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CASE REPORT

# Severe anti NMDA encephalitis and EBV infection

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## Abstract

N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an immunotherapy-responsive panencephalitis. Patients usually present with characteristic clinical features in a specific order. We describe a patient who developed anti NMDA receptor encephalitis with a positive liquor EBV titer, suggesting formation of antibodies including anti NMDA. After a prolonged ICU stay the patient had a slow but full recovery. Despite severe neurological symptoms, in general, the prognosis of anti NMDA receptor encephalitis is good and warrants prolonged intensive care treatment when indicated.

## Introduction

N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an immunotherapy-responsive panencephalitis.[1-3] Patients usually present with characteristic clinical features in a specific order.[1,2,4] After a prodomal flu-like illness, patients develop psychiatric symptoms with short term memory loss followed by orofacial dyskinesias, limb choreoathetosis, catatonia and autonomic instability. Another characteristic feature is a persistent amnesia of the entire process.[5] This report describes a patient with chronic use of immunosuppressants and with a positive spinal fluid Epstein Barr virus (EBV) titer who developed anti NMDA encephalitis.

## Case report

For eight weeks a 26-year-old male had experienced several episodes with blackouts and strong feelings of romantic love and joy, lasting several minutes. These episodes increased in frequency and the patient showed signs of confusion. Two weeks before admission in the referring hospital the patient developed anxiety attacks, became confused and exhibited echolalia. There was also indecisiveness, sleepiness and difficulties with speech. Eight weeks after the first symptoms arose, the patient was admitted to the referring hospital. An EEG was consistent with encephalopathy. Neural imaging including an MRI showed no abnormalities but spinal fluid analysis showed a mild lymphocytic pleocytosis. Cultures of both spinal fluid and blood were negative. The patient became bedridden and because of further deterioration that included inability to walk or speak and increasing confusion, he was transferred to our hospital for evaluation.

The patient had had a renal transplant in 2003 for reflux nephropathy. His medication consisted of prednisone 10 mg once daily and mycofenolatemofetil 500 mg twice daily. After transplantation the patient had multiple urinary tract infections due to kidney stones.

On arrival in our hospital, 12 days after admission in the referring hospital, neurologic examination showed non-fluent speech with difficulty finding words and following more complex commands. The patient had a cautious and broad-based gait and there was a slight tremor of both hands without myoclonus. Deep tendon reflexes were symmetrical and lively, with bilateral clonus of the ankle reflex and Babinski's sign. Testing of cranial nerves, strength, sensibility and coordination showed no abnormalities.

The patient was admitted to the neurology ward. After admission his symptoms progressed. He developed catatonia with dyskinesias in the face and mouth, manifesting as orofacial movements with clenching of the teeth or forcefully opening his mouth for several minutes. Because of catatonia and dyskinesias he was transferred to our medium care unit five days after admission, where he was given midazolam intravenously. Thyroid and adrenal function were normal. Kidney and liver function tests as well as a full blood count were normal. CSF showed lymphocytic pleocytosis and an increased protein concentration (95% lymphocytes, protein 864 mg/l). Cultures of blood and CSF were negative. Viral studies of blood and CSF for neurotropic viruses, HSV, CMV, enterovirus, parechovirus and varicella zoster were negative. However, a PCR for EBV from CSF became positive with 30,000 copies per ml and EBV ebna IgG 152 U/ml and EBV vca IgG >200 U/ml in blood became positive a few days later. A diagnosis of EBV encephalitis was made and ganciclovir 200 mg twice daily

was started and mycofenolatemofetil discontinued. An initial MRI showed no abnormalities, but a second T2-FLAIR* MRI showed a subtle diffuse increase of signal intensity of the white matter bilaterally (*figure 1*). An EEG showed slow delta-theta activity.

