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Anti-NMDA Receptor Encephalitis in Children

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Abstract **Case Report**

Anti-NMDAR encephalitis is a type of neurological syndrome that can be paraneoplastic or non-paraneoplastic in nature. It is a recently discovered that is becoming much more recognized in children. The symptoms of anti-NMDAR encephalitis occur as a result of autoimmune antibody binding to the NMDA receptor on certain neuronal cell surfaces. Patients with anti-NMDAR encephalitis are described as having a change in mental status manifested by abrupt changes from calm behaviors to agitation, aggression or extreme irritability. In children, the first symptom to be recognized is often non-psychiatric: convulsion, status epilepticus, dystonia, verbal reduction or mutism .The diagnosis is clinical and confirmation is easy with demonstration of antibodies in serum and CSF; Early diagnosis and aggressive immunotherapy are imperative. Anti-NMDA receptor encephalitis can be reversible if diagnosed and treated early.

Keywords: Encephalitis; Auto-immunity; Anti-NMDA-receptor antibody.

INTRODUCTION

Encephalitis associated with anti-NMDA receptor antibodies is of recent description in the field of paraneoplastic and autoimmune encephalitis. We report an observation collected in the pediatric neurology department P2 at the Children's Hospital of Rabat in Morocco, illustrating the clinical presentation and evolution of this entity.

OBSERVATION

An 8-year-old female child who initially consulted for a localized left linguofacial dystonia of rapid generalization with the appearance of choreoathetoid movements and left hemi-corporeal seizures. The evolution was marked by severe malnutrition with self-aggression, continuous abnormal movements and then a disorder of consciousness. The paraclinical workup found a normal brain MRI, a normal metabolic workup and an EEG, but anti NMDA receptor antibodies in the cerebrospinal fluid were positive. Thoracic-abdominal-pelvic CT scan for neoplasia revealed a thymoma for which the patient was operated. The patient was put under protocol "bolus of corticoids associated with immunoglobulin" with a favorable evolution in spite of persistence of some learning difficulties.

DISCUSSION

Anti-NMDAR encephalitis is a type of neurological syndrome that can be paraneoplastic or non-paraneoplastic in nature. The discovery of anti-glutamate NMDA receptor (anti-NMDA-R) antibodies by Dalmau and colleagues in cases of limbic encephalitis revolutionized the field of paraneoplastic and autoimmune encephalitis. Anti-R-NMDA autoantibody encephalitis was first described in 2007.

It is the most common autoantibody encephalitis. Its exact incidence is unknown but it represents about 4% of the causes of encephalitis. The median age median age of patients with anti-R-NMDA autoantibody encephalitis is between 8 and 10 years, 80% of patients are female.

NMDA receptors are glutamate-dependent membrane receptors located on the surface of surface of the central nervous system cells. They are voltagedependent ion channels. Under normal conditions, NMDA receptors are inactive. Their activation requires the agonist (glycine or D-serine) and glutamate. The ion channel linked to the receptor is permeable to Na+, K+ and Ca2+ ; extracellular Mg2+ induces a voltage-dependent blocking of the channel by binding to the of the channel by binding inside the pore.

The biophysical, pharmacological and functional properties of NMDA receptors depend on their composition in NR1, NR2 and NR3 subunits. The content of the NR2 subunit of the receptor confers characteristic properties to it, in particular with regard to the kinetics of activation and deactivation of the currents, the conductance, the probability of channel opening, sensitivity to Mg2+, agonists and antagonists. R-NMDAs have a role in glutamatergic synaptic maturation, in synaptic plasticity and in the development synaptic plasticity and in the development of neuronal circuits. These functions are known to play a role in learning, memory and cognitive processes.

Anti-R-NMDA antibodies seem to play a direct role in the occurrence of neurological neurological disorders. Studies have shown the absence of a role for complement and the predominant involvement of humoral-mediated immunity in anti-RNMDA encephalitis. Ectopic expression of a neuronal R-NMDA antigen by a tumor or by an unknown mechanism leads to the activation of humoral immunity and the synthesis of anti-R-NMDA antibodies anti-R-NMDA antibodies by plasma cells in the blood or in the CNS.

