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ANTI-NMDA RECEPTOR ENCEPHALITIS

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ABSTRACT
Anti N-methyl-D-aspartate receptor (NMDA)receptor encephalitis is one of the most common type of auto immune encephalitis. Its diagnosis is often delayed due to initial clinical presentation with psychiatric clinical features. Initial clinical features resemble those of acute psychosis or depression which later evolve into frank neurological dysfunction. This was first described in association with ovarian teratoma, but it was later also found to exist without neoplastic association and in men as well. It occurs more frequently in younger age group, mostly below 50 years of age. Diagnosis is established with the help of cerebrospinal fluid (CSF) analysis for oligo clonal bands and presence of Anti NMDA receptor antibodies in serum or CSF. CSF assay for antibody is more sensitive compared to serum. This case report is of a young girl who initially presented with behavioral abnormalities to a psychiatry outpatient and was later diagnosed with anti NMDA receptor encephalitis after she developed seizures.

KEYWORDS: N-methyl-D-aspartate receptor encephalitis, encephalitis, neuropsychiatry, case report, encephalitis, NMDA, Anti NMDA receptor encephalitis.

INTRODUCTION
AntiN-methyl D-aspartate (NMDA) receptor encephalitis was first described in 2007 in association with teratoma of ovaries in women.[1]It was later discovered that anti NMDA receptor encephalitis can occur without association with cancer as a primary autoimmune disorder and can occur in men and women of all age groups.[2] However, it is more common in younger age groups and women.[3,4]

Anti NMDA receptor encephalitis occurs due to autoimmunity against NR1 subunit of the NMDA receptor. There exists a significant overlap between early symptoms of anti NMDA receptor encephalitis and psychiatric disorders, currently, the understanding of symptomatology of anti NMDA receptor encephalitis follows a multiphase model that includes a prodromal phase of flu like illness followed by phase of psychiatric manifestations that includes paranoia, depression, agitation, irritability, aggression and hallucinations. The psychiatric phase is followed by a phase of frank neurological dysfunction; this phase is heralded by presence of clinical signs such as catatonia,seizures, decreasing conscious level, coma and a variety of movement disorders.[5] A significant percentage of patients may also develop autonomic instability causing heart rate and blood pressure abnormalities and may cause significant morbidity and mortality.[6] A study published by Herken and Pruss[7] has included a list of Red flag signs and milder "yellow flag" signs that suggest presence of anti NMDA receptor encephalitis in a patient. "Yellow flag" signs include decreasing consciousness, catatonia, abnormal movements, focal signs. Red flag signs include CSF and neuroimaging abnormalities, Faciobrachial movements, Generalized seizures, and abnormal movements.

Our case reports detail a young girl who initially presented with behavioral abnormalities and was later diagnosed with anti NMDA receptor encephalitis.

CASE PRESENTATION:
Patient is a 14 years old girl who first presented withcomplaints of crying episodes and insomnia. Patient had recently resumed school afterayearlongphysical absence from school due to COVID-19 pandemic and history suggested presence of stress due to school and from teachers of student. She was started on low dose anti-depressant medications. She presented a few days later to Emergency department when her behavioural abnormalities had become considerably worse and she had complaints of worsening insomnia,hyper religiousness, extreme feelings of guilt and self-harm. She had no past history

or family history of psychiatric illness or substance abuse. Patient was admitted and she gradually became catatonic over the next three days despite treatment with anti-depressants and antipsychotics. New onset abnormal movements of her lips and chewing were observed one day after admission which resulted in lip and tongue biting. On the second day of admission patient developed two episodes of generalized tonic clonic seizures. Patient was started on antiepileptic medication along with antibiotics and anti-viral drugs and workup for possible encephalitis was started. The patient at that time was catatonic with rigidity and abnormal posturing of body. Patient's labs showed normal blood counts and chemistries with moderate elevation of CPK which was tested after the generalized tonic clonic seizure.

Patient's routine analysis, Culture and HSV PCR was all normal, making the chances of an infectious encephalitis low(Table 1).

	Value	Normal range
Total protein	15.6 mg/dL	15–45 mg/Dl
Glucose	59.8 mg/dL	40–70 mg/Dl
Color/appearance	Colorless/clear	Colorless/clear
White blood cells	7/mm^3	0–10/ mm^3
Red blood cells	0/mm^3	0/ mm^3
Neutrophils (%)	2%	-
Mononuclear cells (%)	98%	-
LDH	19	-
Albumin	7	0-9
Bacterial Culture	Negative	Negative
HSV PCR	Negative	Negative

Table 1. Cerebrospinal fluid analysis report

Patient underwent an MRI of the brain which showed few small non-specific hyperintense foci on FLAIR and T2WI in frontal and fronto-parietal areas without any contrast enhancement or diffusion restriction (Figure 1). These foci were located in white matter and grey-white matter junction.

