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A Case of Anti NMDA Antibody Encephalitis

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Abstract

Antibody-mediated encephalitides constitute a group of inflammatory brain diseases that are characterized by prominent neuropsychiatric symptoms and are associated with antibodies against neuronal cell-surface proteins, ion channels, or receptors. Common clinical features include a change in behavior, psychosis, seizures, memory and cognitive deficits, abnormal movements, dysautonomia, and a decreased level of consciousness. The estimated annual incidence of all types of encephalitis is approximately 5 to 8 cases per 100,000 persons, and in 40 to 50% of the cases, the cause cannot be established. A prospective, multicenter, population-based study suggests that autoimmune disorders are the third most common cause of encephalitis, after infections, usually viral, and acute disseminated encephalomyelitis, which is typically a postinfectious disorder. The frequency of the most common form of autoimmune encephalitis, the type with antibodies against the *N*-methyl-d-aspartate receptor (NMDAR), surpasses the frequency of any individual viral cause of encephalitis in young persons, and in one retrospective study, anti-NMDAR encephalitis accounted for 1% of all admissions of young adults to an intensive care unit.

The patient discussed here is a 47- year old male who presented to our casualty as a case of fever and abnormal behaviour which started suddenly. Patient was evaluated thoroughly and the diagnosis of anti- NMDA antibody encephalitis was made. Patient was treated with IV methylprednisolone 1g for 5 days after which he didn't improve much. An alternative therapy with IVIGs was made after which patient improved significantly.

Keywords: NMDA Receptor Antibody, autoimmune encephalitis, Methylprednisolone, IVIGs,

Case Presentation

A 47 year old male with no known comorbidities, presented to casualty with 3 day history of fever and abnormal behaviour. Patient had started with low grade fever which gradually worsened over some hours and was followed by abnormal behaviour in the form of irrelevant talking, abusive language and disorientation. There was no history of weakness of any side of body, history suggestive of cranial nerve palsies or bowel or bladder involvement. Patient's past history was medically insignificant.

Patient was admitted and clinical examination revealed a GCS of 14/15 (E4V4M6), pulse of 102 beats/minute, temperature of 101 F. There was no pallor, icterus,

cyanosis or edema. Respiratory, cardiovascular system and abdominal examination was unremarkable. CNS examination revealed impaired higher mental functions with no apparent cranial nerve palsies. Motor system examination was unremarkable. Planters showed bilateral flexor response. Meningeal signs were present.

Investigations revealed a normal collective blood count, normal KFTs/LFTs/ ABG/ normal spot urine and a normal NCCT head. CSF analysis was done which revealed 110 cells with predominantly lymphocytes (90%) with normal protein and glucose. HSV PCR was negative, so was staining for AFB and fungal elements. CSF ADA was within normal limits. CEMRI brain was done which showed hyperintensity in T2 weighted and FLAIR images in left temporal lobe. Patient was started on Acyclovir in view of lymphocytic pleocytosis of CSF with normal sugar and protein and MRI brain. Patient showed transient mild improvement after receiving Acyclovir but subsequently worsened in terms of his behaviour.

A repeat CSF analysis was done in view of patient's worsening symptoms which showed no cells with protein of 96mg/dL and normal glucose. HSV PCR was again negative, so was the staining for AFB and fungal elements. CSF cultures were sterile.

In view of his clinical condition, patient was further investigated in order to rule out autoimmune and limbic encephalitis. Systemic screening by means of CECT chest/abdomen/pelvis was done which was unremarkable apart from mild emphysematous changes in both lung fields. Paraneoplastic panel was also negative while CSF came out to be positive for NMDA antibody.

Patient was managed as **anti NMDA antibody encephalitis** and was started on IV methylprednisolone. He received 5 doses of the drug but did not show much improvement. An alternative therapy with IVIgs was started. After receiving 5 doses of IVIg at a dose of 25g/day (400mg/Kg/day), patient started improving.

