Anti-N-Methyl-D-Aspartate receptor encephalitis associated with Lyme neuroborreliosis : diagnostic and therapeutic challenges

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ABSTRACT

Background : Autoimmune encephalitis (AIE) is a group of rare neurological diseases characterized by various neuropsychiatric signs associated with antibodies targeting proteins expressed on the surface of neuronal cells or intracellular neuronal antigens. Anti-N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis is an AIE which was recently described in the pediatric population. The auto-immunity can be triggered by infection, vaccine or undiagnosed tumor. The aim of this paper was to report an original pediatric case of anti-NMDAR Encephalitis to show an unusual onset of this neurological disease and factors related to poor outcome.

Case : An 9-year-old girl was admitted for status epilepticus associated to hypersomnia, hallucination and unmotivated laughter evolving for 3 months. Diagnosis of AIE associated with Lyme neuroborreliosis was made when tests confirmed positive anti-NMDAR antibodies in CSF and positive Lyme antibodies in serum and in CSF. The outcome has been good after receiving tow doses of Intravenous Immunoglobulin and appropriate antibiotics.

Conclusion : Suspecting auto-immune encephalopathy is essential in the differential diagnosis of encephalitis, as early treatment can significantly enflence the outcome. In some cases there are others prognostic factors such as concomitant neurological infectious diseases or other coexisting auto-immunes affections.

Key words : Children, Limbic encephalitis, anti-N-Methyl-D-Aspartate Receptor antibodies; Neuroborreliosis

INTRODUCTION

Autoimmune encephalitis (AIE) is a pediatric neuro-inflammatory disorder of the central nervous system (CNS). Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is one of the most frequently reported causes of AIE in children [1]. Infectious encephalitis has historically been the most common; however, AIE has become increasingly recognized and described. AIE is as common as viral encephalitis. AIE occurs mainly in female pediatric population [2,3]. Although AIE has a standard clinical manifestations, some patients can have unexpected and severe initial symptoms. An unusual evolution may be hiding an underling infection or autoimmune system disease.
The aim of this paper was to report an original pediatric case of AIE to show an unusual onset of this neurological disease and factors related to poor outcome.

CASE

A 9-year-old girl was admitted for status epilepticus with history of abnormal behavior for about 3 months duration made of hypersomnia, visual hallucinations (big spider climbing on the walls) and unmotivated laughter. She had normal family history. She had no neonatal problems and she had a normal psychomotor development. Her neurological examination findings were normal. The evolution was characterized by failure of antiepileptic drugs in controlling seizures (clonazepam, levetiracetam). Brain computed tomography (CT) scan was normal. Lumbar puncture revealed pleocytosis (118 cells/mm3 with 80% lymphocytes) (normal range 0-10/ mm3) with normal protein and glucose level.
On the third day of hospitalization, the child presented reduced communication, multiple focal and general seizures, aggressive behavior, self mutilation, amnesic disorders and frequent hypersialorrhea. Viral screening (polymerase chain reaction) in cerebrospi-

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nal fluid (CSF) specimen was normal. Brain magnetic resonance imaging (MRI) was normal. EEG showed moderate slowing of background activity and spikes were seen on both temporal and occipital regions.
On the seventh day of hospitalization the child presented left facial nerve palsy. A second brain MRI was performed and showed diffuse pachymeningeal enhancement. A second CSF analysis showed 196 cells/mm3 (100% lymphocytes) (normal range 0-10/mm3). Further investigations revealed positive NMDAR antibodies in CSF and in serum. The child received corticosteroids and Intravenous Immunoglobulin but there was no sign of recovery. Serological tests (ELISA) showed positive Borrelia afzelii IgM and Borrelia afzelii IgG. This result was confirmed by Western Blot. In search of other etiologies of encephalitis, we found out Borrelia specific IgG antibodies in CSF. Therefore we gave the patient intravenous Ceftriaxone 100 mg/Kg/ day during 21 days associated to a second dose of IVIG. Tumor marker tests were normal. Pelvic MRI was normal. The patient was discharged two weeks after the second dose of IVIG with partial improvement. She was transferred to the neuropediatrics department for follow-up.

