ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 02 | February - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ANTI N-METHYL-D-ASPARTATE RECEPTOR (NMDAR) ANTIBODY ENCEPHALITIS MASQUERADING AS NEUROLEPTIC MALIGNANT SYNDROME: CASE REPORT AND EMPHASIS ON HIT FIRST AND HIT HARD WITH RITUXIMAB

Neurology

Dr Ishank Goel DM Neurology Resident, Mahatma Gandhi Medical College And Hospital, Jaipur

Dr Gaurav Goyal Associate Professor, Department of Neurology, Mahatma Gandhi Medical College And Hospital, Jaipur

Dr Tarun Kumar Jain Assistant Professor, Nuclear Medicine, Mahatma Gandhi Medical College And Hospital, Jaipur

ABSTRACT

N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is a form of autoimmune encephalitis with up to 500 cases reported till date. The syndrome is reported more in females as compared to the males and can affect any age group. Patients mostly present with neuropsychiatric signs and symptoms especially convulsions and altered sensorium. The diagnostic test for the disease is expensive, so a clinical diagnosis of the disease is often useful in resource constraint settings. Immunotherapy with IVIG and treatment of the underlying malignancy aids in the treatment of the disease.

KEYWORDS

Anti-NMDAR antibody, Encephalitis, FDG-PET, Rituximab

INTRODUCTION

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis was first described in 2007 presenting as psychiatric and neurologic symptoms in women with ovarian teratomas(1). Later studies reported patient without tumor involvement(2)(3). Epidemiological studies suggest that anti-NMDA receptor encephalitis may be the most common cause of autoimmune encephalitis after acute demyelinating encephalitis(4). It is well described that antagonists of NMDA receptors (e.g. phencyclidine (PCP) produce a clinical syndrome that closely resembles negative symptoms of schizophrenia and induce neuropsychological and sensory processing deficits that are very similar to those observed in this disease(5). Maneta *et al summarized autoimmune encephalitis* into early, middle and late symptoms, initially involving a prodrome, followed by more overt psychiatric manifestations and later physical symptoms(6).

Diagnosis of autoimmune encephalitis is often missed, that leads to delay in diagnosis and treatment. If left untreated, it can lead to cognitive deficit and death. Clinical presentations often mimic other psychiatric disorders including neuroleptic malignant syndrome. Timely recognition and proper treatment can significantly improve clinical outcomes. Surgical excision of the tumor (if present) and aggressive immunotherapy are currently mainstay of treatment for anti-NMDA receptor encephalitis. First line immunotherapeutics commonly include steroid, IvIg and plasmapheresis. First line immunotherapy is often insufficient in the treatment of anti-NMDA receptor encephalitis, and second line immunotherapeutic agents are typically used. Rituximab and cyclophosphamide are the most commonly used second line immunotherapeutics in anti-NMDA receptor encephalitis. Observational studies conclude that second line immunotherapeutics result in better functional outcomes and lower relapse rates with manageable adverse effects. We report a case of anti-NMDA receptor encephalitis presenting as neuroleptic malignant syndrome (NMS) like presentation and treated early with second line immunotherapy. He was prescribed antipsychotic medications for primary psychiatric symptoms. It is difficult to differentiate whether NMS-like clinical presentations are due to anti-NMDA receptor encephalitis or antipsychotic medications induced NMS.

CASE REPORT

A 30-year-old male without significant past medical history presented with behavioral issues in the form of depression and manic episodes along with involuntary movements of the hand and the legs. For psychiatric symptoms, he took consultation from psychiatrist. After taking psychiatric medications, patient had complaints of fever which was moderate grade, intermittent type, used to respond to medications. Patient became mute for the last 20 days before presentations with involuntary facial movements in the form of myokymia and orofacial dyskinesia. Patient had excessive sweating and excessive salivation since then. Patient took multiple drugs for the various psychiatric symptoms. Patient also started having multiple episodes of convulsions each lasting for 3-5 minutes, with up rolling of eyeballs along with post-ictal drowsiness for the last 8-10 days before presentation. Semiology of convulsions was generalized tonic-clonic seizures.

He was admitted to the intensive care unit for close neurologic monitoring and further workup. Acyclovir was started empirically given the concern for viral encephalitis as the patient was febrile and in altered sensorium at the time of presentation.

He had features of dysautonomia. Neurological examination was suggestive of expressive aphasia, inability to follow commands, and orientation to self only. Cog wheel rigidity was present in all 4 limbs, Babinski response was present bilaterally. Hyperreflexia was found in both lower and upper extremities. Laboratory studies were s/o mildly deranged liver enzymes and high CPK value. In view of prior history of psychiatric medicines intake, fever, altered sensorium, dysautonomia and raised total CPK, possibility of Neuroleptic Malignant syndrome was kept. Psychiatric medicines were discontinued. He was started on benzodiazepine along with Bromocriptine and hydration. He was tracheostomised in view of altered sensorium and need of ventilatory support.

