Review Article

Anti-N-Methyl-D-Aspartate Receptor Encephalitis in Pediatrics: A Review of Clinical Manifestations, Treatment, and Prognosis

Sawsan Ali Hussein, Basma Adel Ibrahim, Wasnaa Hadi Abdullah

Department of Pediatrics, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq

Abstract

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAR) is a severe autoimmune disease caused by the development of immunoglobulin G antibodies against the NMDAR's GluN1 subunit in the cerebrospinal fluid. It is characterized by a wide range of clinical features including psychological manifestations, dyskinesia, and epileptic seizures. Intravenous methylprednisolone, intravenous immunoglobulin, and plasma exchange are the first-line treatments. Early diagnosis, treatment, monitoring, and follow-up of the disease are crucial as it results in favorable prognosis. In the pediatric age group, relapse is possible.

Keywords: Anti-N-methyl-D-aspartate receptor, encephalitis, pediatrics

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a severe autoimmune disease caused by the development of immunoglobulin G (IgG) antibodies against the NMDAR's GluN1 subunit in the cerebrospinal fluid (CSF). It's a serious medical condition, but fortunately can be managed.[1,2] The first diagnosed NMDAR encephalitis was in a lady complained from teratoma of the ovaries in 2007.[3] Previous studies indicate anti-NMDAR encephalitis affects one of 1.5 million people per year.[4] Anti-NMDAR encephalitis is thought to affect about 37% of newborns and children, with an average age of 10 years among youngsters.[5] It is more common in females than male children and adolescents.[6] Anti-NMDAR encephalitis has been identified as the most common autoimmune encephalitis in children, second only to acute demyelinating encephalomyelitis, since its first report in 2007.[7]

Etiology

Anti-NMDAR encephalitis is induced by a B-cell-mediated autoimmune response that caused by viral infections such as herpes simplex virus encephalitis or tumors such as ovarian teratomas leading to the formation of autoantibodies directed toward synaptic NMDARs.[8,9] Synaptic transmission, hippocampus potentiation, learning, and memory formation are all mediated by NMDARs, which are ligand-gated cation channels.[3] Blockade of NMDARs through antibodies leads to dysfunction in frontostriatal connections and prefrontal networks, resulting in psychiatric symptoms, seizures, autonomic dysfunction, movement disorders, and memory problems.[10] However, in some patients, the etiology of autoantibody production remains unclear.[8] Before the detection of these antibodies, patients with neurological symptoms that resembled anti-NMDAR encephalitis were frequently misdiagnosed as encephalitis of unknown origin after viral and immunological causes were ruled out.[11]

Clinical Manifestations

Anti-NMDAR encephalitis is a severe disorder characterized by a wide range of clinical features including psychological manifestations, dyskinesia, epileptic seizures, disturbed level of consciousness, and hypoventilation.[11]

Access this article online

Quick Response Code:

Website: http://www.mmjonweb.org

DOI: 10.4103/mj.mj_6_22

Address for correspondence: Dr. Wasnaa Hadi Abdullah, Department of Pediatrics, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq.
E-mail: wasnaa.hadi@uomustansiriyah.edu.iq

Submitted: 30-Jan-2022 **Revised:** 16-Mar-2022 **Accepted:** 19-Mar-2022 **Published:** 02-Jan-2023

How to cite this article: Hussein SA, Ibrahim BA, Abdullah WH. Anti-N-Methyl-D-Aspartate receptor encephalitis in pediatrics: A review of clinical manifestations, treatment, and prognosis. Mustansiriya Med J 2022;21:96-9.

In pediatrics, extended cognizance of this disorder is essential because of small series or single case reports,[12,13] and the most important experience was a 32 patient series in the United States, eight of whom came from a single organization.[14] This and subsequent research suggested that the younger the child, the less probable a tumor would be detected, and that the disorder's onset and presentation in the pediatric age group may differ from that of adults.[14,15] There are three clinical stages of anti-NMDAR encephalitis: a prodromal stage, an early which is the psychotic and/or the seizure phase, and a later on is the hyperkinetic stage.[16]

