OSP Journal of Case Reports

Case Report

Anti NMDA Antibody Encephalitis: A Case Report and Review of the Literature

Christian P[1], Atimad C[1, 2*]

[1]*Laboratory of Nervous System, Neurosensorial and Disability Diseases, Faculty of Medicine and Pharmacy of Casablanca, Hassan II University, Morocco*

[2]*Abderrahim Harouchi Mother and Child Hospital, CHU Ibn Rochd, Faculty of Medicine and Pharmacy of Casablanca, Hassan II University, Morocco*

Corresponding Author: Chemaou Atimad, Laboratory of Nervous System, Neurosensorial and Disability Diseases, Faculty of Medicine and Pharmacy of Casablanca, Hassan II University, Morocco. Email: chrispopongo@gmail.com

Received: December 11, 2021; **Accepted:** December 16, 2021; **Published:** December 30, 2021

Abstract

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAR) is a rare autoimmune encephalitis, recently described and characterized by neuropsychiatric symptoms associated with antibodies directed against the RN1 or RN2 subunits of NMDA receptors. We are reported a rare case of autoimmune encephalitis in a 9-year-old girl admitted for a convulsive state with behavioral disturbances and abnormal movements. The cerebrospinal fluid tested positive for anti-NMDAR antibodies and no association with teratoma was found. The patient was treated initially with intravenous corticosteroid therapy, then with intravenous immunoglobulin, and finally with rituximab. Rituximab resulted in a clear clinical improvement as the regained the ability to eat and social interaction with resumption, without behavioral disturbance

Keywords

Autoimmune Encephalitis; Anti-NMDAR Antibodies; Child

Introduction

N-methyl-D-aspartate receptor encephalitis (anti-NMDA-R) is a rare autoimmune encephalitis first described in 2007[1]. It is the most common autoimmune encephalitis in children [2]. It is characterized by neuropsychiatric symptoms, and is complicated by cognitive and psychomotor sequelae in the absence of early treatment. The diagnosis is based on the search for specific antibodies in the CSF and/or blood [3]. We report the case of a 9-year-old girl admitted for a seizure disorder with behavioral problems in whom the diagnosis of NMDA receptor encephalitis was confirmed.

Observation

This is a nine-year-old girl admitted to the pediatric emergency room for an apyretic convulsive state. She is the eldest of two siblings, born at full term after a normal delivery, with a good adaptation to extra-uterine life. She reports no personal pathological history, and there is the notion of epilepsy in one of her cousins. She has a good psychomotor development. The onset of her symptomatology was progressive and dated back to four days before admission, and this by the occurrence of tonic-clonic convulsive seizures, hemi-body with right and then left tilting, iterative with recovery of consciousness in the inter-critical period for which hospitalization and a check-up was requested (EEG and cerebral MRI) were indicated. On the day of her readmission, the patient presented a behavioral disorder with agitation and visual hallucinations, followed by a convulsive seizure that lasted more than an hour. On examination, the patient was in postcritical coma with a Glasgow score of 8/15, apyretic at 36.8° C, normotensive at 100/60 mm Hg, normocardial at 110 beats/ minute, eupneic at 30 cycles/ minute with an oxygen saturation in free air at 98%.On somatic examination, she had no facial dysmorphia, no skin involvement, nor any other detectable clinical abnormality. Neurologically, there was no meningeal syndrome, but she had a motor deficit with left hemiparesis, left facial paralysis, photo-motor reflexes were present, and sharp patellar reflexes. There were no sphincter disorders, thermoalgesic sensitivity was preserved and proprioceptive sensitivity was difficult to evaluate, with disorientation and agitation on awakening. A workup was performed including a brain scan in search of a malformative anomaly, acquired or congenital, was normal; a blood and urine toxicology screening was negative. Blood count, blood ionogram and C-reactive protein (CRP) were normal. The lumbar puncture performed after stabilization showed a clear CSF, with a protein count of 0.19 g/L, a glycorrhaphy of 0.81 g/L, and a white blood cell count of 5 cells/mm3. The direct examination and the culture were negative. Viral research by gene amplification (multiplex PCR) was negative. The evolution was marked by the persistence of seizures, the occurrence of abnormal movements, dysautonomic signs with hypertensive peaks, as well as a behavioral disorder of the following type aggression, ag-

