

Antecedent anti-NMDA receptor encephalitis in two patients with multiple sclerosis

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder characterised by psychiatric symptoms, movement disorder and seizures often evolving into a severe encephalopathy.¹ It is characterised by the presence of IgG autoantibodies against the NMDAR in CSF and/or serum and predominantly affects young women.¹ Despite marked neurological disturbance, only 35-50% of patients have abnormal neuroimaging and the course of the disease is typically monophasic.² An overlap has recently been recognised between anti-NMDAR encephalitis and inflammatory demyelinating disorders, particularly neuromyelitis optica spectrum disorder (NMOSD).³ We describe two patients with an initial presentation consistent with anti-NMDAR encephalitis who have subsequently developed relapsing-remitting multiple sclerosis (MS).

Case 1

A 32 year old woman presented with seizures, abnormal movements affecting the right shoulder and encephalopathy. An MRI scan of the brain showed multiple T2-hyperintense brain and spinal cord lesions typical for demyelination (Figure 1a and b). None of the lesions showed enhancement after the administration of gadolinium contrast. A cerebrospinal fluid (CSF) examination showed a mild lymphocytic pleocytosis (white cell count $12 \times 10^6/L$, protein 61mg/dL) and unmatched oligoclonal bands not present in serum. Anti-NMDAR antibodies were positive in serum and not checked in CSF. A whole body CT-PET scan and pelvic ultrasound showed no underlying neoplasm. Attempts at immunotherapy were not tolerated and the symptoms partially improved spontaneously but she had persisting cognitive impairment.

Sixteen months later, she presented with a two week history of double vision, facial weakness and cerebellar ataxia in the absence of encephalopathy. Repeat MRI brain showed multiple new brain and spinal cord lesions, including a new contrast-enhancing lesion in the dorsal pons (Figure 1c and d). Anti-NMDAR, anti-aquaporin 4 (AQP4) and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies were negative. She commenced disease-modifying treatment 10 months later and remains free of relapses.

Case Two

A 29 year old man presented with psychosis and seizures. An MRI scan of the brain showed T2-hyperintense lesions typical of demyelination (Figure 2a-c) and a CSF examination showed unmatched oligoclonal bands. Anti-NMDAR antibodies were positive in serum and CSF. No underlying malignancy was identified and his symptoms improved spontaneously without immunotherapy. Two years later he developed sensory symptoms in the lower limbs ascending to a level on the trunk. An MRI scan of the spinal cord showed an area of T2 hyperintensity at the level of T11 (Figure 2d). A repeat CSF examination showed persistence of oligoclonal bands but negative for anti-NMDAR antibodies. Following the episode of partial myelitis a diagnosis of MS was made using the McDonald 2010 criteria.

Discussion

We report two patients with a clinical phenotype and serology compatible with anti-NMDAR encephalitis but also asymptomatic T2-hyperintense lesions typical for demyelination and positive oligoclonal bands at presentation. Both patients developed new neurological symptoms highly suggestive of MS (brainstem syndrome, short-segment myelitis), coupled with MRI evidence of dissemination in time and space, fulfilling both clinical and radiological criteria for relapsing-remitting MS.

The cases described build on the three existing reports of anti-NMDAR encephalitis occurring in patients with established MS.⁴⁻⁶ These cases outline patients with relapsing-remitting MS who had developed encephalopathy. In two of the previously reported cases, a prompt diagnosis was crucial to commence appropriate immunotherapy and to avoid neuro-psychiatric deficits. In the other reported case, a retrospective diagnosis of NMDAR encephalitis (on saved CSF samples) was made six years after a female patient diagnosed with relapsing-remitting MS had presented with severe cognitive impairment; despite stabilisation of her condition with immunotherapy, she required admission to a nursing home two years after her initial presentation.

Another recent case reported the incidental finding of anti-NMDAR antibodies in a patient with MS. Despite careful evaluation, he did not demonstrate any features of NMDAR encephalitis but was still treated with rituximab.⁷ In contrast to MS, anti-

NMDAR encephalitis may overlap much more frequently with NMOSD.² In a recent large series of 691 patients with anti-NMDAR encephalitis, 3.3% had clinical and/or imaging evidence of a demyelinating disorder, usually with features suggestive of NMOSD (longitudinally-extensive transverse myelitis, bilateral optic neuritis) and most (18 out of 23) had anti-AQP4 or anti-MOG antibodies.³ In half of cases the demyelinating events were concurrent with the anti-NMDAR encephalitis and half were disseminated in time.³

An unanswered question is whether the overlap between anti-NMDAR encephalitis and the idiopathic inflammatory demyelinating disorders represents a chance occurrence or whether they may be mechanistically linked. The reported frequency of NMOSD in patients with anti-NMDAR encephalitis in the series described above would argue against chance alone, although, any association is in part clouded by the high rate of co-morbid autoimmune disorders in patients with NMOSD. Another possibility is that inflammatory demyelination may trigger anti-NMDAR encephalitis. Recently, anti-NMDAR encephalitis has been identified as a major cause of relapsing neurologic symptoms in patients with herpes simplex virus encephalitis (HSE), after excluding inadequately treated infection.⁸ The mechanism by which HSE might give rise to parainfectious anti-NMDAR encephalitis is uncertain, but neuronal infection and inflammation might expose antigens that generate an autoimmune response. Whether inflammatory demyelination might also trigger anti-NMDAR encephalitis by a similar mechanism is unclear.

Based on the small number of reports to date, anti-NMDAR encephalitis does not appear to commonly overlap with MS. In the largest study to date investigating the

prevalence of anti-NMDAR antibodies in patients with established MS, only 1 of 89 patients tested was positive and that patient had a history of typical anti-NMDAR encephalitis that developed 3 years after the diagnosis of relapsing-remitting MS⁵.

However our two cases, in conjunction with other reports, suggest that there is a degree of overlap between anti-NMDAR encephalitis and MS that is attributable to more than chance.

Encephalopathic relapses, psychosis, severe cognitive impairment and unusual movement disorders have all been described people with MS. In settings where patients with MS develop unusual symptomatology, testing for anti-NMDAR antibodies should be considered in order to guide the most appropriate immunotherapy.

References

1. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091-8
2. Barry H, Byrne S, Barrett E, et al. Anti-NMDAR encephalitis: A review of clinical presentation diagnosis and treatment. *BJPsych Bull* 2015; 39(1): 19–23.
3. Titulaer MJ, Hoftberger R, Iizuka T, et al. Overlapping demyelinating syndromes and anti-NMDA receptor encephalitis. *Ann Neurol*. 2014;75(3):411-28
4. Uzawa A, Mori M, Takahashi Y, et al. Anti-N-methyl D-aspartate-type glutamate receptor antibody-positive limbic encephalitis in a patient with multiple sclerosis. *Clin Neurol Neurosurg* 2012;114:402-4
5. Ramberger M, Bsteh G, Schanda K, et al. NMDA receptor antibodies: A rare association in inflammatory demyelinating diseases. *Neurology(R) neuroimmunology & neuroinflammation* 2015;2:e141.
6. Fleischmann R, Pruss H, Rosche B, et al. Severe cognitive impairment associated with intrathecal antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor in a patient with multiple sclerosis. *JAMA neurology* 2015;72:96-9
7. Waschbisch A, Kallmunzer B, Schwab S, et al. Demyelinating disease and anti-NMDAR IgG antibodies: a case report. *Ann Neurol* 2014; 75(3): 411–428
8. Armangue T, Titulaer MJ, Málaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr*. 2013 Apr;162(4):850-856