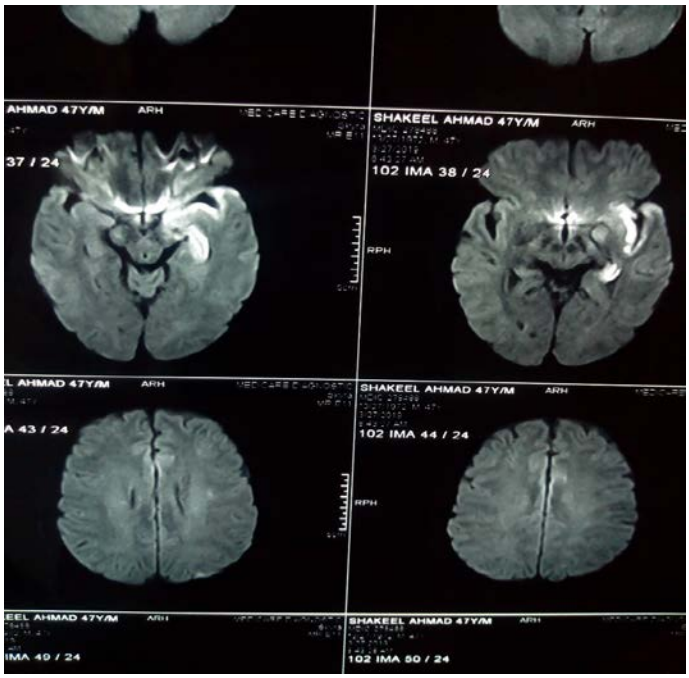

Figure 1

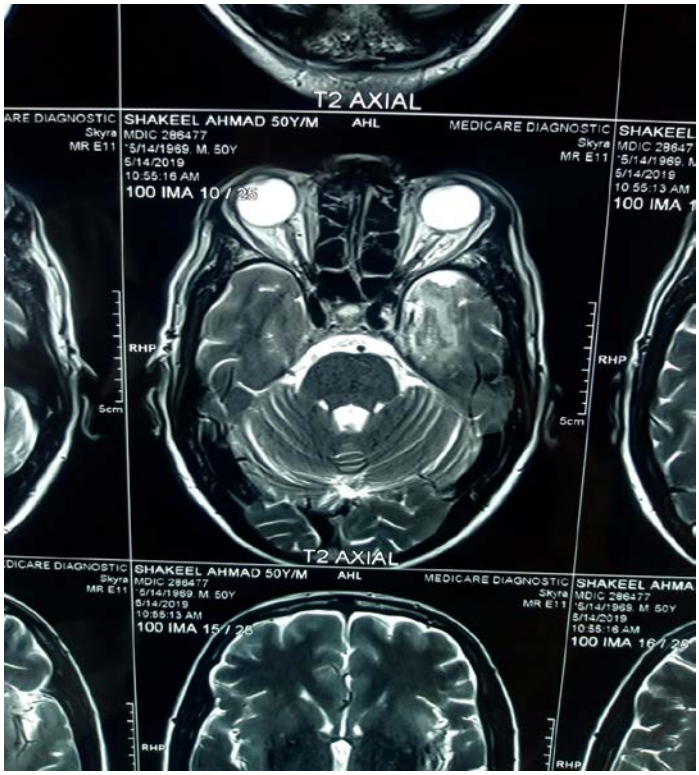

Figure 2

Altered signal that is hypointense on T1WI and hyperintense on T2WI and FLAIR images showing restricted diffusion on DWI is seen involving the external capsule, insular cortex and medial temporal lobe on left side.

Needs clinical correlation for viral (herpes) encephalitis

Anti-NMDA receptor encephalitis : a review of literature

Anti-NMDA receptor encephalitis is the best characterized of the autoimmune encephalitis syndromes and is associated with a predictable set of symptoms that combine to make up a characteristic syndrome [47-51].

