CASE REPORT

# NMDAR (N-methyl-D-aspartate receptor) encephalitis in a patient with MS (multiple sclerosis): a rare and challenging case

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## SUMMARY

We present a rare case of N-methyl-D-aspartate receptor (NMDAR) encephalitis in a 41-year-old Caucasian woman, who initially presented with prominent neuropsychiatric symptoms on the background of pre-existing multiple sclerosis. Here, the authors navigate the muddy water between neurology and psychiatry, describing the caveats of antibody testing with a misdiagnosed case of acute and transient psychotic episode. NMDAR encephalitis in MS is a rare condition, which can be easily confused with a new onset psychotic episode. This case report can be helpful in recognition and diagnosis of this rare condition. Making the right diagnosis is important since it can prevent an unnecessary radical treatment and long-term neuropsychiatric complications.

## BACKGROUND

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a severe autoimmune disorder which can be life threatening if not diagnosed and treated promptly. Most patients die with cardiac arrest, serious infections due to the use of powerful immunosuppressive drugs and other complications related to long stay in hospital.[1] It largely affects young women and is often associated with an ovarian teratoma. It has a mortality rate up to 25%.[2] The true prevalence of anti-NMDAR encephalitis in general population and in patients with psychosis is not yet fully clarified; however, according to the epidemiological studies, it can be the most common cause of autoimmune encephalitis after acute demyelinating encephalitis.[2]

The typical clinical features include severe psychiatric symptoms (auditory and visual hallucinations with delusional beliefs), memory loss, seizures, behavioural changes (frequently with agitation), motor disturbances (ranging from dyskinesia to catatonia) and autonomic dysregulation.[1]

Here, we describe a case of anti-NMDA receptor encephalitis in a female patient with history of multiple sclerosis (MS), particularly where there is no history of severe psychiatric illness or substance misuse, presenting predominantly with psychiatric symptoms. The patient was considered by the medical team to have a primary psychiatric disorder at various points over the course of illness. As a potentially treatable differential for symptoms and signs seen in neurology and psychiatric clinics, we strongly believe that psychiatrists/physicians should be alerted to the possibility of this disorder when assessing patients with acute onset of confusion, visual hallucinations, persecutory delusions and memory and behavioural problems.

## CASE PRESENTATION

A 41-year-old white British woman was initially admitted on acute medical unit on 20 April 2017 with acute onset of persecutory delusions and visual hallucinations associated with odd behaviour (shouting and walking around with a knife) on a background history of MS. Family reported her to be unwell for about 8 weeks with slowly worsening confusion and memory problems.

On admission, respiratory, cardiovascular and abdominal examinations were normal. Neurological examination revealed horizontal nystagmus, bilateral reduced tone in lower limbs with exaggerated reflexes in both upper and lower limbs without any evidence of neck stiffness or photophobia. There was no abnormality in cranial nerves. Muscle bulk was also preserved in upper and lower limbs with flexor planter response.

There was history of postnatal depression at age of 19, which was managed by her general practitioner. MS was diagnosed at the age of 34. Tecfidera (dimethyl fumarate) was started by the neurologist for relapsing MS in November 2016. She suffered with a chest infection about 2 months before the admission, which was treated with a course of amoxicillin.

Personal history revealed a difficult childhood due to her mother being an alcoholic. She had been repeatedly assaulted sexually by an unfamiliar perpetrator from the age of 5 to 12. She was independent in all activities of daily living inclusive of budgeting. She was working as a councillor in drug and alcohol services and was living with her three children with support from her ex-husband before becoming unwell. Family history was positive for breast cancer with no other mental health problems. There was no history of illicit drugs or alcohol abuse, but she was an excessive smoker.

## INVESTIGATIONS

On initial blood tests, white cell count was slightly raised ($15.4 \times 10^9$/L), which became normal after 6 days. All other baseline bloods including kidney function tests, liver function tests, C reactive



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protein, thyroid function tests, vitamin B12, folate, bone profile and magnesium levels were normal. Pregnancy test was negative. There was no evidence of hepatitis B or hepatitis C.

Lumbar puncture revealed no signs of infection (no pleocytosis, normal glucose ratio and normal protein level) or malignancy. High (20.1) oligoclonal bands and high (0.068) IgG (cerebrospinal fluid, CSF) with high CSF index (0.72) were suggestive of inflammation of the central nervous system. However, we also acknowledged that this could be due to MS.

Neuroimaging revealed new white matter lesions but no signs of tumour or haemorrhage.

