CASE REPORT

JIACM 2023; 24 (2): 146-48

Autoimmune Encephalitis: Look Beyond the Obvious

Pooja Gautam, Shah Yash Rakesh**, Sumeet Singla***, S Anuradha*****

Abstract

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a life-threatening autoimmune condition caused by antibody production against NMDA receptors leading to its dysfunction. The disease generally affects young females and is frequently associated with neoplasms like ovarian teratoma. Early diagnosis is often missed, as patients may present with psychiatric manifestations. We report the rare case of anti NMDAR encephalitis in a 13-year-old female who presented with headache, vomiting, fever, altered sensorium, and involuntary movements. The patient responded well to treatment.

Key words: Autoimmune encephalitis, Anti-NMDAR, paraneoplastic, dyskinesia.

Key message

- *Autoimmune encephalitis is an uncommon condition mostly affecting young girls.*
- *Due to it's protean manifestations, there is diagnostic confusion and delay; patients may be labelled as psychiatric disease, epilepsy, or infectious (tubercular/viral) disorder.*
- *A subacute onset syndrome of psychiatric, cognitive and behavioral abnormalities, exclusion of commoner etiologies and CSF/serum autoantibody testing can reveal the diagnosis.*
- *With correct recognition, the treatment is fairly simple and clinical features are fully reversible with gratifying results.*
- *A search for underlying malignancy must be carried out in every patient of autoimmune encephalitis.*

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a life-threatening autoimmune condition caused by antibody production against NMDA receptors leading to dysregulation of neurotransmission. Described initially by Dalmau *et al*, it is four times commoner in females and 37% of the patients are < 18 years at presentation[1] with an estimated prevalence of 13.7 per 1,00,000 population[2]. Clinical presentations include cognitive or memory deficits, altered consciousness, seizures, movement disorders, and neuropsychiatric symptoms[3,4]. It is highly responsive to treatment if recognised early, nearly 75% of patients recover completely[1]. It can be a para-neoplastic manifestation of a tumour, most commonly, an ovarian teratoma[5-8]. The relapse rate is 15.9% with most (82.0%) patients experiencing it in 24 months[9]. We report Anti NMDAR encephalitis in a 13-year-old girl who presented with encephalitis syndrome and involuntary movements.

Case report

A previously healthy 13-year-old girl, resident of Delhi, presented to the emergency department with complaints of headache for 3 months, vomiting for 10 days, fever for 6 days and altered sensorium for 3 days. There were behavioural disturbances in terms of agitation, decreased verbal output and non responsive to commands for the last 3 days. There was no history of weight loss, cough, or contact with a case of tuberculosis. There were no history of similar complaints or any long-standing psychiatric illness in the past.

On examination, the patient was conscious, but disoriented (agitated). Her vitals were within normal range. She was febrile (axillary temperature 101° F). General physical examination was unremarkable. The girl exhibited involuntary movements such as orofacial dyskinesia and tremors in the right hand. Terminal neck rigidity was present, but Kernig's/Brudzinki's sign were absent. During the hospital stay, she had one episode of generalised tonic clonic seizure. A provisional diagnosis of meningo-encephalitis was made and the patient was started on intravenous ceftriaxone, vancomycin, acyclovir, dexamethasone and mannitol. A lumbar puncture and was performed. The results of CSF analysis, laboratory investigations, radiological investigations and EEG results

Senior Resident, **Post-Graduate, ***Professor, ****Director Professor, Department of Medicine, MAMC and LNJP Hospital, New Delhi - 110 002.

Corresponding Author: Dr Pooja Gautam, Senior Resident, Department of Medicine, MAMC and LNJP Hospital, New Delhi - 110 002. Phone: , E-mail: Pooja.1919149@gmail.com.

are compiled in Table I.