Clinical features: Many patients present with prodromal headache, fever, or a viral-like process, followed in a few days by a multistage progression of symptoms that include:

Prominent psychiatric manifestations (anxiety, agitation, bizarre behavior, hallucinations, delusions, disorganized thinking); isolated psychiatric episodes may rarely occur at initial onset or at relapse [52],insomnia, memory deficits, seizures, decreased level of consciousness, stupor with catatonic features, frequent dyskinesias: orofacial, choreoathetoid movements, dystonia, rigidity, opisthotonic postures, autonomic instability: hyperthermia, fluctuations of blood pressure, tachycardia, bradycardia, cardiac pauses, and sometimes hypoventilation requiring mechanical ventilation, language dysfunction: diminished language output, mutism, echolalia.

Children as young as eight months have been reported with this syndrome [49,58-61]; In children, the symptoms are similar to those of the adults, with prominent early psychiatric symptoms in most patients; dysautonomia and hypoventilation are less frequent and severe. Presenting symptoms usually include acute behavioral change, seizures, language dysfunction, and prominent dyskinesias, including dystonia and chorea [62,63]. Although rare, approximately 5 percent of patients are >45 years of age [64].

Diagnosis and differential diagnosis — The disorder should be suspected in adults or children that develop the above clinical symptoms, usually accompanied by:

- Cerebrospinal fluid (CSF) lymphocytic pleocytosis or oligoclonal bands (although basic CSF parameters can be normal initially).
- Electroencephalography (EEG) with infrequent epileptic activity, but frequent slow, disorganized activity that does not correlate with most abnormal movements [65].
- Brain magnetic resonance imaging (MRI) that is often normal or shows transient fluid-attenuated inversion recovery (FLAIR) or contrast-enhancing abnormalities in cortical (brain, cerebellum) or subcortical (hippocampus, basal ganglia, white matter) regions [48,66]. While not routinely performed, positron emission tomography (PET) reportedly shows a characteristic increase in the frontal-occipital gradient of cerebral glucose metabolism, which correlates with disease severity [67].

The diagnosis of anti-NMDA receptor encephalitis is confirmed by the detection of immunoglobulin G (IgG) antibodies to the GluN1 (also known as NR1) subunit of the NMDA receptor in serum or CSF (table 3) [68]. CSF IgG antibody testing is highly sensitive and specific for anti-NMDA receptor encephalitis; false-positive and -negative results may occur when testing only serum [69]. IgM and IgA antibodies against the NMDA receptor, which have been described in some patients with chronic schizophrenia or other chronic neurologic disorders, are

nonspecific, do not alter NMDA receptors in vivo, and have no additional value in the diagnosis of NMDA receptor encephalitis [70,71].

CSF antibodies are always present at the time of presentation; most patients have intrathecal synthesis of antibodies [72]. After treatment or in advanced stages of the disease, the CSF antibodies usually remain elevated if there is no clinical improvement, while serum antibodies may be substantially decreased by treatments [66,73,74]. The titer of CSF antibodies appears to correlate more closely with the clinical outcome than serum titers [48,66,69,73].

The differential diagnosis of this clinical presentation includes primary psychiatric disorders (acute psychosis or schizophrenia), malignant catatonia, neuroleptic malignant syndrome [75], viral encephalitis [76], and encephalitis lethargica [77], among others [78].

Association with ovarian teratoma and other tumors — The detection of an ovarian teratoma is age dependent; approximately 50 percent of female patients older than 18 years have uni- or bilateral ovarian teratomas, while less than 9 percent of girls younger than 14 years have a teratoma [51]. Ovarian teratomas are often revealed by MRI and computed tomography (CT) of the abdomen and pelvis, along with abdominal or transvaginal ultrasound [66]

In male patients, the detection of a tumor is rare. Cases with associated tumors other than ovarian teratoma include testicular germ cell tumor [79], teratoma of the mediastinum, small cell lung cancer (SCLC) [48], Hodgkin lymphoma [80], ovarian cystadenofibroma [81], and neuroblastoma [82]. The frequency of underlying tumors in older patients (>45 years) is low, and when present, tumors are more often carcinomas instead of teratomas [64].

