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AUTOIMMUNE ENCEPHALITIS MASQUERADING AS VIRAL ENCEPHALITIS - A CASE SERIES

Neurology

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ABSTRACT

Encephalitis is defined as inflammation of the brain parenchyma associated with neurologic dysfunction. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a form of autoimmune encephalitis.Due to the variability of the initial symptoms, antiNMDAR encephalitis is not only underdiagnosed but also can be misdiagnosed as viral encephalitis or other pathologies. The origin of this disease is often paraneoplastic. AntiNMDAR encephalitis preferentially affects children and young adults, and it has a male/female ratio of 1/4. Patients generally have impaired memory and cognition and neuropsychiatric manifestations over a period of days or weeks. However a careful history and examination may show early clues to particular autoimmune causes, such as seizures, dystonia, abnormal movements, psychosis or presence of particular tumours.In case of clinical suspicion, electroencephalogram and brain magnetic resonance imaging are useful, but lumbar puncture for cerebrospinal fluid analysis and appropriate autoantibody testing can confirm specific diagnosis when infectious etiology is excluded, autoimmune encephalitis must be considered which is potentially reversible with immunomodulation therapy.Here we describe case reports of two female with pure neuropsychiatric features positive anti NMDA and normal MRI finding, while one middle aged male with features resembling viral encephalitis,MRI finding with changes of encephalitis and positive anti NMDA .All three managed with IVIG and steroids and showed clinical improvement.Hence, this case series highlights how presentation of autoimmune encephalitis can mimic viral encephalitis and the importance of early diagnosis and appropriate treatment leading to reduction of mortality and morbidity.

KEYWORDS

Neurology, Psychosis, Autoimmune encephalitis, Confusion

INTRODUCTION

Autoimmune encephalitis (AE) comprises a group of non-infectious immune-mediated inflammatory disorders of the brain parenchyma. Autoimmune encephalitis commonly presents an immune response against neuronal autoantigens with production of antibodies.. Anti-neuronal antibodies are classified into antibodies against

1. cell surface antigens (CSAab),
2. synaptic antigens (SyAab)
3. intraneuronal antigens (INAab), also known as onconeural antibodies.

It can be triggered by tumors, infections, or it may be cryptogenic. The neurological manifestations can be either acute or subacute and usually develop within six weeks. The clinical manifestations include behavioral and psychiatric symptoms, autonomic disturbances, movement disorders, and seizures.

- The first group involves autoantibodies to extracellular epitopes of ion channels, receptors and other associated proteins, such as the NMDA receptor. The cancer associations are variable, and the prognosis tends to be much better. The antibodies in these disorders are thought to be directly pathogenic, causing reversible effects on synaptic function in neurons with relatively little neuronal death.
- Second group includes diseases with autoantibodies to intracellular synaptic proteins such as GAD65.
- The third group includes the classic paraneoplastic disorders associated with antibodies to intracellular antigens, such as anti-Hu. These disorders are strongly cancer associated and involve T-cell responses targeting neurons. The prognosis tends to be poor due to irreversible neuronal killing by these mechanisms.
- Autoimmune encephalitis presents with mainly following features: psychatric manifestation, Abnormal movements such as dystonia, chorea Seizures, cerebellitis features such as ataxia, nystagmus, limb movement, vertigo.

Following antibodies are associated with autoimmune encephalitis:

1. Anti NMDA
2. AntiLGl
3. CASPR
4. GABAB5.
5. AMPA
6. Paraneoplastic(antiHu/ma2)

Incidence of autoimmune encephalitis increased over time from 0.4/100,000 person-years to 1.2/100,000 person-years.

Anti-N-methyl-d-aspartate (NMDA) receptor encephalitis is a rare autoimmune disease that is frequently under- diagnosed. The Patho-physiology of this disease results from the binding of anti-NMDA antibodies to NMDA receptors, causing neuronal dysfunction and the disruption of fronto-striatal connections. The clinical presentation of this disease is manifested by non-specific influenza symptoms, such as headache, fever, nausea and upper respiratory symptoms .Subsequently, acute psychiatric symptoms appear, such as agitation, visual and auditory hallucinations, anxiety, emotional lability, catatonia and disorganized thoughts. neurological deterioration typically occurs 1–3 weeks after the onset of symptoms,including abnormal movements, seizures and autonomic nervous system disorder.

Diagnostic criteria for possible autoimmune encephalitis are as follows:

1. Subacute (<3 months) onset of memory deficits or altered mental status or psychiatric symptoms
2. Atleast one of additional findings

New focal CNS symptoms New onset seizures CSF pleocytosis (>5/cubic mm) MRI suggestive of inflammation 3.Exclusion of other causes Here with we presents 3 cases of anti NMDA positive autoimmune encephalitis.

Case 1

15 year old previously healthy muslim female presented to emergency room with chief complains of altered behavior (With anger of burst , crying spells, laughing episodes in between), spoiling of clothes which progress over 1.5 month. She exhibited bizarre behavior with inappropriate smiling, poor self-care, altered sleep pattern. She had repeated breath holding episodes and lip smacking movements. She had no history of fever, convulsions, vomiting, headache.