DISCUSSION

Our case had two original particularities. The first one was related to the initial clinical presentation characterized by a rapid neurological worsening with no imaging abnormality. The second particularity related to the prognosis because this rare association was the cause of initial poor response to treatment and the poor outcome.
AIE with anti NMDAR antibodies are the most dominant limbic encephalitis in children and teenagers. They represent 4% of all encephalitis among pediatric population and they just come after viral infections encephalitis in rank [4,5]. Anti-NMDAR encephalitis is a disease with a progressive clinical course and significant morbidity; it may require management in ICU [2]. However if the diagnosis is made early and the management is effective, the outcome is favorable. Anti-NMDAR encephalitis is more common in children. A multicenter observational study of 577 patients showed that 37% were under 18 years old [3]. There is a female predominance with a sex ratio of 4:1.
Typical clinical manifestations of anti-NMDAR encephalitis include psychiatric symptoms, behavioral disorders, seizures, involuntary movements, recent memory impairments, speech disorders, and dysautonomia [3]. Our patient had the majority of these clinical signs. But the onset was rapidly progressive and the signs were severe. Hypersialorrhea or excessive salivation hypersialorrhea was secondary to autonomic dysfunction. In deed autonomic dysfunctions in anti-NMDAR encephalitis include many symptoms such as tachycardia-bradycardia, arrhythmia, cardiac arrest, central hypoventilation, excessive ventilation, diarrhea and hypersialorrhea like our second patient [6]. Dysautonomia can directly affect the patient's prognosis and may be the main cause for ICU support. Dysautonomia is the clinical consequence of the presence of anti NMDAR antibodies on the dopaminergic, cholinergic and noradrenergic pathways [6].
Seizures are common clinical manifestation of anti-NMDAR encephalitis. Epilepsy concerns three quarters of cases, occurring in about 60-70% of patients [7]. Seizures are more common in children. Seizure symptoms are various and can include generalized tonic-clonic seizures, focal seizures, temporal seizures, and status epilepticus (SE). SE is a manifestation of anti-NMDAR encephalitis, requiring immediate evaluation and management in ICU to prevent significant morbidity and mortality. Some patients may have two or more types of seizures. This was showed in our case.
Identification of anti-NMDAR antibodies in CSF confirms the diagnosis and should lead to the search for a tumor, which, if present, is usually an ovarian teratoma that contains nervous tissue and expresses NMDAR [8].
The most important factors of poor outcome in our case were status epilepticus and symptoms of dysautonomia. In a lot of survey, the predictors of poor outcome involved young age, memory deficiency, female gender, consciousness deterioration, delayed treatment and high antibody titers [7,8]. However, two independent predictors of good outcome were reported : the lower severity of symptoms, assessed as no need for admission to an intensive care unit, and the prompt initiation of immunotherapy and tumor removal, if appropriate. In our case, there are other prognostic features not described in the literature. Our patient prognosis was worsening by neuro-psychiatric symptoms of Lyme tick borne disease as it may cause persistent inflammation and molecular mimicry effects from cross-reactive epitopes [9]. Recognizing Lyme disease early in its course was not easy since the child's mother didn't pay attention to erythematous rash that appeared weeks before her admission. Lyme disease has a long latency period before the onset of symptoms and patients don't recall the tick-bite or rash in the majority of cases [10]. It has been proving that inflammatory mediated mechanisms in tick Borne disease have the same neurological pathways as the NMDA receptor limbic encephalitis [11]. Few cases of anti-NMDAR-encephalitis with concurrent positive Borrelia IgM and IgG production in CSF were published proposing Lyme neuroborreliosis as a trigger of anti-NMDAR encephalitis [12]. Other authors suggested that Lyme neuroborreliosis may be associated with an unspecific reaction towards NMDA receptor antigen that can be interpreted as a positive anti-NMDAR antibody result [13].

CONCLUSION

Limbic encephalitis with anti NMDAR antibodies should be suspected whenever a child has appealing symptoms such as behavioral disorders, mood swings and epilepsy but also when a child has dysautonomia symptoms. The heterogeneous symptoms of anti-NMDAR encephalitis may hinder early diagnosis, causing treatment delays and disease progression, leading even to death. Once the diagnosis is made, and the child received the appropriate treatment, an unusual evolution should make the clinician consider aggravating factors such as concomitant infection of the central nervous system or another auto-immune process related to an underlying system disease.

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