Association with HSVE: Although preceding infections have been suspected to play a role in triggering autoimmune encephalitis, to date this has only been demonstrated for herpes simplex viral encephalitis (HSVE). Studies have shown that approximately 20 to 30 percent of patients who are NMDA receptor antibody-negative in serum and CSF at the time of HSVE infection seroconvert to positive NMDA receptor antibodies (or less commonly other antineuronal antibodies) in the setting of relapsing symptoms not attributable to HSVE relapse [84-87]. A smaller proportion develop NMDA receptor or other antibodies in the absence of clinical symptoms [87].

Symptoms of anti-NMDA receptor encephalitis in these cases begin at a median of four to six weeks after initial viral infection and may occur in contiguity with or after recovery from the HSVE [85,87-91]. In a series of 58 patients with antibody-confirmed autoimmune encephalitis after HSVE (74 percent with NMDA antibodies), the most common symptoms were change of behavior (93 percent), decreased level of consciousness (57 percent), choreoathetosis (47 percent, all in children four years of age or younger), seizures (38 percent), and dysautonomia (27 percent) [87]. In most pediatric cases, symptoms have included choreoathetosis and/or orofacial dyskinesias [85]; teenagers and young adults are more likely to develop behavioral and psychiatric symptoms [86]. Prompt diagnosis and treatment with immunotherapy improve symptoms and outcome despite persistence of deficits from the HSVE, especially in older children and adults [85,87].

In addition to NMDA receptor antibodies, antibodies to gamma-aminobutyric acid A (GABA-A), dopamine 2 receptor, and unknown neuronal cell-surface antigens have been reported in patients with autoimmune encephalitis after HSVE [86,87].

Treatment and prognosis: Treatment options include immunosuppression and tumor resection when indicated [51,66,73,92]. Progressive neurologic deterioration and death can occur without treatment. However, spontaneous recovery has also been described in a few patients after several months of severe symptoms [93].

In the absence of prospective and randomized data, treatment decisions should be individualized and take into consideration patient age, the presence or absence of a tumor, and symptom severity. Based on observational studies reviewed below and clinical experience, we suggest initial treatment with intravenous methylprednisolone (eg, 1 gram daily for five days in an adult) and either intravenous immunoglobulin G (IVIG; eg, 400 mg/kg per day for five days) or plasma exchange in most patients, in addition to tumor removal when appropriate. It is unknown whether IVIG and plasma exchange have similar efficacy; some clinicians may find IVIG easier to administer in patients with anti-NMDA receptor encephalitis, who may be very young and have severe dyskinesias, agitation, and autonomic instability.

If there is no evidence of clinical improvement with initial therapies, we proceed with second-line therapies including rituximab (either 375 mg/m^2 weekly for four weeks, or 1 g twice two weeks apart), cyclophosphamide (750 mg/m^2 monthly for four to six months depending on results), or both.

An alternative approach to stepwise escalation of immunotherapy is to use rituximab in combination with steroids and IVIG or plasma exchange as initial therapy. As noted above, patients with anti-NMDA receptor encephalitis are at risk for relapse. Relapse occurs in 15 to 24 percent of patients, sometimes after several years [48,66,101]. Relapse may occur in the absence of a tumor or in association with an occult or recurrent teratoma. In several series, relapses were more common among those who did not receive immunotherapy with the initial presentation [51,101]. Relapses are typically treated similarly to the approach in newly diagnosed patients, with a lower threshold to initiate second-line therapies early in the course of the relapse.

Pregnancy and fetal effects — Transplacental transfer of IgG anti-NMDA receptor antibodies has been documented in serum of babies born to mothers with anti-NMDA receptor encephalitis. The effect of these autoantibodies on the fetus is not well described and may be variable.

Case reports have described short-term fetal outcomes ranging from normal to early neonatal death [102-107]

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