She had no significant past history with no any addiction history. no any significant family history or medication history. On examination: Patient was disoriented to time, place, person with rest of general examination were unremarkable and neurological examination was normal.

Investigations: routine hematological investigations including CBC, peripheral smear and biochemical parameters including renal function , liver function, serum electrolytes, random blood sugar were normal. HIV was negative.

MRI Brain with contrast was normal, CSF routine & micro reveals no any abnormality. Primary treatment with i.v acyclovir, steroids and carbamazepine was started. CSF culture came negative, CSF viral panel including hsv were negative. EEG suggestive of generalised neuronal hyperexcitability.

CSF autoantibodies panel were sent and it cames positive with Anti NMDA antibodies. We started inj. Intravenous immunoglobulin 0.4 gm/kg/day for 5 days with injection methylprednisolone 500 mg/day for 5 days. Later on IVIG extended for 2 days.

Other assessment were done including CT abdomen and MR pelvis (to look for any ovarian tumor) were normal. Patient showed significant improvement in orientation and behavioral changes within 2 month. She was discharged with tapering methylprednisolone and carbamazepine.She came for follow up with choreiform movement which improves with tetrabenazine.

Case 2

A 16 year old girl previously healthy hindu female presented to OPD with chief complains of altered behavior, irrelevant talk, spoiling of clothes, forgetfulness over 15 days. She had no complaints of fever, convulsions, vomiting, headache, blurring vision. She had no significant past history. No history of any medication or addiction, consuming vegetarian diet, with altered sleep pattern.

Patient was disoriented and general examinations were normal. Rests of neurological examination were normal including reflexes, tone, cranial nerves.

Investigation: All routine hematological and biochemical parameters including CBC, renal function test, liver function test, electrolytes, blood sugar, thyroid function, vit. B12 were normal. HIV was negative.

MRI brain with contrast was normal. CSF analysis showed raised protein of 67 mg/dl with no wbcs and normal glucose . CSF culture was sent and patient started primarily on injectable acyclovir,, dexamethasone,antibiotics and risperidone. CSF culture was negative. ANA profile was negative. EEG was abnormal suggestive of generalised neuronal hyperexcitability.

CSF autoantibodies panel was sent. During hospital stay of 5th day patient developes sinus Bradycardia and hypotension Features suggestive of autonomic dysfunction.

With strong suspicion of autoimmune encephalitis patient started on injection intravenous immunoglobulin 0.4gm/kg/day for 5 days. After IVIG started, CSF autoimmune antibody panel cames with positive anti NMDA antibodies. MRI pelvis and CT abdomen were done to look for any tumor and were normal. After 2 weeks patient started improving and regained her consciousness and at end of 3rd week patient was discharged.

Case 3

A 38 years old male presented with fever, blurring of vision, and altered behavior since 7 days. He had a high grade fever, acute in onset, remittent, not relieved by medications. Blurring of vision was insidious and gradually progressive. The patient's relative gave a history of improper behavior with anger outbursts, memory loss and irritability .This neuropsychiatric symptoms were insidious in onset and rapidly progressive.

Patient had no other significant past ailments and habit of tobacco chewing since 15 years. In the emergency department, the patient's mental status rapidly worsened and was shifted to ICU care with a pulse rate of 88/min, blood pressure of 90/60 mm of Hg, Neurological examination shows inability to follow verbal commands, bilaterally symmetrical and reactive pupils ,normal cranial nerves, normal tone in all four limbs with no hyperreflexia, no signs of meningism and bilateral plantar reflexes were downwards.

Gait of the patient could not be assessed. Blood picture of the patient revealed mild neutrophilic leucocystosis with a total WBC count of 13400/cumm. Serum electrolytes and Renal function test were within normal limits. Fever Profile was negative. CSF sample showed no cells, protein- 22.5 mg/dl, glucose-69 mg/dl. A CSF culture was negative for any bacterial organism and CSF viral panel was negative for HSV- 1 and HSV-2. CSF ADA was within normal limits and CSF GeneXpert study was negative for Mycobacterium tuberculosis complex. MRI Brain with contrast was suggestive of patchy meningoencephlitis. Patient was diagnosed to have viral meningoencephlitis but the patient failed to improve on anti-virals and steroids. ANA profile by indirect immunofluoroscence showed no intensity. An autoimmune encephlitis Antibody panel was positive for NMDA receptor Antibody positive.

HRCT Thorax, USG for Abdomen and pelvis were negative for any tumor that may have led to antibody formation. Patient was managed with inj. IVIG 0.4 gm/kg/day for 5 days and inj. Methylprednisolone 500 mg for 5 days. After 10 days patient's sensorium improved and later on discharged with tapering steroids.

