During physical examination she had also major axial hypotonia, with inability to sit. The brain MRI was normal, and CSF study revealed the presence of oligoclonal bands. The ictal EEG showed rhythmic epileptiform activity in the left posterior quadrant (Figure 2). The next interictal EEGs showed focal epileptiform activity in the temporo-occipital region. Screening for cancer was negative. She was treated with sodium valproate and risperidone, received two cycles of Immunoglobulin IV (2g/kg complete each cycle) with progressive recovery of symptoms after nine months of onset. She had full recovery of extrapyramidal, behavioral and sleep disorders, but keeps mild dysarthria and a mild atactic gait.

Case 2 - A boy previously healthy. He started symptoms at 25 months of age: behavioral changes, agitation, aggression, reduction of spontaneous speech and ataxia. Later, he had impairment of consciousness, which was consistent with non-convulsive status epilepticus according to the EEG. He was treated with phenytoin, showing improvement of the level of consciousness and of the EEG. Then, he presented generalized choreoathetosis, aphasia, dysphagia, and insomnia. In addition, he presented fluctuations in blood pressure and heart rate. The brain MRI was normal and CSF showed mild pleocytosis without presence of oligoclonal bands. Screening for cancer was negative. In subsequent EEGs there was focal interictal epileptiform activity in the fronto-temporal region (Figure 3). He was treated with antiepileptic medications - phenytoin during status epilepticus, followed by valproic acid and clobazam. He received also haloperidol for choreoathetosis and 2 cycles of Immunoglobulin IV (2g/kg on each cycle). After nine months of treatment, the patient had almost full recovery of symptoms with improvement of behavioral complaints, no evidence of movement disorders, associated with no return of symptoms to date, keeping just mild ataxia and dysarthria.

Case 3 - A boy previously healthy. At two years old, he presented status epilepticus, and then focal motor clonic seizures in his left foot. He required hospitalization for seizure control. After that, he showed irritability, altered sleep cycle, mental delay, regression of speech, ataxia, self-injury and finally generalized choreoathetosis. The brain MRI was normal and CSF showed moderate pleocytosis without presence of oligoclonal bands. Screening for cancer was negative. The interictal EEG showed moderate to severe slow disturbance of background activity (Figure 4). In subsequent EEGs we observed interictal, independent, focal epileptiform activity in frontal regions abd slow background activity. Study of autoimmune antibodies tested positive for anti-NMDAR, both in serum and CSF. (Figure 3). He received the following antiepileptic medications: sodium valproate, phenytoin, carbamezepine, phenobarbital and clobazam. He also received risperidone, later with levetirapmazine, corticosteroids (methylprednisolona pulses), followed by prednisone, plus immunoglobulin (3 cycles of 1 month between each one). He showed no improvement after the 4th immunoglobulin cycle and there’s still no tumor associated.

**DISCUSSION**

Anti-NMDA (N-methyl-D-aspartate)-receptor encephalitis was firstly described in 2007 by Dalmau initially as a paraneoplastic manifestation in young adult women associated with ovarian teratomas. Subsequently, it was noted the occurrence of cases in both sexes and in children, often without neoplasms identified. Since then, a growing number of cases have been reported in the pediatric age group, turning this disease an important cause of immune-mediated encephalopathy in childhood.

Our three patients were similar to that described in adults, although there are differences in the frequency and manifestation of certain symptoms. They had a common clinical presentation of choreoathetosis, new onset status epilepticus with good response to diazepam. But, they did not present hypoventilation and the finding of tumor.

Studies show that the chance of finding associated tumors varies with age, sex and ethnicity of the patient, being much lower in children and in males, and higher in afro descended. Thus, there is a proportional relationship to the finding of tumor and the patient age. Younger the patient, lower the probability of identifying tumor. Ovary teratoma is the most often tumor associated with this encephalitis, but there are references to testicular teratoma, small cell lung carcinoma, Hodgkin’s lymphoma, and neuroblastoma.

The disease can present with nonspecific prodromal symptoms, characterized by low fever, headache, malaise, vomiting or diarrhea, which was observed only in one of our patients.

However, as occurred in adults, all children reported neuropsychiatric symptoms, such as agitation, changes in behavior, mood or personality, sleep cycle disturbance, psychosis, irritability, accompanied by changes in speech,
such echolalia, coprolalia, reduction of spontaneous speech or mutism. Because NMDARs are expressed on neurons throughout the brain; their highest densities are found in the amygdala, hypothalamus, prefrontal cortex, and hippocampus, about 80% of patients experience seizures during the first few weeks of the disease in parallel with neuropsychiatric symptoms. The initial seizures (during the first stage) are of extratemporal origin but they can manifest as nonconvulsive status epilepticus or refractory temporal lobe epilepsy. After the first stage of the disease, patients usually progress to a more severe phase with a characteristic choroathetoid movement disorder, dysautonomia, and impaired consciousness but undetectable seizures. There are reported cases of status epilepticus and two of them with complex partial seizures, like patient 4. The association of movement disorders with encephalitis anti-NMDAR was also present in all of them. In children, choreoathetosis is more common, different from the findings in adults, which characteristically presents dyskinesias, oculogyric crises, myoclonus, dystonia and stiffness. Some of these movements were suspicious for seizures. The icatal changes were often subclinical with EEG correlate. Correspondingly, the EEG shows diffuse slowing. Occasionally, different phenotypes may occur in association with NMDAR antibodies. Patients may have a pure seizure disorder without prominent neuropsychiatric involvement. They present with nonconvulsive status epilepticus or refractory temporal lobe epilepsy. Dysautonomic changes are described as tachycardia or bradycardia, hypop or hyperventilation, hypop or hypertension, increased salivation, intestinal pseudo-obstruction that increase morbidity, often leading to the need for intensive care and even death. The autonomic manifestations in children appear to be less severe than in adults. While 66% of patients in the original series exhibited central hyperventilation usually requiring weeks of mechanical support, none of our patients presented this symptom. Recovery is slow, from weeks to months until the first sign of improvement, and often occurs in the reverse order of presentation of symptoms. Many patients require hospitalization for months and may require intensive care for extended periods. The autonomic manifestations in children appear to be less severe than in adults. While 66% of patients in the original series exhibited central hyperventilation usually requiring weeks of mechanical support, none of our patients presented this symptom. Recovery is slow, from weeks to months until the first sign of improvement, and often occurs in the reverse order of presentation of symptoms. Many patients require hospitalization for months and may require intensive care for extended periods. Relapses occur in up to 25% of patients and there may be several recurrence intervals of major improvement between them. Mortality rate is about 4% of patients, complications related disease or adjacent to the tumor.

