

Case Report

Catatonic Syndrome in Anti-NMDA Receptor Encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a newly recognised autoimmune condition. With its typical clinical pattern, consistent association with the presence of auto antibodies and rapid improvement with immunotherapy, this condition is giving insights into the boundaries between psychiatry and other neurosciences, and is opening avenues for future research. In a young lady who presented with catatonia, we considered anti-NMDA receptor encephalitis, after ruling out other aetiologies. After a positive antibody test we treated her with immunotherapy. She showed gradual improvement in her psychotic and catatonic symptoms. Knowledge regarding the nature and function of NMDA receptors and pathophysiology of this particular encephalitis is important for psychiatric practice. The great opportunity for research in this area due to its association with psychotic disorders is evident but an appeal to temper the enthusiasm by considering the historical lessons learnt from Karl Jaspers' critique of General Paresis of Insane, is in place. Catatonic syndrome has to be conceptualised broadly and should be recognised with a separate nosological position.

Key words: Anti-NMDA receptor encephalitis, catatonia, neuropsychiatry, NMDA receptor hypofunction hypothesis, schizophrenia

INTRODUCTION

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a newly recognised autoimmune encephalitic syndrome with specific pattern of presentation, course, and outcome. After the initial reports by Dalmau *et al.*, in 2007,^[1] multiple centres around the world reported similar cases. Initially conceptualised as a paraneoplastic syndrome, it was later defined as autoimmune encephalitis with

varied immunological aetiologies like paraneoplastic condition, microdeletions in HLA system etc.

The syndrome predominantly presents in young women with 60% of them having a neoplasm (usually, ovarian teratoma). The clinical course is characterised by five stages^[2] – prodromal stage, neuro-behavioural stage, nonresponsive stage, hyperactive stage and gradual recovery stage. Children may present with speech regression and irritability instead of catatonia or psychosis.

Early identification and intervention is paramount in its management. Though magnetic resonance imaging (MRI) brain, electroencephalogram (EEG) and cerebro-spinal fluid (CSF) analysis are abnormal, the changes are not specific to this disease entity. IgG autoantibodies against NR1 subunit of NMDA receptor is taken as definitive for making the diagnosis. Paired serum and CSF sample has been found to be more useful for detection than either sample alone.

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Management is the prompt use of immunotherapy, with tumour resection if present. First line immunotherapy is with Intravenous (IV) Ig, Corticosteroids or Plasmapheresis. If there is less than adequate or no response, treatment is with second line therapy of Cyclophosphamide or Rituximab. After recovery, some recommend continued immunosuppression for at least 1 year in view of relapses. Up to 75 % of patients recover. Even after recovery, Dalmau *et al.*, recommend periodic screening for ovarian teratoma for up to 2 years.^[3]

CASE REPORT

A 27-year-old married lady, with no family history or personal history of psychiatric or neurological illness, with normal intellectual development presented to us with 2 years duration of illness. It was characterised by acute onset of posturing and involuntary movements of left toes, reduced arm swing and generalized slow movements, progressing to fearful and preoccupied attitude, crying spells and hallucinatory behaviour accompanied by functional deterioration. She was treated with antipsychotic agents and electroconvulsive treatment which improved the psychotic symptoms but her motor symptoms worsened.

At presentation to our centre, she was mute with episodes of agitation and hallucinatory behaviour. On examination, she was oriented and conscious with catatonic symptoms of mutism, negativism and gegenhalten. Tone was rigid in all four limbs without involuntary movements but had normal motor power. Baseline Bush-Francis catatonia rating scale score was 24. We made a presumptive diagnosis of a neurodegenerative disease with probable autoimmune aetiology, after ruling out other differentials like Schizophrenia with drug induced parkinsonism, SSPE, Wilsons disease, Nieman pick disease and Neuroferritinopathy with appropriate evaluation.