Many patients with anti-NMDAR encephalitis suffer from prodromal headache, increase body temperature, or a viral-like illness, followed by psychiatric symptoms including anxiety, agitation, odd behavior, delusions, hallucinations, and psychosis, in addition to sleep disorders, including sleep reduction at disease onset and hypersomnia during recovery, impaired memory, seizures, disturb the level of consciousness, dyskinesias, autonomic instability, and language disorder.[17] Seizures are more likely in children at first presentation, and aberrant movements, particularly limb dystonia, are also more common in children.[18]

Diagnosis

Diagnostic criteria for anti-NMDAR encephalitis included clinical and serological findings including serum and CSF IgG antibodies against the GluN1 subunit of NMDAR.[6] The likelihood of CSF versus serum positivity for anti-NMDAR antibodies remains unclear.[6,16] Anti-NMDAR encephalitis diagnosis is significantly more sensitive and specific when CSF IgG antibody is detected rather than serum antibodies alone.[19] CSF antibodies are always present at the time of presentation; most patients have intrathecal synthesis of antibodies.[20] If there is no clinical improvement following treatment, CSF antibodies usually stay elevated, although serum antibodies may be dramatically lowered,[21] CSF antibody titers appear to be more closely linked to the clinical outcome than serum titers.[22]

Other investigations support the diagnosis of anti-NMDAR encephalitis, is electroencephalogram (EEG).[17] Common electroencephalogram (EEG) findings include excessive beta activity range 14–20 Hz, generalized rhythmic delta activity, and extreme delta brush which is supposed to be specific to anti-NMDAR encephalitis.[5,6] On the other hand, some studies claim that the precise EEG patterns and evolution of EEG findings at various stages of the disease, as well as the prognostic rate of positive EEG findings such as severe delta brush are incompletely understood.[17] Brain magnetic resonance imaging (MRI) is frequently unremarkable or shows transient fluid-attenuated inversion recovery or assessment-enhancing abnormalities in cortical or subcortical regions.[22]

A systematic review revealed that cerebellar atrophy is an MRI finding of prognostic significance in patients with anti-NMDAR encephalitis.[23] Increase in the frontal-occipital gradient of cerebral glucose metabolism is seen in positron emission tomography, while not routinely performed; this finding is characteristic and found to be correlated with disease severity.[24]

Treatment

The aim of treatment of anti-NMDAR encephalitis is to remove the anti-NMDAR antibodies as it is the main cause of the disease.[25]

If the anti-NMDAR encephalitis associated with a tumor, for example, an ovarian tumor, the first step in the management is the tumor removal and subsequently, treatment with immunotherapy medications.[18] Intravenous methylprednisolone to suppress the immune system, intravenous immunoglobulin, and plasma exchange to eliminate autoantibodies are the first-line treatments, and they are effective in 53%–80% of patients and when the first-line medications are ineffective after 10–14 days, the second-line treatments will be used, which include rituximab, azathioprine, cyclophosphamide, and mycophenolate mofetil. Rituximab is the most commonly utilized among them.[25] Once patients show substantial improvement, these treatments are usually discontinued.[18]

Prognosis

The recovery rate in children less than or equal to 6 years was significantly higher than those >6 years and also more psychiatric symptoms were present in those >6 years.[6] Approximately half of the children diagnosed recover with minor deficits.[16] Abnormal EEG leads to the increased likelihood of intensive care unit admission or less favorable outcome and may help in the decision to start more aggressive treatment options.[26]

A retrospective examination of 577 patients was used to analyze therapy effects and outcomes in the biggest published study on anti-NMDAR encephalitis treatment and prognosis.[27] Nearly, all patients (94%) were treated with tumor removal and first-line immunotherapeutic agents, including steroids, intravenous immunoglobulin, with/without plasma exchange procedure.

- Within the first 4 weeks of treatment, 50% of patients improved. Of these, 97% had a good outcome at 24-month follow-up
- Of the 221 patients who did not improve within the initial 4 weeks of the first-line therapy, 125 (57%) received rituximab, cyclophosphamide, or both. Those who received second-line therapy had better clinical outcomes than those who did not. Response rates were similar in adults and children
- By 24 months, approximately 80% of patients achieved a good outcome and 30 patients had died. Their health improved for up to 18 months for the beginning of disease
- Relapses occurred in 12% of patients within the first 2 years after the original assault. Patients without a tumor

and those who did not get second-line immunotherapy were more likely to relapse.