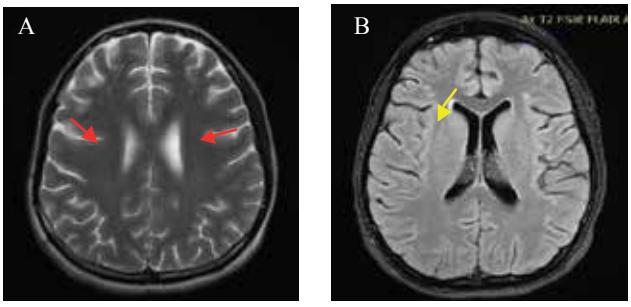

Figure 1. MRI brain plain. T2 weighted (A) and FLAIR (B) axial images.

A and B showhigh signal foci in bifrontal and parietal region in white matter and grey-white matter junction.

Patient's CSF for autoimmune encephalitis antibody panel was sent at the same time as other investigations and was reported three days later with a positive titre of anti NMDA receptor antibodies, at the same time her HSV PCR was reported as negative. Patients antiviral and meningitis antibiotic cover was stopped. Patient was started on IV methylprednisolone one gram daily for 5 days followed by 5 cycles of alternate day plasma exchanges started 5 days after stopping methylprednisolone because patient had mild improvement of symptoms, her conscious level was still low and she continued having seizures. Screening for aetiology of anti NMDA receptor encephalitis was done including CT scan of chest, abdomen and pelvis and Antinuclear Antibody testing, both of which came out negative. Patient was discharged on oral steroids and antiepileptic medications as her condition started to improve. On discharge the patient was fully conscious and takin orally but still had deficits in attention and memory and calculation. Patient was called for follow up in opd to access improvement and need for on going immuno suppression.

DISCUSSION:

Case reports of patients with symptoms that were later ascribed to anti NMDA encephalitis were published in 1997 and 2005 in females and then the symptoms in all these cases resolved with removal of tumors.[8] It was postulated in these case reports that the symptoms could be the result of a neoplasm associated vasculitis which was confirmed in 2007 by Dalmau and colleagues who published a case series of 12 patients who had antibodies to NMDA receptors on the surface of hippocampal neurons. 11 of the these patients had ovarian teratomas and improved after removal of tumour. To date over a 1000 cases have been published, It was discovered that anti NMDA receptor encephalitis can occur without association with cancer; as a primary autoimmune disorder and even though all age groups and genders have been implicated;published data shows that 80% of the patients were women and less than 50 years of age with a median age of 21.[2,10]Anti NMDA receptor encephalitis is now considered to be the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis (ADEM). Majority of patients report a flu like prodromal illness with low grade fever, nausea, headache, myalgias, and fatigue. This is followed by development of psychiatric symptoms including delusions, hallucinations, paranoia, depression and self-harm.[3] Most patients

present at this stage of illness and can be mistaken for acute psychosis and/or substance abuse. In general, the patients with anti NMDA receptor encephalitis are less responsive to anti-depressant and anti-psychotic medication for above symptoms compared to those with primary psychiatric diagnoses.[6] The psychiatric symptoms evolve over days into catatonia, it is at this stage that the illness can mimic a neuroleptic malignant syndrome secondary to use of antipsychotic drugs. Majority of patients eventually go on to develop generalized seizures, prompting a neurological evaluation and an investigation for a possible encephalitis ensues.[12] Abnormal facial and arm movements are present in a variable number of patients and when present are an early red flag sign to direct attention towards diagnosis of autoimmune encephalitis even before the onset of catatonia and seizures.

CSF analysis is the cornerstone of diagnosis of anti NMDA receptor encephalitis. CSF routine analysis can show mild pleocytosis and protein elevation. Oligoclonal bands can be present in CSF. CSF analysis for anti NMDA receptor antibody is confirmatory of diagnosis, the antibody can be found in serum but is less sensitive than CSF assay.[11] All patients diagnosed should undergo investigations for presence of tumour such as an ovarian teratoma. This can be done with CT scans of chest and abdomen and pelvis or ultrasound and tumour markers.

Treatment consists of steroids followed by immunotherapy with IVIG or plasma exchanges. IVIG is preferred in younger age group and those who have autonomic disturbances causing hemodynamic compromise during plasma exchange procedures. Ovarian teratomas where identified should be removed and their removal is associated with improvement in patient symptoms. Some patients with autoimmune anti NMDA receptor encephalitis may require use of second line immunotherapy with Cyclophosphamide or Rituximab.[6] A surveillance for ovarian teratomas should be done for 2 years for patients who have initially tested negative for ovarian malignancy.

The mortality rate for acute encephalitis is around 4%, up to75% recover completely while the remaining have some neurological disability.[11]. Relapses are more common in those without teratomas. Predictors of good outcome include shorter time to diagnosisand timely initiation of treatment, admission not requiring ICU care, and less severe symptoms.

CONCLUSION:

Anti NMDA receptor encephalitis is an increasingly diagnosed cause of encephalitis associated with psychiatric and neurological manifestations that can be associated with malignancies. Because of nonspecific symptoms and overlapping symptoms with other diseases in early stages delay in diagnosis and treatment is common and can lead to permanent neurological deficits and even death. Awareness regarding its symptoms and signs among clinicians overall and neurologists specifically can lead to earlier diagnosis with the help of neuroimaging and CSF analysis for antibodies with proceeding early treatment leading to better outcomes. The better outcomes are more emphasized because a significant cohort of anti NMDA receptor encephalitis patients are young and neurological deficits can lead to lifelong disability.

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