Research Paper

Volume : 2 | Issue : 4 | Apr 2013 • ISSN No 2277 - 8179

Anti- NMDAR Encephalitis: a House Afire

Medical Science

KEYWORDS : NMDAR encephalitis, autoimmune encephalitis, ovarian teratoma

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ABSTRACT

Limbic encephalitis is an inflammatory disorder of limbic system. It is a form of autoimmune encephalitis the predominant neuropsychiatric manifestations frequently delay the early recognition of the entity. We report a patient with limbic encephalitis associated with anti NMDA receptor antibodies. She was admitted with history of fever, psychiatric symptoms (change of behavior and personality, auditory and visual hallucinations), seizure, abnormal movements (orofacial dyskinesias). The diagnosis was challenging as the neuroimaging and Cerebro spinal fluid (CSF) study was non contributory. The patient responded well to intravenous immunoglobulin.

BACKGROUND

The term anti-NMDAR encephalitis became well known in 2005 which comprises of constellations of symptoms including catatonia, sub acute memory disturbance, Seizures, abnormal movements and reported in four young women with history of ovarian teratomas [1]. Apart from anti NMDAR encephalitis, other autoimmune encephalitis includes AMPA receptor (AMPAR), the γ-amino-butyric acid-B receptor (GABAB-R), and leucine-rich, glioma inactivated 1 (LGI1) receptor mediated encephalitis. Anti NMDAR encephalitis predominantly affects patients of younger age group associated with or without tumor. Younger female with this disorder frequently searched for ovarian teratomas. Patients may be treated with tumor resection if present, immunotherapy (corticosteroids, intravenous immunoglobulin, or plasma exchange) and less frequently second-line immunotherapy (cyclophosphamide or rituximab, or both) More than 75% of all patients have substantial clinical improvement with treatment [2]. We reviewed a 30 year old women presented with constellations of symptoms and atypical presentations compatible to anti NMDAR encephalitis who responded well to intravenous immunoglobulin.

CASE PRESENTATION

A 30 years old women presented with history of fever for 3 days. On remission of fever, she developed abnormal behavior in the form of talking excessively about religious matters. She had auditory hallucination as if she is with lord Krishna and other Hindu Gods and goddesses. She became hyper religious. Sometimes she started dancing and cheerful. This event was persisting most of the time in awake state for three consecutive days. She was treated as acute transient psychotic disorder with neuroleptics from psychiatrist. During the same time, there is fluctuation in the level of orientation to time place and person. Her sleep rhythm was reversed. She had excessive day time sleepiness. Her bowel, bladder function and vital parameters were normal during this period. After a period of three days, there was deterioration in patient's clinical condition. Gradually she became unresponsive to verbal command and later on painful stimuli with Glasgow coma scale (GCS) E2M1V1. Neurology examination showed normal cranial nerve with generalized moderate to marked rigidity, brisk reflexes and flexor plantar response.

Chest and cardiac status were normal. Before coming to our hospital she was admitted in a private hospital where Cerebro spinal fluid(CSF) study done showed 5 cells (all lymphocytes), protein was 62.3 mg/dl , glucose was 71mg/dl , PCR for tuberculosis was negative and MRI brain was normal. Empirically she was treated with injection acyclovir and anti- tubercular medications keeping possibility of herpes simplex encephalitis or tubercular meningitis due to commonality. There was no improvement in clinical conditions. Subsequently she was transferred to our hospital.

INVESTIGATIONS

Laboratory findings indicated the following: hemoglobin 12.5gm/dl, TLC-6120 /cmm, DLC-neutrophils-75%, lymphocytes 19%, eosinophils-2%, monocytes 4%. Her liver and kidney functions, serum calcium, blood glucose and anti nuclear antigen (ANA) were normal. Routine blood, urine and CSF examination was non contributory. As the differential counts of white blood cells was normal and HIV status was non reactive, she was considered to be immunocompentent. CSF for HSV DNA PCR was negative. Her brain MRI, CECT abdomen and chest were also normal. EEG showed generalized back ground slowing indicating diffuse electrophysiological dysfunction. Other non invasive procedure like ECG, Chest x-ray, ultrasound of abdomen and EEG were normal. Patient was investigated for autoimmune encephalitis with serum anti- NMDAR antibody and Anti- VGKC antibody of which the former was positive conforming the diagnosis of anti NMDAR encephalitis.

DIFFERENTIAL DIAGNOSIS

The current patient presented with low-grade fevers, and auditory hallucination and acute transient psychotic behaviour like symptoms, including disorganized thinking, followed by neurologic deterioration in form of deterioration of sensorium, rigidity, autonomic instability. The symptoms most frequently considered in the differential diagnosis are:

HSVencephalitis, neuroleptic malignant syndrome and autoimmune encephalitis, serotonin syndrome and organic catatonia.

Neuroleptic malignant syndrome (NMS), serotonin syndrome, or lethal catatonia can present with change in mental status, generalized rigidity, and autonomic dysfunction. They can present with muscle hyperactivity, hyperthermia, metabolic acidosis, rhabdomyolysis, seizures, elevated creatine kinase (CK), and sometimes renal failure [5]. So because of this distinct clinical features anti-NMDAR encephalitis are confused with NMS and serotonin syndrome. These patients are initially managed at psychiatric centers with neuroleptics and patient usually not improved without specific interventions [6].

TREATMENT

Initially she was given injection acyclovir 10mg/kg/8h. It was stopped after positive report of anti NMDAR antibody. The patient was given injection methyl prednisolone 1 gram daily for five days. However patient did not respond clinically. Patient was tried with intravenous immunoglobulin 2gm/kg over 5 days and the patient responded well.

OUTCOME AND FOLLOW-UP

There was marked improvement in her neuropsychiatric symptoms during her hospital stay. She was discharged with satisfactory clinical improvement as she became independent in doing daily activities. During her follow up in the outpatient department she was maintaining well except mild attention deficit and recent memory loss. She was on cognitive behavioural therapy.

DISCUSSION

Encephalitis has numerous causes, and most patients have to undergo extensive investigation to identify the etiologies. The association between limbic encephalitis and malignancy was made for the first time in the late 1960s. Subsequently number of anti neuronal antibodies were discovered and seen to be associated with cancers, presenting with neuropsychiatric symptoms. Recently in 2007 the antibodies which have been recognized is the NR1 subunit of the N-methyl-D-aspartate receptor (NMDAR). This antibody respond to immunotherapy or with the removal of tumor if present [7, 8].

The diagnosis was challenging as the neuroimaging, CSF study and other investigation mentioned above were non contributory. Young women are mostly affected and this disorder is associates with antibodies to NMDAR, who are treated at psychiatry center with wrong diagnoses [9, 10]. NMDAR antibodies are present in CSF and serum, which are usually with intrathecal synthesis, but occasionally detected in the CSF only. NR1/NR2 heteromers of the NMDAR are the main target epitopes. Hippocampus and forebrain are the site where NR1/NR2B, is normally expressed [11]. Patients usually responds to tumor resection if present, immunotherapy (corticosteroids, intravenous immunoglobulin, or plasma exchange) and less frequently second-line immunotherapy (cyclophosphamide or rituximab, or both) More than 75% of all patients have substantial clinical improvement with treatment [2].

LEARNING POINTS

- Young women presenting with psychiatric abnormalities, autonomic instability, short-term memory loss, hypoventilation, orofacial dyskinesias, seizures suspected to be NMDAR encephalitis.
- Diagnosis is challenging when the neuroimaging, Cerebro spinal fluid and EEG are non contributory.
- The best treatment approach is tumor removal if present or immune therapy.

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