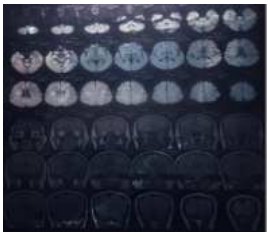

Image 1 : MRI Brain with contrast suggestive of patchy meningoence phlitis

DISCUSSION

Autoimmune conditions are not a common cause of encephalitis. however, with recognition of newer antibodies, diagnostic serology is becoming increasingly available. The above cases are encountered within an 1 year period

Case 1 and 2 describes two young female with Anti NMDA positive encephalitis with pure neuropsychiatric features and abnormal movement in case 1, while Case 3 describes middle aged male with Anti NMDA positive encephalitis with fever and features resembling viral encephalitis. Case 1 and 2 have normal MRI finding while Case 3 had changes of encephalitis in MRI brain. 60% cases have normal MRI brain finding. It is commonly associated with tumors especially ovarian teratoma (70%), but in our cases it was not associated. All 3 patients responded to IVIG and methylprednisolone.Many cases have no imaging finding, especially early in the course of disease. Having said that, MRI with contrast is considered most sensitive imaging modality, and findings are present in over half of the individuals. The most common location of involvement is the mesial temporal lobes and the limbic system, typically manifested by cortical thickening and increased T2/FLAIR signal intensity of this region. Bilateral involvement is most common (60%) although often asymmetric. The lateral temporal lobe and insula are less commonly involved, whereas the basal ganglia in contrast is frequently involved which helps in distinguishing it from HSV encephalitis which characteristically spares the basal ganglia. Although far less common essentially any part of the central nervous system can be involved. The presence of hemorrhage on susceptibility weighted images is in favor of other diagnoses such as herpes simplex encephalitis which has otherwise very similar imaging appearance to limbic encephalitis.

EEG in both case 1 and 2 shows generalized neuronal hyper

excitability. In CSF analysis case 2 and 3 shows CSF pleocytosis while Case 1 had no pleocytosis.

CONCLUSION:

Autoimmune encephalitis should be in differential diagnosis in patients with neuropsychiatric features if no infectious cause is found as autoimmune encephalitis is rapidly progressive and reversible with treatment. If patients diagnosed Early and timely managed is likely to improve outcome.

The origin of this disease is often paraneoplastic. Approximately 50% of women over 18 years and only 9% of girls under 14 years have an ovarian teratoma . In men, the presence of tumors is rare .

The diagnosis is confirmed by the detection of IgG antibodies directed against the GluN1 subunits of the NMDA receptors in serum and CSF which is not available at the time of presentation to the emergency department. Therefore, when a patient presents to the emergency department with suggestive clinical picture, lumbar punction should be performed to look for CSF pleocytosis or oligoclonal band. EEG is useful and shows abnormal results in the majority of cases but nonspecific with a slow and disorganized epileptic activity. Brain MRI is often normal especially early in course of disease. 40% of patients had increased FLAIR or T2 signal in the cortical or subcortical areas (hippocampus, basal ganglia, white matter).

The differential diagnosis includes acute primary psychiatric disorder, neuroleptic malignant syndrome, malignant catatonia, drug intoxications, viral encephalitis, and lethargic encephalitis.However, the diagnosis of anti-NMDA receptor encephalitis remains difficult due to the vagueness of the primary clinical picture. anti-NMDA antibodies are found in 50% of patients diagnosed with lethargic dyskinetic encephalitis. In addition, 20–30% of patients with herpes simplex virus (HSV) infection show positive seroconversion with anti-NMDA antibodies as part of a relapse not attributable to HSV relapse .

In the absence of reliable statistical data, there is no standard treatment; instead, treatment should be individualized according to age, the severity of symptoms, and the presence or absence of a tumour. Treatment can include immunosuppression and tumour resection when indicated. In the presence of CSF pleocytosis or oli- goclonal band at lumbar punction and abnormal EEG or pathologic brain MRI, immunosuppressive treatment should be started.

In conclusion, anti-NMDA receptor encephalitis is a rare disease under diagnosed due to the variability of the initial symptoms. In general, emergency physicians are not familiar with this disease. In case of patient with suggestive clinical picture of anti NMDAR encephalitis presenting to the emergency room, lumbar puncture should be performed as soon as possible to look for CSF pleocytosis and oligoclonal bands. Abnormal EEG findings and brain MRI can help to not delay the initiation of immunosuppressive treatment. The diagnosis is confirmed by the detection of antibodies anti-NMDAR in the CSF. The possibility of this pathology should be taken into account as a differential diagnosis for patients presenting with acute psychosis or encephalitis before diagnosing a psychiatric illness.

Table 1 : Summary of above mentioned cases

CASE	1	2	3
AGE/SEX	15/F	16/F	38/M
CLINICAL FEATURES	Neuropsychiatric features	Neuropsychiatric features	Neuropsychiatric features
CSF	Normal	Pleocytosis	Pleocytosis
MRI	Normal	Normal	Patchy meningoencephalitis

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