Imaging including CT and MRI of the brain revealed no intracranial lesion. CSF analysis was done to rule out any infection which came out to be negative. Multiple EEGs were suggestive of isolated spikes in the temporal and central regions for which antiepileptic were stepped up **(Figure 1).**

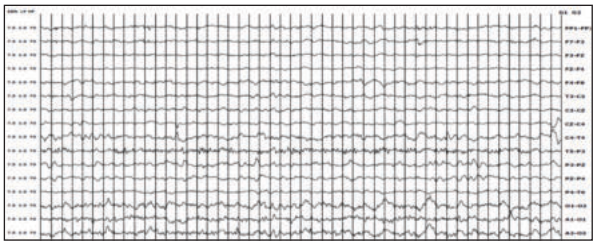

Figure 1: EEG shows isolated spikes in the temporal and central region

Tests for HIV, herpes, and syphilis were negative. He had no response on management of Neuroleptic Malignant syndrome. Considering high index of suspicion, autoimmune encephalitis panel was sent which turned out to be positive for NMDA (anti-glutamate receptor against NR1 subunit). In order to assess for paraneoplastic syndrome, USG of the chest, abdomen and pelvis was done which came out to be normal. Patient underwent PET scan to rule out any underlying malignancy which showed decreased metabolism in the bilateral medial temporal cortices, bilateral cingulate cortices, left posterior parietal cortex, bilateral medial prefrontal and left lateral frontal

cortices **(Figure 2).**

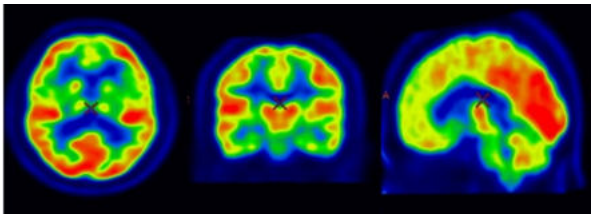

Figure 2: PET scan showing decreased metabolism in the bilateral medial temporal cortices, bilateral cingulate cortices, left posterior parietal cortex, and bilateral medial prefrontal and left lateral frontal cortices.

Patient was started on Injection IVIG (2gm/kg) with Injection MPS (1gm/day) for 5 days. He completed a 5-day course of IVIG and was discharged. His NMS-like symptoms were gradually disappeared. He had some improvement in the Neurological status on follow up, though he was unable to perform daily activity unassisted and had persistent cognitive deficit. Decision to start early second line immunotherapy was taken after discussion with family. So, patient was started on Injection Rituximab 1000mg fortnightly (2 doses) and found to have significant improvement in the Neurological symptoms. On follow up of 1 month after rituximab, patient resumed day to day activity unassisted and joined his profession.

DISCUSSION

Diagnosing anti-NMDA receptor encephalitis can be difficult and challenging because it can mimic other clinical conditions especially psychiatric disorders. There are few case reports that anti-NMDA receptor encephalitis could mimic NMS. Clinical presentation of anti-NMDA receptor encephalitis can overlap with NMS, e.g., hyperthermia, obtundation, catatonia and dysautonomia. Gulyayeva et al(7) reported NMDAR encephalitis in a woman who had NMS. He emphasized the need for high clinical suspicion for anti-NMDA receptor encephalitis in patients those have worsening of mentation and movement disorders after treatment with neuroleptics.

Our patient, initially presented with psychiatric symptoms in the form of mania and depression. He developed neurological manifestation in form of seizures, worsening of mentation, and movement disorders after administration of psychiatric treatment in form of neuroleptics. His condition was not improved with discontinuation of neuroleptics and administration of benzodiazepine. Benzodiazepines are drug of choice for NMS. Once identified and neuroleptics are discontinued, NMS is usually self-limited. The mean recovery time is 7-10 days after withdrawal of offending drugs. Development of unexpected, severe or refractory neurological symptoms to neuroleptics should arose the suspicion of autoimmune encephalitis in psychiatric patients. Other clue is refractoriness to conventional treatment to NMS.

Differential Diagnoses considered are viral encephalitis in view of history of fever, cerebral vasculitis or autoimmune encephalitis(8). Recent studies explore the possibility that anti-NMDA receptor encephalitis, or other similar autoimmune conditions, may present with a more typical schizophrenia like picture and be responsible for as much as 5–10% of first-onset psychosis(9).

Psychiatric symptoms are prominent including agitation, bizarre and disinhibited behavior, delusions and auditory and visual hallucinations(10). In one series of 100 individuals with encephalitis, 86% had headache, low-grade fever or a viral-like illness (headaches, respiratory or gastrointestinal symptoms) in the weeks prior to acute presentation(10).

The diagnosis of NMDA receptor encephalitis requires antibody level detection from the serum and CSF. There is an ongoing controversy as to whether serum or CSF is better. Dalmau recommends testing of both(11). Whereas Irani & Vincent et al, report that serum levels of anti-NMDA receptor antibodies were similar or higher to those of CSF(12). The clinical symptoms correlate well with the antibody titre(10). EEGs generally reveal nonspecific abnormalities such as diffuse slowing. They may reveal extreme versions of the 'delta brush pattern', which are transient patterns characterized by a slow delta wave with superimposed fast activity(13).