Anti-R-NMDA antibodies are IgG antibodies that specifically target the N-terminal domain of the extracellular domain of the NR1 subunit. They cause the internalization of R-NMDA internalization, which is dependent on the level of antibodies and reversible with the disappearance of the antibodies. The internalization of R-NMDA leads to a decrease in synaptic current mediated by R-NMDA and a defect in R-AMPA endocytosis leading to an increase in extracellular glutamate concentrations and dysregulation of gabaergic neurons. This leads to disinhibition of the excitatory pathways that cause the symptoms.

An episode of HSV viral encephalitis may induce anti-RNMDA autoantibody encephalitis. This is marked by a clinical relapse between 1 and 6 weeks after the initial diagnosis of encephalitis, the absence of new necrotic lesions on brain MRI, the absence of virus in the CSF and the presence of anti-RNMDA autoantibodies.

The mechanism of anti-R-NMDA antibody synthesis after viral encephalitis is unknown, the virus could induce the synthesis of antibodies by molecular mimicry with R-NMDA or by antigen release during neuronal lysis. The inflammation caused by the infection could be at the origin of a breach of the blood-brain barrier allowing antibodies and/or serum memory T and B lymphocytes to enter the CSF.

Clinically, prodromes such as headaches, fever, nausea, vomiting, diarrhea or respiratory signs are described, followed two weeks later by the appearance of psychiatric symptoms such as anxiety, insomnia, fear, delirium, social withdrawal and stereotyped behaviors. The oro-lingual-facial dyskinesias are the most characteristic movements but other types can appear such as choreo-athetosis.

The diagnosis of autoimmune encephalitis is confirmed by testing for NMDA receptor antibodies in CSF and blood: lymphocytic pleocytosis, normal or moderately elevated proteinorachy, oligoclonal bands, and intrathecal synthesis of anti-NMDA synthesis of anti-R-NMDA antibodies.

The presence of anti-R-NMDA antibodies in the CSF is diagnostic. C. Brain MRI may be normal or may show T2 signal hyperintensity in the hippocampus , cerebellum , cerebral cortex, fronto-basal areas, basal ganglia , and brainstem. Cerebral MRIs during the course of the disease may remain normal or show diffuse hippocampal or cerebral atrophy in cases of unfavorable evolution. The EEG shows slow delta activity, either focal or generalized, sometimes associated with paroxysms. The focal character of the disorder is more prognostic than a diffuse slowing down. A particular aspect named Extreme Delta Brush (EDB) has been recently highlighted, it is about slow delta waves notched with fast rhythms. This pattern is specific to anti-R-NMDA antibody encephalitis.

Management is based on the combination of corticosteroid therapy with human immunoglobulin. The median time from symptom onset to initiation of treatment is approximately 20 days. First-line treatment may include intravenous corticosteroid boluses, polyvalent immunoglobulin infusions and/or plasma exchange.

Intravenous corticosteroid therapy consists of boluses of methylprednisolone 1g/day for 5 days. Polyvalent immunoglobulin infusions at a dosage of 0.4g/kg/day may be given for 5 days. Second-line treatment is started if no efficacy is noted within 10 days of first-line treatment. after administration of the first-line treatment, administration of rituximab or cyclophosphamide. The second-line treatment is stopped when the patient goes into remission, Maintenance treatment with mycophenolate mofetil (Cellcept®) or azathioprine (Imurel®), two purine synthesis inhibitors, is instituted to prevent relapses. It is continued for at least 12 months. continued for at least 12 months;

A close follow-up is necessary; an MRI and an abdomino-pelvic ultrasound are required every 6 months, 2 years after the treatment. The median time to improvement is 3 months and the median time to cure is 12 months. Relapses may occur. Mortality is estimated to be between 4 and 10%. The most frequent causes of mortality are sepsis, cardiorespiratory arrest, status epilepticus and progression of the underlying tumor.

CONCLUSION

Anti-NMDA receptor encephalitis is probably not rare in children; it can be reversible if diagnosed and treated early. It is important to know how to think about it in front of any encephalitis picture in children.

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