Asian Journal of Pediatric Research

Volume 14, Issue 11, Page 22-26, 2024; Article no.AJPR.125860
ISSN: 2582-2950

A Case Report on Anti-N-Methyl-D-Aspartate Encephalitis

Sowndharya S [a++*] and John Felix S N [a++]

[a] C L Baid Metha College of Pharmacy, Affiliated to "The Tamilnadu Dr. MGR Medical University", Thoraipakkam, Chennai – 97, Tamil Nadu, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2024/v14i11399

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/125860

Case Report

Received: 20/08/2024
Accepted: 24/10/2024
Published: 30/10/2024

ABSTRACT

Aim: The case study aims to describe and evaluate the initial neuropsychiatric symptoms, therapeutic methods, and diagnostic criteria, of a 3-year-old girl who had been diagnosed with anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis. This case study implies the importance of early detection and treatment in pediatric autoimmune encephalitis, highlighting its diagnostic challenges and the successive use of immunotherapy and outcomes.

Presentation of Case: A 3-year-old developmentally normal girl child was brought to the hospital with C/O fever for 2 days. Following this she had seizures lasting for around 2 minutes and followed by shivering movements in the right leg for 15 minutes and then she regained consciousness after 25 minutes. CSF analysis showed pleocytosis. Serological tests (Typhoid IgM, Rapid Malaria, Scrub IgM, Dengue IgM, Japanese Encephalitis, and Herpes Simplex Virus IgM) were negative. MRI indicated diffuse encephalopathy, and EEG detected epileptic activity. Further antibody testing in serum and CSF revealed positive Anti-NMDAR antibodies. The patient was treated with amoxicillin-clavulanate(400mg), ceftriaxone(750mg), and acyclovir(130mg) intravenously initially. Once the definitive diagnosis was made, she was treated with IVIG(26g), methylprednisolone(390mg), and levetiracetam(280mg).

[++] Pharm. D Intern;
**Corresponding author: Email: sowndharyasri21@gmail.com;*

Cite as: *S, Sowndharya, and John Felix S N. 2024. "A Case Report on Anti-N-Methyl-D-Aspartate Encephalitis". Asian Journal of Pediatric Research 14 (11):22-26. https://doi.org/10.9734/ajpr/2024/v14i11399.*

Discussion: Anti-N-Methyl-D-Aspartate Receptor Encephalitis is an autoimmune encephalitis characterized by complicated neuropsychiatric symptoms and immunoglobulin G (IgG) antibodies against the NR1 subunit of the NMDA receptors in the central nervous system.
Conclusion: The appropriate diagnosis and treatment of autoimmune encephalitis necessitate an organized approach. A wide range of autoantibody tests can be performed to identify or rule-out specific autoimmune causes. Patients may relapse and require appropriate follow-up care.

Keywords: Autoimmune encephalitis; anti-NMDAR encephalitis; anti-NMDAR antibodies; IV immunoglobulin.

1. INTRODUCTION

"Anti-N-Methyl-D-Aspartate Receptor Encephalitis is an autoimmune encephalitis characterized by complicated neuropsychiatric symptoms and immunoglobulin G (IgG) antibodies against the NR1 subunit of the NMDA receptors in the central nervous system. These antibodies are detectable in serum or cerebrospinal fluid. This autoimmune encephalitis develops due to the development and attachment of IgG (G1 and G3) antibodies to the NR1 subunit of the NMDA receptor. This subsequently results in the internalization of receptors, reduction in neuronal calcium influx, and decrease in receptor-dependent synaptic currents" (Dalmau et al. 2008, Hughes et al. 2010).

"In certain patients, antibody production is caused by an accompanying ovarian teratoma and, in rare cases, additional malignancies. The development of autoimmune encephalitis can follow viral encephalitis, especially Herpes Simplex Virus encephalitis, and is correlated with the generation of NMDAR antibodies within the next three weeks" (Armangue et al. 2018).

"Autoimmune encephalitis is a rare disease with an incidence rate of 1 in 1.5 million people per year, and anti-NMDAR encephalitis is the most common of all autoimmune encephalitis cases reported. Anti-NMDAR encephalitis has been documented in newborns as young as 2 months and as old as 85 years. Females are affected four times more frequently" (Dalmau et al. 2019).

1.1 Pathophysiology

Autoimmune encephalitis is classified based on the targets of the antibodies. The classical paraneoplastic encephalitis is mediated through a T-cell-mediated mechanism with cytotoxic T cells demonstrated in the pathological specimens. The immune responses are caused by molecular mimicry between neural tissue antigens and tumor antigens. The antibodies themselves are not pathogenic.