itation, visual hallucinations, and insomnia. A brain MRI was performed but did not show any abnormalities. The initial EEG showed a diffuse slowing of the baseline pattern. The diagnosis of autoimmune encephalitis was therefore evoked in view of the neuropsychological picture, the normality of the CSF, the inflammatory workup and the cerebral MRI, and the negativity of the virological investigation. The search for anti-NMDAR antibodies in the CSF was positive. Abdominal and pelvic ultrasound and alpha-fetoprotein and beta-HCG assays were performed to rule out a paraneoplastic origin, particularly an ovarian teratoma. These were normal. The patient initially received intravenous corticosteroid therapy with 3 boluses of methylprednisolone followed by oral corticosteroid therapy (prednisolone) at a dose of 2 mg/Kg per day for 2 weeks with a gradual decrease. She also received an intravenous immunoglobulin infusion, which was repeated after one week when she did not improve. In the absence of obvious clinical efficacy and the persistence of antibodies in the CSF after four weeks of corticosteroid therapy, the patient was put on biotherapy, and received four injections of rituximab at a rate of one injection per week, with a regression of the behavioral disorder, as well as of the seizures allowing a return to the home. At six months, independent feeding, social interaction and language were resumed. On the other hand, ataxia and slowness of language persisted with a slow recovery of cognitive and psychic functions. At the 6-month check-up, MRI showed cortico-subcortical atrophy with persistence of anti NMDA AC in the blood.

Discussion

N-methyl-D-aspartate receptor encephalitis is a serious pathology, described and named by Joseph Dalmau in 2007 by Dalmau [2]. Approximately 40% of patients are under 18 years of age with a clear female predominance (80%) [3]. It is an autoimmune disease due to the production of antibodies against the RN1 or RN2 subunits of NMDA receptors. Its exact incidence is unknown but it represents about 4% of the causes of encephalitis. It is the second most common cause of autoimmune encephalitis in children after acute disseminated encephalomyelitis and the most common autoantibody encephalitis [4, 5].

Anti-NMDAR Ac encephalitis is associated in some cases with ovarian tumor pathology, especially teratomas. The presence of a tumor depends on the patient's age, sex, and ethnicity. Female gender and black ethnicity are predisposing factors. At In children, the incidence of the tumor is much lower. It has been described in 6% of cases, in girls younger than 12 years [6, 7].

Because of the possible discovery of a teratoma several months after the encephalitis episode, biannual surveillance by ultrasound or MRI seems prudent in girls older than 12 years of age for at least two years after the encephalitis diagnosis [3]. Antibodies against the RN1-RN2 subunits of the NMDA subtype of glutamate receptors are thought to develop in response to this abnormal tissue.

Regarding the mechanisms involved in NMDAR autoantibody encephalitis, the antibodies bind to NMDA-type glutamate receptors and seem to produce a selective and reversible decrease of NMDA receptors in postsynaptic dendrites, thus inducing a hypo-functionality of NMDA receptors, which is probably at the origin of the psychotic and even thymic symptoms found in this type of encephalitis [8].

Anti-NMDAR encephalitis generally has a stereotyped presentation that classically evolves in four phases [9]; a prodromal phase during which 50 to 70% of patients present non-specific flu-like symptoms that may last from a few days to two weeks with fever, headache, digestive symptoms (nausea, vomiting, diarrhea), and upper respiratory tract infection [3, 6, 10]. A psychiatric phase in which the majority of patients present psychiatric symptoms associating behavioral disorders, hallucinations, sleep disorders, agitation and hyperreactivity. A neurological phase characterized by language and memory disorders, convulsive seizures and/or abnormal movements such as dyskinesias, particularly oral-facial, and signs of dysautonomia (hyperthermia, tachycardia, hyper salivation, hypertension, bradycardia, hypotension, etc.). And finally, a recovery phase which is progressive and occurs in the opposite direction of the appearance of the symptoms. Psychiatric symptoms and cognitive disorders disappear slowly [11, 12].

In children, the clinical picture often begins with complex convulsive seizures or even status epileptics; these motor seizures may alternate with abnormal movements [10, 13, 14].

Brain MRI is abnormal in 31 to 55% of cases with T2 and FLAIR abnormalities of non-specific signal, at the cortical and subcortical level [6, 15, 16]. The EEG is abnormal in 90 to 100% of cases, revealing most often a slow and disorganized non-specific activity with sometimes paroxysmal discharges. A characteristic appearance of the EEG, the name Extreme Delta Brush (EDB) should raise the diagnosis; it consists of slow waves notched with fast rhythms. This pattern is present in 30% of cases and is specific to anti-NMDAR encephalitis [4, 13, 15]. The CSF shows a lymphocytic pleocytosis in 45% of cases, a normal or moderately elevated protenorachy, and oligoclonal bands in 60% of patients. The diagnosis is confirmed by the presence of anti-NMDAR antibodies in CSF and/or blood [11, 16].