The diagnosis is made by clinical findings and complementary exams, associated with the presence of antibody in CSF or blood. Studies suggest that there is intrathecal antibody synthesis, and in all cases there is the presence of antibodies in the cerebrospinal fluid while the disease is active, but the blood may be seronegative after completion of treatment. Analysis of the cerebrospinal fluid may be normal initially, and become altered in the course of the disease. The CSF findings referred in the literature are lymphocytic pleocytosis, protein concentration and the presence of oligodendral bands. A magnetic resonance imaging is normal in most cases, with changes in about 31-55% of patients, most frequent hyperintense on Flair / or areas of T2 contrast in one or more brain region, but no clinical correlation. In EEG records, three quarters of the cases displayed predominantly delta slow activity in the frontal regions, with focal abnormalities in 10%.

The EEG may show slowing or disorganization of background activity and focal or generalized epileptiform activity, intermittent or even continuous, featuring status epilepticus. There is presence of epileptic activity in 28-50% of patients, although there is usually no clinical correlation in most cases between the suspicious movements and electroencephalographic changes. The presence of delta waves or focal or diffuse theta is the second most frequent EEG abnormality described in the literature.

Treatment involves removal of the tumor when present, and immunotherapy. The first line treatment is human immunoglobulin, corticosteroids and plasmapheresis with equal efficacy reported by the literature. In the refractory cases second-line drugs should be used, like rituximab, cyclophosphamide, or both, with a good response. There are isolated reports of the use of mycophenolate mofetil and azathioprine.

The response to treatment depends on the presence or absence of tumors, and in cases where there is no identified tumor or late identification is usually more refractory. The studies recommend periodic screening of cancer, particularly teratomas, due to the risk of later emergence of the paraneoplastic teratomas. This screening can be done with ultrasound, CT or MRI of the abdomen and pelvis for at least two years after cessation of symptoms. The patient evolution is determined by the therapy performed. The ones that not undergo early treatment with immunotherapy have a worse evolution than those treated early and aggressively. The rapid administration of second-line drugs in refractory cases brings significant improvement in the recovery of the disease, reducing the severity of symptoms and also the chance of relapse.

**CONCLUSION**

This report highlights the importance of high index of suspicion for encephalitis with anti-NMDA receptor in the pediatric population. Although it is a relatively uncommon disease, it is underdiagnosed and with potential high morbidity. This is a disease that should be suspected in children with acute psychiatric disorders, alteration of consciousness that develop status epilepticus and chorea, requiring multidisciplinary management. In addition, permanent deficits are potentially preventable if the diagnosis is suspected and if appropriate treatment is established immediately.

**REFERENCES**


CORRESPONDENCE
Fernando Cendes
Departamento de Neurologia - FCM, Unicamp
Rua Tessália V. de Camargo 126
Campinas, SP, Brasil 13083-888
fecedes@unicamp.br
FIGURES

**Figure 1:** Evolution of the three patients described.

- **Prodromal symptoms**
  - Diarrhea
  - Fever
  - Vomiting (n=1)

- **Hospital admission**
  - **ALL PATIENTS:**
    - Psychomotor agitation (aggressiveness, irritability)
    - Speech regression
    - Insomnia
    - Ataxia
    - Status epilepticus (convulsive or non-convulsive)
    - Autonomic instability
    - Chorea (movement disorders: dyskinesia)
    - Self-aggression (n=1)

- Week 1
- Week 2
- Week 3
- Week 4
- Week 5

**Figure 2:** Patient 1 - A) Ictal EEG: Rhythmic sharp waves in the left posterior quadrant region. B) Brain MRI FLAIR coronal normal. C-D) Indirect immunofluorescence. Substrate: transfected cells. Positive reaction with transfected cells expressing the NMDAR. C) Serum reactivity of the patient. D) CSF reactivity of the patient.
Figure 3. Patient 2 - A) Interictal EEG Sharp waves frequent in the fronto-temporal regions. B) Brain MRI coronal FLAIR normal. C-D) Indirect immunofluorescence. Substrate: transfected cells. Positive reaction with transfected cells expressing the NMDAR. C) Serum reactivity of the patient. D) CSF reactivity of the patient.

Figure 4: Patient 3 - A) Interictal EEG with slow background activity. B) Brain MRI coronal FLAIR normal. C-D) Indirect immunofluorescence. Substrate: transfected cells. Positive reaction with transfected cells expressing the NMDAR. C) Serum reactivity of the patient. D) CSF reactivity of the patient.