MRI brain (T2W and FLAIR) images showed diffuse moderate atrophy in various subcortical and cortical areas along with long TR hyperintensities involving basal ganglia. CSF analysis and EEG were within normal limits. ESR, Thyroid antibodies and dsDNA were normal with antinuclear antibodies (ANA) being weakly positive, similar to a published case.^[4] In view of persisting neurological symptoms and absence of any detectable neoplasm (evaluated with whole body FDG PET scan), we sent for anti-NMDA receptor antibody which came as positive.

She showed gradual improvement after initiating immunotherapy in her psychotic and catatonic symptoms while continuing to have other deficits.

DISCUSSION

NMDA receptors maintain synaptic plasticity and their disruption causes seizures, memory deficits and behavioural problems. Intrathecally produced IgG autoantibodies against the NR1 subunit^[5] of NMDA receptor, cap and internalise them, similar to acetylcholine receptor antibody action in myasthenia gravis, causing their hypofunction and subsequent symptoms. The pathophysiological mechanisms might have ethnic and genetic variability, highlighting the need for research in Indian population.^[3]

FDA has recently approved cell-based qualitative indirect immunofluorescence antibody test which has good specificity.^[6] However, prevalence of anti-NMDA receptor antibodies in the general population, as is known for ANA in SLE,^[7] and the disease correlating antibody titres have to be known for predicting risk and management.

'NMDA receptor hypofunction hypothesis' is proposed in Schizophrenia research. Arguments gain strength from:

1. The association of neuregulin-1 with both Schizophrenia and NMDA receptor hypofunction.
2. The association of Phencyclidine with both psychotic symptoms and NMDA receptor hypofunction.
3. The g-subunit of PP2B, a candidate schizophrenia-gene, is known to promote NMDA receptor internalization.
4. A small subset of first episode schizophrenia were found to have anti-NMDA receptor antibodies.^[8]

Other hypotheses suggested that 'Innate inflammation' causes neurotransmitter abnormalities and oxidative injury.^[9] NMDA receptor dysfunction is also found in Alcohol or Cocaine dependence and Alzheimer's dementia.

This provides a tremendous opportunity to study the biological factors behind many neuropsychiatric conditions and to direct drug discovery. The enthusiasm should also be tempered, as there can be unintended consequences. When General Paresis of Insane (GPI) was delineated from Dementia Praecox (the erstwhile Schizophrenia) and treatments were being rationalized for GPI, findings were extrapolated to all cases of Dementia Praecox resulting in biological reductionism in Schizophrenia research and management. Karl Jaspers, in his General Psychopathology, gives a valid critique that GPI is not Schizophrenia and that it is a purely neurological condition which has no new psychopathological entity to be psychologically characterised.^[10] Unlike GPI, Schizophrenia has lot of subjective meaning to the symptoms which can

be influenced by the psycho-social causal factors and their interaction with the underlying biology. Same critique can be appropriately applied to Anti-NMDAR encephalitis.

Catatonia is a motor dysregulation syndrome presenting with various organic (e. g., high fevers like typhoid, CNS-lupus, non-convulsive status epilepticus and encephalitis) and non-organic psychiatric disorders. Catatonia is a clinical syndrome with varied aetiologies, similar to Delirium. To restrict catatonia to non-organic conditions might deny neurology-patients with appropriate catatonia management.^[11] Though DSM-5^[12] has acknowledged the varied causes of catatonia, it still placed it in the schizophrenia spectrum, strengthening the notion that catatonia is related to psychotic disorders alone.

Being aware of the different presenting symptoms, course of illness and epidemiological factors will help us to differentiate this potentially treatable condition from non-organic psychiatric disorders and provide appropriate management. The present case emphasizes the need for improving knowledge and practice of Neuropsychiatry in India. Neuropsychiatry clinics, consultation services and training can improve patient management and research in both psychiatry and neurosciences.

CONCLUSION

Anti-NMDA receptor encephalitis gives us the opportunity to reconsider the rigid boundaries between neurology and psychiatry. Future research should aim for a non-reductionistic integration of these two disciplines.

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