Poor response to the treatment and suspicion of organic psychosis led to multiple tests including extensive antibody screening. Blood tests showed positive anti-NMDAR antibodies after 1 month and 10 days of initial presentation. There was no evidence of any other autoimmune diseases, infections or paraneoplastic syndrome. IgA, IgG and IgM were normal with negative antimitochondrial antibodies, antinuclear antibodies, double stranded DNA, extractable nuclear antigen antibody, anti-contactin-2-associated protein, anti-leucine-rich glioma inactivated 1, anti-aquaporin 4, ICPE Screen (carbapenemase-producing Enterobacteriaceae), antibodies to glycine receptors and syphilis antibodies (including treponemal antibodies).

Further investigations were performed to rule out any association with tumours especially ovarian teratoma. Ovaries unlikely appeared to be a source of NMDAR encephalitis, and there was no evidence of other malignancies on blood tests. A CT and MRI of the abdomen were unremarkable.

Electroencephalogram showed normal background alpha activity with no diagnostic encephalopathic changes. Tuberculosis test was negative. Chest X-ray was normal, and there was no history of recent travel.

The Mini-Mental Score Examination score was 26/30, and the Montreal Cognitive Assessment score was 22/30. The points were lost on recall and orientation on both scales. Following assessment by the care of elderly mental health liaison team (MHLT), it was highlighted that poor concentration and attention was mainly due to the psychological impact of childhood trauma (sexual abuse) on the background of MS. It was advised that the patient might have mild cognitive impairment rather than dementia. The score on Addenbrooke's test was 80/100 (attention 15/18, memory 16/26, fluency 11/14, language 22/26 and visuospatial 16/16).

## DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of anti-NMDAR encephalitis includes viral and other autoimmune encephalitis (including paraneoplastic/limbic encephalitis) and progressive multifocal leukoencephalopathy. It is important to consider that NMDAR encephalitis significantly differs from other paraneoplastic encephalitis in the nature and prominence of presenting psychiatric problems. This difference is vast and is mainly based on prominent features of anxiety and agitation, delusional beliefs with or without paranoia, visual and auditory hallucinations and bizarre behaviour in NMDAR encephalitis rather than predominant symptoms of memory changes or disorientation.[3]

In our case report, acute psychotic episode was suspected by medical team due to poor response to the treatment of MS, worsening psychosis and behavioural problems. Acute and transient psychosis is an important differential diagnosis; however, it is important to rule out all the organic causes before consideration of this diagnosis.

## TREATMENT

The patient was initially treated with a short course of steroids (methylprednisolone) for suspected exacerbation of MS due to new lesions on brain MRI scan. Steroids were stopped soon due to emerging features of mania. After 5 days of her admission, she became extremely agitated and anxious, requiring hospital security to maintain her safety. At this point, referral was made to the MHLT with a suspicion of new onset psychotic episode. PRN haloperidol and benzodiazepines were used for agitation and psychotic symptoms. Haloperidol was later changed to olanzapine. Sertraline was added predominantly to treat any underlying anxiety symptoms. The MHLT had an impression of organic psychosis based on fluctuating confusion, acute onset of psychotic symptoms accompanied with unusual behaviour. An extensive diagnostic study allowed for the diagnosis of NMDAR encephalitis after 1 month and 10 days of initial admission. The patient was transferred to the neurology ward after confirmation of NMDAR encephalitis, and intravenous immunoglobulin (IVIg) (Privigen) 2 g/kg was commenced which was followed by rituximab (two courses) and five sessions of plasma exchange therapy. Following the antipsychotic and immunoglobulin treatment, her psychotic symptoms were completely resolved. She also made significant improvement in terms of mood and behaviour. Over a period of time, the dose of olanzapine was reduced with the plan to stop it eventually. The patient continued to have problems with short-term memory which had adversely impacted on her social skills, hence she was awaiting rehabilitation with the Neuropsychiatry Department at the time of writing up this case report.

## OUTCOME AND FOLLOW-UP

Patient showed significant improvement after treatment with antipsychotic and immunotherapy. She will be followed up with the neurology and community mental health team for further monitoring on her discharge from neurology ward.

## DISCUSSION

Anti-NMDA receptor encephalitis is a severe autoimmune disorder first described by Dalmau and his colleagues in 2007. Anti-NMDA is associated with antibodies against NR1 and NR2 subunits of the NMDA receptor. A multicentre observational study of 577 patients shows the disease predominance mainly in young individuals (549 (95%) younger than 45 years and 211 (37%) younger than 18 years) with female sex predominance of 4:1. The frequency of underlying tumour (mainly ovarian teratoma) was 58% in women older than 18 years.[4]

Anti-NMDA receptor encephalitis usually has an acute onset. Often, it starts with a viral-like prodrome with presenting complaints of headache, fever, gastrointestinal upset, insomnia and upper respiratory tract symptoms.[1] Our patient had chest infection roughly 2 months before this admission. A few days to weeks later, patients may develop psychiatric symptoms, short-term memory loss, abnormal movements, seizures and speech changes. Various case studies (Dalmau 2007–2008, Lizuka 2008, Florence 2009, Gable 2012, Lin 2014 and Wang 2015) showed that 59%–100% of patients with anti-NMDAR encephalitis had psychiatric symptoms, whereas 31%–50% of patients had memory deficits.[1] In our case report, patient presented with an acute onset of fluctuating confusion, visual hallucinations, paranoia, short-term memory difficulties and behavioural problems; however, there was no evidence of any abnormal movements or speech changes.