Pregnancy and Fetal Effects

The transfer of anti-NMDAR IgG antibodies transplacentally has been documented in serum of babies born to mothers with anti-NMDAR encephalitis. Nevertheless, newborn outcomes appear to be good in most cases.

In a review of 21 previously published cases and 11 new cases of women who either developed anti-NMDAR encephalitis while pregnant or became pregnant while recovering from the encephalitis, the majorities of newborns were healthy and had no evidence of neurodevelopment delay with follow-up ranging from 6 to 36 months.[28-34] Transient respiratory distress or neuromuscular deficits at delivery rarely occurred. Such complications spontaneously recovered and were considered secondary to antiseizure and sedative medications given to the mothers. Adverse outcomes included one infant with cortical dysplasia, developmental disorder, and seizures as a result of a complicated pregnancy due to uteroplacental insufficiency.[29] There was one neonatal death reported,[28] in this case, the mother had recovered from anti-NMDAR encephalitis 18 months before delivery and presented with eclampsia without prior knowledge of the pregnancy or prenatal care.

Obstetric complications were reported in approximately one-third of the women who developed anti-NMDAR encephalitis during pregnancy, mostly due to pathologic pregnancy or spontaneous miscarriage, supporting close monitoring in intensive care units focused on pregnancies with a high risk of complications.[34]

Conclusions

Anti-NMDAR encephalitis is a difficult condition to diagnose since it manifests as a subacute onset encephalopathy with seizures, extrapyramidal symptoms, behavioral symptoms, speech problems, and autonomic involvement. It frequently necessitates a series of supportive investigations. Early diagnosis, treatment, monitoring, and follow-up of the disease are crucial as it results in favorable prognosis. In the pediatric age group, relapse is possible.

Acknowledgment

To our beloved University; Al-Mustansiriyah for continuous support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Suwarba IG. Anti-NMDAR encephalitis in 10-year-old girl: Sanglah Hospital, Bali, Indonesia. Int J Health Sci 2021;5:1-8.
2. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63-74.
3. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, *et al.* Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.
4. Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, *et al.* An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: Mechanisms and models. Lancet Neurol 2019;18:1045-57.
5. Goenka A, Jain V, Nariai H, Spiro A, Steinschneider M. Extended clinical spectrum of anti-N-Methyl-d-aspartate receptor encephalitis in children: A case series. Pediatr Neurol 2017;72:51-5.
6. Sai Y, Zhang X, Feng M, Tang J, Liao H, Tan L. Clinical diagnosis and treatment of pediatric anti-N-methyl-D-aspartate receptor encephalitis: A single center retrospective study. Exp Ther Med 2018;16:1442-8.
7. Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, *et al.* Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013;162:850-6.e2.
8. Armangue T, Spatola M, Vlagea A, Mattozzi S, Cárceles-Cordon M, Martinez-Heras E, *et al.* Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: A prospective observational study and retrospective analysis. Lancet Neurol 2018;17:760-72.
9. van Coevorden-Hameete MH, Titulaer MJ, Schreurs MW, de Graaff E, Sillevis Smitt PA, Hoogenraad CC. Detection and characterization of autoantibodies to neuronal cell-surface antigens in the central nervous system. Front Mol Neurosci 2016;9:37.
10. Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, *et al.* Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci 2010;30:5866-75.
11. Prüss H, Dalmau J, Harms L, Höltje M, Ahnert-Hilger G, Borowski K, *et al.* Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010;75:1735-9.
12. Luca N, Daengsuwan T, Dalmau J, Jones K, deVeber G, Kobayashi J, *et al.* Anti-N-methyl-D-aspartate receptor encephalitis: A newly recognized inflammatory brain disease in children. Arthritis Rheum 2011;63:2516-22.
13. Bseikri MR, Barton JR, Kulhanjian JA, Dalmau J, Cohen RA, Glaser CA, *et al.* Anti-N-methyl D-aspartate receptor encephalitis mimics viral encephalitis. Pediatr Infect Dis J 2012;31:202-4.
14. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, *et al.* Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11-8.
15. Titulaer M, McCracken L, Cuellar IG, Martinez-Hernandez E, Graus F, Balice-Gordon R, *et al.* Clinical features, treatment, and outcome of 500 patients with anti-NMDA receptor encephalitis (PL01. 001).” 2012. PL01-001.
16. Remy KE, Custer JW, Cappell J, Foster CB, Garber NA, Walker LK, *et al.* Pediatric Anti-N-Methyl-d-aspartate receptor encephalitis: A review with pooled analysis and critical care emphasis. Front Pediatr 2017;5:250.
17. Nathoo N, Anderson D, Jirsch J. Extreme delta brush in anti-NMDAR encephalitis correlates with poor functional outcome and death. Front Neurol 2021;12:686521.
18. Pruetarat N, Netbaramee W, Pattharathitikul S, Veeravigrom M. Clinical manifestations, treatment outcomes, and prognostic factors of pediatric anti-NMDAR encephalitis in tertiary care hospitals: A multicenter retrospective/prospective cohort study. Brain Dev 2019;41:436-42.
19. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, *et al.* Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: A retrospective study. Lancet Neurol 2014;13:167-77.
20. Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 2011;77:589-93.
21. Okamoto S, Hirano T, Takahashi Y, Yamashita T, Uyama E, Uchino M. Paraneoplastic limbic encephalitis caused by ovarian teratoma with