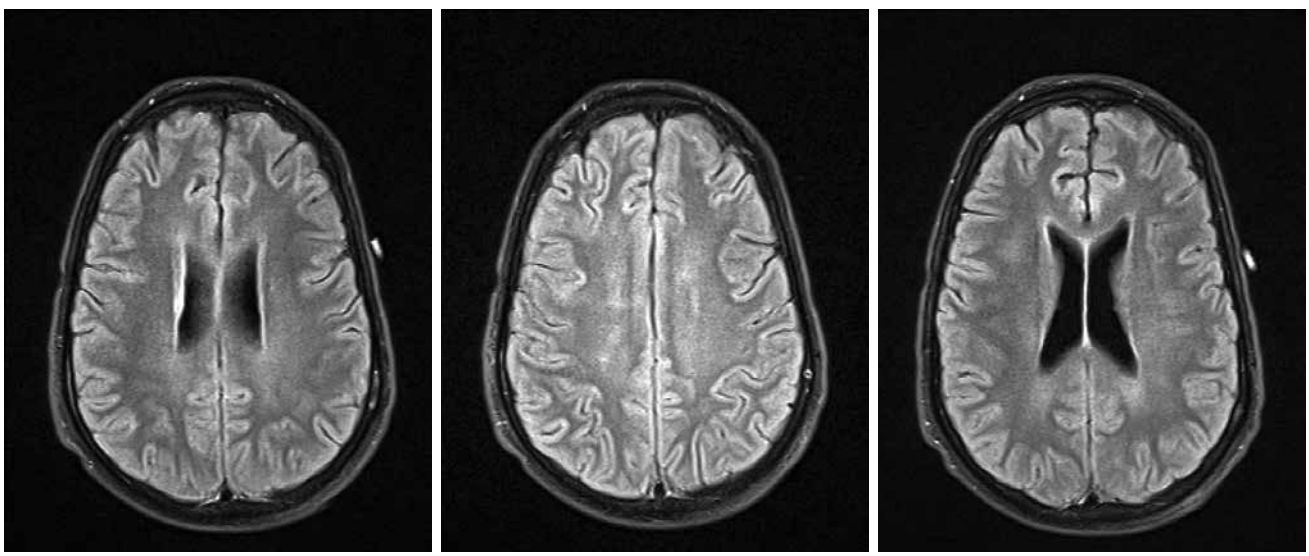
After an initial improvement and despite aggressive treatment of the EBV encephalitis with ganciclovir and immunoglobulins, given at a dose of 0.4 gr/kg/day for five days, epileptic seizures continued and the patient became catatonic for longer periods. During the following four weeks the patient deteriorated further and needed continuous sedation to treat the seizures and catatonia.

Three weeks after admission, the patient was transferred to the ICU for mechanical ventilation. Since there had been no improvement after the start of antiviral treatment and because of the sequence of symptoms and by now nearly permanent catatonia – only interrupted by seizures – limbic encephalitis was suspected. CSF auto-antibody testing was performed and was positive for anti N-methyl-D-aspartate (NMDA) receptor antibodies. Subsequently a diagnosis of anti NMDA (receptor) encephalitis was made. The patient was treated with immunoglobulins, in the same dose as mentioned, and methylprednisolone, with little improvement. For two weeks the patient exhibited signs of autonomic instability, with fluctuations of blood pressure, cardiac rhythm and fever and he was eventually treated with rituximab (700 mg; 375 mg/m2) weekly for four weeks. Thereafter the patient improved slowly and was extubated after four weeks and discharged eight days later. The patient continued to improve but on discharge he still showed apathy, marked rigidity and short term memory loss. A few months after discharge the patient had made a full recovery. An extensive work up (abdominal/scrotal ultrasound; CT scan thorax/abdomen; PET-CT) showed no evidence of an underlying tumor.