Regarding association of MS with anti-NMDAR encephalitis, a clinical and radiological analysis of a cohort of 691 patients by Maarten and colleagues (*Ann Neural* 2014, Mar) showed that the patients with anti-NMDAR encephalitis may develop a concurrent or separate episode of demyelinating disorder, and conversely, patients with neuromyelitis optica or demyelination disorders with atypical symptoms (dyskinesia and psychosis) may have anti-NMDAR encephalitis.[5] The patient in our case study had a new demyelinating lesion on MRI brain scan, it can be concurrent or separate episode of demyelination. It is important to remember for clinicians to rule out anti-NMDAR encephalitis for patients with demyelinating diseases who present with atypical symptoms of new onset psychosis.

Another previous case report by Anne Waschbisch in 2014 showed the presence of anti-NMDAR antibodies in a patient with a definite diagnosis of MS, but patient did not have any neuropsychiatric symptoms which raises the question of further research for association of MS and anti-NMDAR antibodies.[6]

The best treatment approach for anti-NMDAR encephalitis includes combination of tumour resection (if related to tumour), immunotherapy, intensive care, rehabilitation including physiotherapy and symptomatic treatment of psychotic and behavioural problems.[7] In patients without a tumour, the first-line immunotherapy, using corticosteroid, IVIg and plasma exchange may not be effective; thus, second-line immunotherapy (rituximab and/or cyclophosphamide) is usually needed.[8]

## Learning points

- Organic psychosis should be considered in differential diagnosis for young patients presenting with first episode psychosis.
- Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis should be ruled out in patients with demyelinating diseases who present with atypical symptoms of new onset psychosis.
- As it is more common in women, emergency physicians and medical teams should suspect anti-NMDAR encephalitis in any young woman, who presents with new onset seizures, psychiatric symptoms, memory loss, dyskinesia and/or change in speech to avoid delay in definite diagnosis.

Since the initial description of anti-NMDAR encephalitis, there has been ongoing research on this rare condition, but very little literature is available on its association with MS.

Based on our case study, we urge the importance of psychiatrists and medical teams especially accident and emergency (A&E) practitioners to be aware of this rare diagnosis when assessing patients with new onset psychiatric symptoms. In majority of cases, there is a delay in diagnosis due to extensive psychiatric symptoms on initial presentation, and the patients end up in psychiatric wards prior to definitive diagnosis. Delay in definite diagnosis and relevant treatment can cause significant comorbidities.

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## REFERENCES

1 The Anti NMDA Receptor Encephalitis Foundation. What is NMDA receptor encephalitis? http://www.anti NMDA foundation.org/theillness/ what-is-NMDA-receptor-encephalitis (accessed 18th Jun 2017).
2 Baker J, Jeziorkowski C, Siebe C, *et al*. Two cases of anti-NMDA receptor encephalitis. *West J Emerg Med* 2016;17:623–6.
3 Kayser MS, Kohler CG, Dalmau J. Psychiatric manifestations of paraneoplastic disorders. *Am J Psychiatry* 2010;167:1039–50.
4 Graus F, Titulaer MJ, Balu R, *et al*. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391–404.
5 Titulaer MJ, Höftberger R, Iizuka T, *et al*. Overlapping demyelinating syndromes and anti–N-methyl-D-aspartate receptor encephalitis. *Ann Neurol* 2014;75:411–28.
6 Waschbisch A, Kallmünzer B, Schwab S, *et al*. Demyelinating disease and anti-N-methyl-D-aspartate receptor immunoglobulin G antibodies: a case report. *BMC Res Notes* 2014;7:948.
7 Chapman MR, Vause HE. Anti-NMDA receptor encephalitis: diagnosis, psychiatric presentation, and treatment. *Am J Psychiatry* 2011;168:245–51.
8 Ikeguchi R, Shibuya K, Ikiyama S, *et al*. Rituximab used successfully in the treatment of Anti-NMDA receptor encephalitis. https://www.ncbi.nlm.nih.gov/pubmed/22728495 (accessed 31 Oct 2017).