autoantibodies to glutamate receptor. Intern Med 2007;46:1019-22.
22. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, *et al.* Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-8.
23. Bacchi S, Franke K, Wewegama D, Needham E, Patel S, Menon D. Magnetic resonance imaging and positron emission tomography in anti-NMDA receptor encephalitis: A systematic review. J Clin Neurosci 2018;52:54-9.
24. Leypoldt F, Buchert R, Kleiter I, Marienhagen J, Gelderblom M, Magnus T, *et al.* Fluorodeoxyglucose positron emission tomography in anti-N-methyl-D-aspartate receptor encephalitis: Distinct pattern of disease. J Neurol Neurosurg Psychiatry 2012;83:681-6.
25. Hao XS, Wang JT, Chen C, Hao YP, Liang JM, Liu SY. Effectiveness of mycophenolate mofetil in the treatment of pediatric Anti-NMDAR encephalitis: A retrospective analysis of 6 cases. Front Neurol 2020;11:584446.
26. Gillinder L, Warren N, Hartel G, Dionisio S, O'Gorman C. EEG findings in NMDA encephalitis – A systematic review. Seizure 2019;65:20-4.
27. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, *et al.* Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. Lancet Neurol 2013;12:157-65.
28. Chourasia N, Watkins MW, Lankford JE, Kass JS, Kamdar A. An infant born to a mother with anti-N-Methyl-d-aspartate receptor encephalitis. Pediatr Neurol 2018;79:65-8.
29. Jagota P, Vincent A, Bhidayasiri R. Transplacental transfer of NMDA receptor antibodies in an infant with cortical dysplasia. Neurology 2014;82:1662-3.
30. Hilderink M, Titulaer MJ, Schreurs MW, Keizer K, Bunt JE. Transient anti-NMDAR encephalitis in a newborn infant due to transplacental transmission. Neurol Neuroimmunol Neuroinflamm 2015;2:e126.
31. Magley J, Towner D, Taché V, Apperson ML. Pregnancy outcome in anti-N-methyl-D-aspartate receptor encephalitis. Obstet Gynecol 2012;120:480-3.
32. Kumar MA, Jain A, Dechant VE, Saito T, Rafael T, Aizawa H, *et al.* Anti-N-methyl-D-aspartate receptor encephalitis during pregnancy. Arch Neurol 2010;67:884-7.
33. Lamale-Smith LM, Moore GS, Guntupalli SR, Scott JB. Maternal-fetal transfer of anti-N-methyl-D-aspartate receptor antibodies. Obstet Gynecol 2015;125:1056-8.
34. Joubert B, García-Serra A, Planagumà J, Martínez-Hernandez E, Kraft A, Palm F, *et al.* Pregnancy outcomes in anti-NMDA receptor encephalitis: Case series. Neurol Neuroimmunol Neuroinflamm 2020;7:e668.