Table I: Laboratory Investigations of the patient:

Parameter	Value
CSF total cell count	50 cells/mm3
CSF differential count	50% polymorphs, 50% lymphocytes
CSF sugar/ protein	54/274 mg/dl
CSF Adenosine Deaminase (ADA)	3.8 IU/L
CSF CBNAAT for *M. tuberculosis*	Negative
CSF Cryptococcal Antigen	Negative
CSF Gram's stain	Negative
CSF Antibody for HSV and JE virus	Negative
HIV Antibody	Negative
Hepatitis B virus	Negative
Hepatitis C virus	Negative
ANA by ELISA	Negative
Mantoux	3mm
FT3/FT4/TSH	Normal
Anti TPO (IU/L)	28.5 (0-20)
Serum Ferritin (ng/mL)	92.7 (17-464)
NCCT head	Normal
MRI Brain with MR spine	Normal
Ultrasound Whole abdomen	Normal
FDG-PET scan	Normal
EEG	Normal

CSF: Cerebrospinal fluid, ADA: Adenosine deaminase, CBNAAT: Cartridge based nucleic acid amplification technique, HSV: Herpes simplex virus, ANA: Anti-nuclear antibody, ELISA: Enzyme linked immunosorbent assay, TPO: Thyro-peroxidase antibodies, NCCT: Non contrast computerised tomography, MRI: Magnetic resonance imaging, FDG-PET: Fluorodeoxyglucose-positron emission tomography, EEG: Electroencephalogram.

The CSF for anti NMDAR antibodies was strongly positive by an indirect immunofluorescence assay. Other antibodies in the CSF like α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1 ($AMPAR_1$), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 2 ($AMPAR_2$), contactin-associated protein-like (CASPER), leucine-rich glioma-inactivated 1 (LG-1), and gamma-aminobutyric acid B ($GABA\ B_2$) were all negative.

The patient fulfilled the definitive criteria for Anti NMDAR encephalitis[3]. She was started on IV methylprednisolone pulse therapy at a dose of 1 g for three days along with IV immunoglobulin G (IVIG) 400 mg/kg/day for five days. She made a remarkable clinical recovery and the abnormal behaviour and involuntary movements completely subsided by day 8 - 10 of treatment initiation. Since the patient had a severe episode at presentation and as the disease has a high relapse rate, she was given further immunosuppression with Rituximab at a dose of 375 mg/m^2 once in a week IV infusion for four weeks. Screening for an underlying neoplasm via ultrasound and FDG PET scan was done; but no neoplasm was detected. The patient is doing well under follow-up.

Discussion

Anti-NMDAR encephalitis is the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis (ADEM)[10]. However, it is not a diagnosis that is entertained frequently by physicians. This is probably due to a lack of awareness and challenges in confirming the diagnosis. It generally presents with a prodrome of fever and headache with seizures, cognitive and memory deficits along with motor disorders[11]. Due to the neuropsychiatric manifestations, patients may present first to the psychiatrists and an early diagnosis may be missed.

Our patient was initially managed as suspected meningoencephalitis (antibiotics, antiviral, steroids and mannitol) which is also common in childhood and adolescence. However, despite empirical treatment she did not improve adequately. Considering the non-resolution of symptoms, investigations for other causes of encephalitis/ encephalopathy were done.

Our patient fits the definitive criteria for the diagnosis of anti-NMDAR encephalitis (mentioned in Table II), presenting with psychiatric symptoms, speech dysfunction and orofacial dyskinesia.

Table II: Diagnostic criteria for anti-NMDA receptor encephalitis.

Probable anti-NMDA receptor encephalitis
All three criteria must be met:
1. Rapid onset (< 3 months) of at least four of the six following major group of symptpms
• Abnormal behaviour or cognitive dysfunction
• Speech dysfunction
• Seizures
• Movement disorders, dyskinesia, or abnormal postures
• Decreased level of consciousness
• Autonomic dysfunction or central hypoventilation
2. Atleast one of the following laboratory results:
• Abnormal EEG
• CSF with pleocytosis or oligoclonal bands
3. Reasonable exclusion of other disorders
Definite anti-NMDA receptor encephalitis
1. IgG anti-GluN1 antibodies in the presence of one or more of the six major group of symptoms, after reasonable exclusion of other disorders

NMDA: N-methyl-D-aspartate, EEG: Electroencephalogram, CSF: Cerebrospinal fluid, IgG: Immunoglobulin G.