"The other type of autoimmune encephalitis is characterized by antibodies directed against synaptic or cell-surface antigens, such as anti-NMDAR, anti-GAD, and anti-VGKC antibody-mediated encephalitides. These are actual autoimmune encephalitis caused by pathogenic antibodies or B-cell mediated autoimmune encephalitis. Anti-NMDAR antibody immune encephalitis is a B-cell-mediated autoimmune encephalitis with a pathogenic antibody that can be eliminated with plasma exchange, improving the underlying pathology" (van et al. 2016).

"Anti-NMDAR encephalitis comprises five unique phases: prodromal, psychotic, unresponsive, hyperkinetic, and recovery. The disease begins with a prodromal state that resembles common viral infections. However, during the psychotic phase, complicated neuropsychiatric traits appear quickly, within weeks to a few months (less than three months). Children and adults may present with various clinical characteristics. Adults typically present with psychiatric symptoms, whereas movement problems or seizures are the most prevalent presentation in children. Though there is no distinct psychiatric phenotype, these patients with no prior psychiatric diagnosis may experience a variety of positive and negative psychiatric symptoms such as visual or auditory hallucinations, acute schizoaffective episodes, depression, mania, and addictive or eating disorders within days to weeks. Patients with anti-NMDAR encephalitis exhibit both positive and negative symptoms, as opposed to the more common positive symptoms in schizophrenia" (Dalmau et al. 2019).

The psychotic phase transitions to the unresponsive phase, which is marked by mutism, decreased motor activity, and catatonia. Following the unresponsive phase, a hyperkinetic phase with autonomic instability and significant movement abnormalities emerges. Symptoms of

significant autonomic disturbance include erratic blood pressure and heart rate, cardiac arrhythmias, temperature instability, and central hypoventilation (Iizuka et al. 2008, Titulaer et al. 2014).

2. CASE PRESENTATION

A 3-year-old developmentally normal girl child was brought to the hospital with C/O fever for 2 days following this she had seizures lasting for around 2 minutes and followed by shivering movements in the right leg for 15 minutes and she regained consciousness after 25 minutes. The child was drowsy on admission. The antenatal, natal, and post-natal history were uneventful, and the child was immunized up until the age.

A complete blood count disclosed a hemoglobin level of 9.2 g/dL (11-14g/dl), white blood cell count (WBC) of 25600/mm^3(5000-15000/mm^3) and platelet count of 281000/mm^3 (200000-500000/mm^3). Additionally, the CRP levels were also found to be significantly high at 12 mg/dl (<5mg/dl). Other routine biochemical tests were well within normal ranges.

Further CSF analysis revealed pleocytosis with WBC levels of 13 cells/mm^3(<5 cells/mm^3). Other serological tests like Typhoid IgM, Rapid Malaria test, Scrub IgM, Dengue IgM, Japanese Encephalitis serology, and Herpes Simplex Virus IgM turned out to be either negative or nonreactive. MRI brain showed diffuse encephalopathy and EEG revealed epileptic activity.

Since all serological tests turned out to be negative, antibody testing in serum and CSF was carried out. Anti-NMDAR antibodies in serum and CSF turned out to be positive, while other antibodies like anti-VGKC antibody, thyroid antibody, and antinuclear antibody were all negative.

The individual fulfilled the necessary criteria for diagnosing autoimmune encephalitis, including the subacute emergence of symptoms such as seizures and choreoathetoid movements in the limbs. The diagnosis was further supported by findings in the MRI brain scan, which revealed diffuse encephalopathy, as well as the presence of CSF pleocytosis and EEG results indicating 13 cells/mm3 and epileptic activity respectively. Additionally, other potential causes, including viral serology markers, were ruled out during the diagnostic process.

The child was treated with antibiotics and antivirals empirically for the first six days of admission till antibody results came back and this included amoxicillin-clavulanate(400mg), ceftriaxone(750mg), and acyclovir(130mg) intravenously. She was treated with intravenous anticonvulsant levetiracetam(280mg) for the entirety of the hospital stay.

After the definitive diagnosis was made, the child received Intravenous immunoglobulin(26g) as a continuous IV infusion over 3 days at a dose of 2g/kg body weight and intravenous methylprednisolone(390mg) as a continuous IV infusion over 30 minutes for 3 days at a dose of 30mg/kg/day. The patient handled the immunosuppressive therapy well and is been planned for IV methylprednisolone in the outpatient setting every 4 weeks to prevent the relapse of the disease. The patient is currently being followed up.

3. DISCUSSION

IgG antibodies against the NR1 subunit of the central nervous system's NMDA receptors and complex neuropsychiatric symptoms are the hallmarks of anti-NMDA receptor encephalitis, an autoimmune encephalitis.

“Autoimmune encephalitis is a challenging clinical diagnosis since multiple types of autoimmune and infectious encephalitis have identical clinical, imaging, and laboratory findings. Patients typically have poor memory and cognition over a period of days or weeks. The history of physical examination may provide clues to specific reasons, but these indicators are often absent. A wide approach to testing for infectious illnesses and neuronal autoantibodies can result in an accurate diagnosis” (Titulaer et al. 2014).