Treatment is based on immunotherapy and removal of a possible tumor. First-line treatment includes intravenous corticosteroid boluses of methylprednisolone (1g/day for 5 days), polyvalent immunoglobulin infusions at a dosage of 0.4g/ kg/day, which can be given for 5 days, and plasma exchange. In the absence of significant clinical improvement within 10 days of first-line therapy, rituximab at a dose of 375 mg/m2 is indicated as second-line therapy [7, 17, 18]. In all cases, management requires a multidisciplinary approach, with the participation of a neurologist, psychomotor therapist, speech therapist and physiotherapist.

The prognosis is often good in pediatric age, with 85% complete but slow recovery (up to several months) and relapse in the remaining 15% [17]. The predictive factors for a good prognosis are short time to identification and treatment, absence of intensive care unit (ICU) stay and initial non-severe symptomatology.

Conclusion

N-methyl-D-Aspartate receptor encephalitis (anti-NMDA-R) is an entity that is still not widely recognized. It should be sought in the presence of any unlabeled neuropsychiatric picture. The diagnosis is based on the search for specific antibodies in the CSF. It can be reversible and without sequelae if diagnosed and treated early. Management is multidisciplinary.

References

1. Wang RJ., Chen BD., Qi D (2015) Encéphalite des récepteurs anti-N-méthyl-D-aspartate concomitante avec des lésions multifocales de la substance blanche sous-corticale sur l'imagerie par résonance magnétique : un rapport de cas et une revue de la littérature. *BMC Neurol* 15:107.
2. Dalmau J., Tüzün E., Wu HY (2007) Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 61: 25-36.
3. Scheer S., John RM (2016) Anti-N-Methyl-D-Aspartate Receptor Encephalitis in Children and Adolescents. *J Pediatr Health Care* 30: 347-358.
4. Maggio MC., Mastrangelo G., Skabar A (2017) Atypical presentation of anti-N-methyl-D-aspartate receptor encephalitis: two case reports. *J Med Case Rep* 11: 225.
5. Wang RJ., Chen BD., Qi D (2015) Anti-N-methyl-D-aspartate receptor encephalitis concomitant with multifocal subcortical white matter lesions on magnetic resonance imaging: a case report and review of the literature. *BMC Neurol* 15: 107.
6. Dalmau J., Lancaster E., Martinez-Hernandez E (2011) Clinical Experience and laboratory investigations in Patients with ant-NMDAR Encephalitis. *Lancet neurology* 10: 63-74
7. Titulaer MJ., McCracken L., Gabilondo I (2013) Treatment and prognostic factors for long-term outcome in patients with anti- NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 12: 157-165.
8. BenAzouna M., Tatencloux S., Deiva K., Blanca P (2014) Deux cas pédiatriques d'encéphalite auto-immune à anticorps anti-récepteur NMDATwo pediatric cases of anti-NMDA receptor antibody encephalitis. *Archives de Pédiatrie* 21: 1216-1219.
9. Kayser MS., Dalmau J (2011) Anti-NMDA Receptor Encephalitis in Psychiatry. *Curr Psychiatry Rev* 7: 189-193.
10. Suthar R., Saini AG., Sankhyan N., Sahu JK., Singhi P (2016) Childhood Anti-NMDA Receptor Encephalitis. *Indian J Pediatr* 83: 628-633.
11. Dalmau J., Geis C., Graus F (2017) Autoantibodies to Synaptic Receptors and Neuronal Cell Surface Proteins in Autoimmune Diseases of the Central Nervous System. *Physiol Rev*. 97: 839-887
12. Florance-Ryan N., Dalmau J (2010) Update on anti-N-methyl-D-aspartate receptor encephalitis in children and adolescents. *Curr Opin Pediatr* 22: 739-744.
13. Scheer S., John RM (2016) Anti-N-Methyl-D-Aspartate Receptor Encephalitis in Children and Adolescents. *J Pediatr Health Care* 30: 347-35.8
14. Gitiaux C., Simonnet H., Eisermann M., Leunen D., Dulac O., et al. (2013) Early electro-clinical features may contribute to diagnosis of the anti-NMDA receptor encephalitis in children. *Clin Neurophysiol* 124: 2354-23261.
15. Zekeridou A., Karantoni E., Viaccoz A., Ducray F., Gitiaux C., et al. (2015) Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. *J Neurol* 262:1859-1866.
16. Yang S., Yang L., Liao H (2021) Clinical Characteristics and Prognostic Factors of Children With Anti-N-Methyl-D-Aspartate Receptor Encephalitis. *Front Pediatr* 9: 605042.
17. Florance NR., Davis RL., Lam C (2009) Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 66:11-18.
18. Barbagallo M., Vitaliti G., Pavone P., Romano C., Lubrano R., et al. (2017) Pediatric Autoimmune Encephalitis. *J Pediatr Neurosci* 12: 130-134.