As per literature, almost 45% - 53% of the patients with anti-NMDAR encephalitis have a normal MRI[11,12]. The most frequent and most specific EEG finding is a diffuse slowing pattern with no epileptiform discharges and extreme delta brush pattern respectively[13,14]. As antibody testing in serum is less reliable (100% sensitivity for CSF vs 85% for serum), anti-NMDAR IgG testing should always be done with CSF[4]. In our case, CSF anti-NMDAR antibody was strongly positive. Detection of antibody is important especially when MRI and EEG findings are normal.

Since anti-NMDAR encephalitis is frequently associated with paraneoplastic syndromes like ovarian teratoma, imaging should be done to rule this out. The detection of an ovarian teratoma is age dependent; approximately 50% of female patients > 18 years have unilateral or bilateral ovarian teratomas, while 9% percent of girls < 14 years have a teratoma[4].

Our case is noteworthy because of the presentation mimicking an infective meningoencephalitis with orofacial dyskinesia and tremors in a young girl. Ruling-out infective causes, poor response to presumptive treatment, classical neurological manifestations (altered consciousness, seizure, movement disorders) and a normal neuroimaging prompted us to strongly consider the possibility of anti-NMDAR encephalitis.

Conclusion

Anti-NMDAR encephalitis is the 2nd most common cause of autoimmune encephalitis. A young female presenting with neuropsychiatric manifestations, who does not respond well to empirical antibiotic therapy, should prompt a high index of suspicion for this. Investigations such as MRI, EEG, and lumbar puncture for antibody analysis, facilitates early and accurate diagnosis. Timely diagnosis and treatment enable a good clinical outcome.

References

1. Dalmau J, Tuzun E, Wu H *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; 61 (1): 25-36.
2. Dubey D, Pittock SJ, Kelly CR *et al*. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol* 2018; 83 (1): 166-77.
3. Graus F, Titulaer MJ, Balu R *et al*. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; 15 (4): 391-404.
4. Titulaer MJ, McCracken L, Gabilondo I *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 (2): 157-65.
5. Braverman JA, Marcus C, Garg R. Anti-NMDA-receptor encephalitis: a neuropsychiatric syndrome associated with ovarian teratoma. *Gynecol Oncol Rep* 2015; 14: 1-3.
6. Liang Z, Yang S, Sun X *et al*. Teratoma-associated anti-NMDAR encephalitis: two cases report and literature review. *Medicine (Baltimore)* 2017; 96 (49): e9177.
7. Chan SHS, Wong VCN, Fung CW *et al*. Anti-NMDA-receptor encephalitis with atypical brain changes on MRI. *Paediatr Neurol* 2010; 43 (4): 274-8.
8. Acien P, Acien M, Ruiz-Macia E *et al*. Ovarian teratoma-associated anti-NMDAR encephalitis: a systematic review of reported cases. *Orphanet J Rare Dis* 2014; 9: 157.
9. Gong X, Chen C, Liu X *et al*. Long-term Functional Outcomes and Relapse of Anti-NMDA-Receptor Encephalitis: A Cohort Study in Western China. *Neurol Neuroimmunol Neuroinflamm* 2021; 8 (2): e958.
10. Mutti C, Barocco F, Zinno L *et al.* A case of reversible anti-NMDA-receptor encephalitis: neuropsychological and neuroradiological features. *Neurol Sci* 2017; 38 (12): 2231-6.
11. Barry H, Byrne S, Barrett E *et al*. Anti-N-methyl-D-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. *Bjpsych Bull* 2015; 39 (1): 19-23.
12. Heine J, Pruss H, Bartsch T *et al*. Imaging of autoimmune encephalitis – relevance for clinical practice and hippocampal function. *Neuroscience* 2015; 309: 68-83.
13. Bartolini L. How do you treat anti-NMDA-receptor encephalitis. *Neurol Clin Pract* 2016; 6 (1): 69-72.
14. Schmitt SC, Pargeon K, Frechette ES *et al*. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA-receptor encephalitis. *Neurology* 2012; 79 (11): 1094-100.
15. Graus F, Titulaer MJ, Balu R *et al*. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; 15: 391.