“The treatment for autoimmune encephalitis includes plasmapheresis, IVIG and/or steroids. Steroids may prove to be beneficial in a range of autoimmune disorders but could potentially be problematic with the diagnosis of certain disorders such as CNS lymphoma” (Dalmau et al. 2011).

“If a synaptic/cell-surface antibody is discovered and the patient exhibits any severe symptoms, first-line therapy should be initiated if it has not already been attempted. In general, swift intervention and escalation of treatment in patients who stay unwell leads to improved

outcomes. Second-line therapies are usually employed if first-line therapy does not considerably improve the patient's condition. Treatment techniques are comparable in children and adults; however, clinicians may be more hesitant to use cyclophosphamide, preferring rituximab as a second-line treatment. Treatment outcomes are comparable in children and adults, with approximately 50% failing first-line therapy. Ovarian teratoma is less common in female children before puberty, hence tumors are rare in young children" (Titulaer et al. 2013).

4. CONCLUSION

The appropriate diagnosis and treatment of autoimmune encephalitis necessitate an organized approach. To identify particular causes, a comprehensive history and physical examination should be conducted first. A wide spectrum of infections should be investigated, and appropriate testing should be performed to rule out relevant pathogens. Ancillary testing, such as an MRI, EEG, and lumbar puncture, may help to confirm a diagnosis of encephalitis and may point to specific causes. A wide range of autoantibody tests can be performed to identify or rule out specific autoimmune causes. The possibility of a neoplasm should always be evaluated during the initial treatment and follow-up appointments. Treatment should be determined by the pathophysiology of the condition as well as the patient's clinical circumstances. Patients may relapse and require appropriate follow-up care.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

ACKNOWLEDGEMENT

We are indebted to our highly respected and esteemed madam, Dr. C.N. Nalini, M.Pharm., Ph.D., Principal, C L Baid Metha College of Pharmacy for her benevolent and ever-helping arms which provided us with all the essential facilities in bringing out this paper. We would like to thank our beloved parents for trusting and supporting us. Above all, we would like to give thanks and praise to the Almighty God for the grace and blessing throughout the entire work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Dalmau, J., Gleichman, A. J., Hughes, E. G., Rossi, J. E., Peng, X., Lai, M., et al. (2008). Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. *Lancet Neurology, 7*(12), 1091–1098. Available:https://doi.org/10.1016/S1474-4422(08)70224-2

Hughes, E. G., Peng, X., Gleichman, A. J., Lai, M., Zhou, L., Tsou, R., et al. (2010). Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *Journal of Neuroscience, 30*(17), 5866–5875. Available:https://doi.org/10.1523/JNEUROSCI.0167-10.2010

Armangue, T., Spatola, M., Vlagea, A., Mattozzi, S., Cárceles-Cordon, M., Martinez-Heras, E., et al. (2018). Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: A prospective observational study and retrospective analysis. *Lancet Neurology, 17*(9), 760–772. Available:https://doi.org/10.1016/S1474-4422(18)30244-8

Dalmau, J., Armangué, T., Planagumà, J., Radosevic, M., Mannara, F., Leypoldt, F., et al. (2019). An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: Mechanisms and models. *Lancet Neurology, 18*(11), 1045–1057. Available:https://doi.org/10.1016/S1474-4422(19)30244-3

van Coevorden-Hameete, M. H., Titulaer, M. J., Schreurs, M. W., et al. (2016). Detection and characterization of autoantibodies to neuronal cell-surface antigens in the central nervous system. *Frontiers in Molecular Neuroscience, 9*, 37.

Available:https://doi.org/10.3389/fnmol.2016.00037

Iizuka, T., Sakai, F., Ide, T., Monzen, T., Yoshii, S., Iigaya, M., et al. (2008). Anti-NMDA receptor encephalitis in Japan: Long-term outcome without tumor removal. *Neurology, 70*(7), 504–511. Available:https://doi.org/10.1212/01.wnl.0000278388.90370.c3

Titulaer, M. J., Höftberger, R., Iizuka, T., Leypoldt, F., McCracken, L., Cellucci, T., et al. (2014). Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Annals of Neurology, 75*(3), 411–428. Available:https://doi.org/10.1002/ana.24117

Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M. R., & Balice-Gordon, R. (2011). Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurology, 10*, 63–74. Available:https://doi.org/10.1016/S1474-4422(10)70253-2

Titulaer, M. J., McCracken, L., Gabilondo, I., Armangué, T., Glaser, C., Iizuka, T., et al. (2013). Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. *Lancet Neurology, 12*, 157–165. Available:https://doi.org/10.1016/S1474-4422(12)70310-1

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/125860