Recently, FDG-PET has been recognized as a potentially useful biomarker in suspected autoimmune encephalitis. In a recent study, dedicated brain FDG-PET/CT was abnormal in 85% of patients with autoimmune encephalitis. It was found that FDG-PET/CT abnormalities were more sensitive compared to EEG, MRI, or routine CSF findings. Brain region hypometabolism was most commonly noted finding. Brain region hypometabolism in multiple regions likely reflects widespread impairment of neuronal activity. Many of the areas of regional hypometabolism did not correlate with MRI, suggesting the possibility of neuronal dysfunction in the absence of structural disturbance. Our patient had normal MRI but decreased metabolism in the bilateral medial temporal cortices, bilateral cingulate cortices, left posterior parietal cortex, bilateral medial prefrontal and left lateral frontal cortices on FDG-PET. This finding emphasizes the underlying neuronal dysfunction in the absence of structural abnormalities. Whether these changes are reversible with treatment and clinical recovery, it needs further studies and follow up imaging.

Immunotherapy with trials of corticosteroids, intravenous immunoglobulins, or plasma exchange is the treatment of choice along with or without tumor removal. One study suggested choosing concurrent IVIg (0.4 g/kg per day for 5 days) and methylprednisolone (1 g/ day for 5 days) over plasma exchange(3). If patient shows minimal improvement, the next line of therapy is immunosuppression, using rituximab or cyclophosphamide, with continued immunosuppression (mycophenolate mofetil or azathioprine) for at least 1 year(14). The high effectiveness of rituximab in IgG4-related disease further supports the use of rituximab in AE in which antibodies of IgG4 subclass predominate(15). In our case, the patient showed best results with rituximab as emphasized in other studies(16).

Early diagnosis and treatment of the disease gives a very good result. Therefore, awareness and more clinical studies are mandatory.

CONCLUSION

Anti NMDA receptor antibody encephalitis is a seriously fatal disease which resembles schizophrenia spectrum. Heightened sensitivity to neurological side effects of neuroleptics and refractoriness to conventional treatment of NMS may serve as an important clue to the diagnosis of possible autoimmune encephalitis underlying psychosis. It has a good prognosis if diagnosed and treated early and aggressively with immunosuppressant including second like therapy like rituximab.

REFERENCES

1. Dalmau J, Bataller L. [Limbic encephalitis: the new cell membrane antigens and a proposal of clinical-immunological classification with therapeutic implications]. Neurol Barc Spain. 2007 Oct;22(8):526–37.
2. Lim J-A, Lee S-T, Jung K-H, Kim S, Shin J-W, Moon J, et al. Anti-N-Methyl-D-Aspartate Receptor Encephalitis in Korea: Clinical Features, Treatment, and Outcome. J Clin Neurol Seoul Korea. 2014 Apr;10(2):157–61.
3. Rosenfeld MR, Titulaer MJ, Dalmau J. Paraneoplastic syndromes and autoimmune encephalitis. Neurol Clin Pract. 2012 Sep;2(3):215–23.
4. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010 Dec 1;10(12):835–44.
5. Eb B, Ha B. Phencyclidine. Emerg Med Clin North Am. 1990 Aug 1;8(3):541–50.
6. Maneta E, Garcia G. Psychiatric manifestations of anti-NMDA receptor encephalitis: neurobiological underpinnings and differential diagnostic implications. Psychosomatics. 2014 Feb;55(1):37–44.
7. Gulyayeva NA, Massie MJ, Duhamel KN. Anti-NMDA receptor encephalitis: psychiatric presentation and diagnostic challenges from psychosomatic medicine perspective. Palliat Support Care. 2014 Apr;12(2):159–63.
8. Dale RC, Irani SR, Brilot F, Pillai S, Webster R, Gill D, et al. N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. Ann Neurol. 2009 Nov;66(5):704–9.
9. Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein H-G, Vielhaber S, et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. JAMA Psychiatry. 2013 Mar;70(3):271–8.
10. 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 Dec;7(12):1091–8.
11. 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 Jan;10(1):63–74.
12. Irani SR, Vincent A. NMDA receptor antibody encephalitis. Curr Neurol Neurosci Rep. 2011 Jun;11(3):298–304.
13. Whitehead K, Pressler R, Fabrizi L. Characteristics and clinical significance of delta brushes in the EEG of premature infants. Clin Neurophysiol Pract. 2016 Dec 5;2:12–8.
14. Barry H, Byrne S, Barrett E, Murphy KC, Cotter DR. Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. BJPsych Bull. 2015 Feb;39(1):19–23.
15. Brito-Zerón P, Kostov B, Bosch X, Acar-Denizli N, Ramos-Casals M, Stone JH. Therapeutic approach to IgG4-related disease: A systematic review. Medicine (Baltimore). 2016 Jun;95(26):e4002.
16. ccp-rituximab-for-second-line-treatment-for-anti-nmdar-autoimmune-encephalitis.pdf [Internet]. [cited 2020 Aug 23]. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/03/ccp-rituximab-for-second-line-treatment-for-anti-nmdar-autoimmune-encephalitis.pdf