## Discussion

N-methyl-D-aspartate receptor antibody encephalitis is an immunotherapy-responsive limbic panencephalitis.[1-3] This disorder is associated with a misdirected autoimmune response with formation of antibodies against the NR1 subunit of the NMDA receptor.[4-6] NMDA receptors are ligand-gated cation channels on neural cell membranes with crucial roles in synaptic transmission and plasticity and are predominantly concentrated in the hippocampus and forebrain.[4,5] About 60% cases occur as a paraneoplastic process, most commonly an ovarian teratoma.[1] Anti NMDA limbic encephalitis affects young people, predominantly young women.[1] In male patients the detection of a tumor is rare, but testicular germ cell tumors, teratoma of the mediastinum, small cell lung carcinoma, Hodgkin's lymphoma and neuroblastoma have been found.[5,6] Patients present with characteristic clinical features in a specific order and many patients have initially been seen by psychiatrists but subsequently developed seizures and complex symptoms requiring multidisciplinary care.[4,5,7] The

**Figure 1.** T2-FLAIR MRI with subtle diffuse increase of signal intensity of white matter bilaterally.



FLAIR stands for Fluid-Attenuated Inversion Recovery and is the most sensitive MRI sequence. It provides a better contrast range with more conspicuous delineation of pathology. By suppressing CSF intensity (which appears black) and increasing the intensity of edema, even subtle (periventriculair) vasogenic and cytotoxic oedema will be clearly visible.

development of autonomic instability and stupor may require mechanical ventilation for weeks or even months and seizures should be treated aggressively.[1,2] Symptoms usually start with a prodomal flu-like illness with fever, malaise, headache or fatigue, after which psychiatric symptoms develop, the most common being anxiety, agitation, delusions and hallucinations with short term memory loss followed by orofacial dyskinesias, limb choreoathetosis, catatonia and autonomic instability with fluctuations of blood pressure, temperature and cardiac rhythm. Another characteristic feature is a persistent amnesia of the entire process.[1,2,5]

CSF reveals inflammatory changes in >90% of cases with an elevated white cell count, mainly lymphocytes and mildly elevated protein content with oligoclonal bands.[2-4,8] EEG studies are abnormal in >90% of cases and usually show diffuse delta-theta activity.[5,7,9] Brain MRI is often normal initially, but 55% of cases will show non-focal cortical hyper intensity in FLAIR setting, predominantly in the medial temporal lobes.[2-4,8] These findings can be asymmetric. MRI abnormalities are not prerequisite for the diagnosis. The finding of N-methyl-D-aspartate receptor antibodies in CSF, however, together with the characteristic clinical picture confirms the diagnosis.

The concentration of NMDA receptor antibodies correlates well with the clinical state in individual patients.[5,8] Therefore, the major aim of therapy is to reduce NMDA receptor antibodies.[4,5,8] For patients with an underlying tumor, removal of the malignancy is of paramount importance.[1,2,6] In addition, immunotherapies appear to hasten recovery. In nonparaneoplastic cases immunotherapies are administered, again with the aim of reducing NMDA receptor antibody levels. Commonly used immunotherapies in this case series include corticosteroids, intravenous immunoglobulins and plasma exchange. Patients who do not improve with these first line therapies may improve with rituximab and/or cyclophosphamide.[4-6]

Our patient who was known to have a chronic use of immunosuppressants and a positive spinal fluid EBV titer, developed anti NMDA receptor encephalitis. Patients with long term immunosuppressant therapies are typically at risk for infection or reactivation of EBV. A typical aspect of EBV infection is proliferation of B cells with accompanying antibody formation. These antibodies may be directed against the NMDA receptor. Although extensive studies of CSF, brain biopsies and autopsies in other cases of anti NMDA receptor encephalitis were negative for viruses [5,6], a viral pathogenesis in general is suggested by the prodomal flu-like illness and in this case particularly by a concurrent high spinal EBV load (104). This does not mean that EBV encephalitis per se is the cause of anti NMDA receptor encephalitis, but strongly suggests pathogenicity of the anti NMDA receptor antibody itself.

## Conclusion

We describe a specific neurological syndrome (limbic encephalitis) associated with auto antibodies against the NMDA receptor temporarily related to EBV encephalitis. Despite severe neurological symptoms, anti NMDA receptor encephalitis generally has a good prognosis and warrants prolonged intensive care treatment if indicated.

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