

## Case report

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

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## ARTICLE INFO

## Keywords:

Multiple sclerosis  
NMDAR encephalitis  
Atypical symptoms

## ABSTRACT

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. An overlap has recently been recognised between anti-NMDAR encephalitis and inflammatory demyelinating disorders, particularly neuromyelitis optical spectrum disorder (NMOSD).

In this case report, we describe two patients with an initial presentation consistent with anti-NMDAR encephalitis who have subsequently developed relapsing-remitting multiple sclerosis (MS) and discuss the literature pertaining to potential overlap between NMDAR encephalitis and inflammatory demyelinating disorders.

## 1. 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 (Dalmau et al., 2008). It is characterised by the presence of IgG autoantibodies against the NMDAR in CSF and/or serum and predominantly affects young women (Dalmau et al., 2008). Despite marked neurological disturbance, only 35–50% of patients have abnormal neuroimaging and the course of the disease is typically monophasic (Barry et al., 2015). An overlap has recently been recognised between anti-NMDAR encephalitis and inflammatory demyelinating disorders, particularly neuromyelitis optical spectrum disorder (NMOSD) (Titulaer et al., 2014). We describe two patients with an initial presentation consistent with anti-NMDAR encephalitis who have subsequently developed relapsing-remitting multiple sclerosis (MS).

## 1.1. 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 (Fig. 1a and b). None of the lesions showed enhancement after the administration of gadolinium contrast.

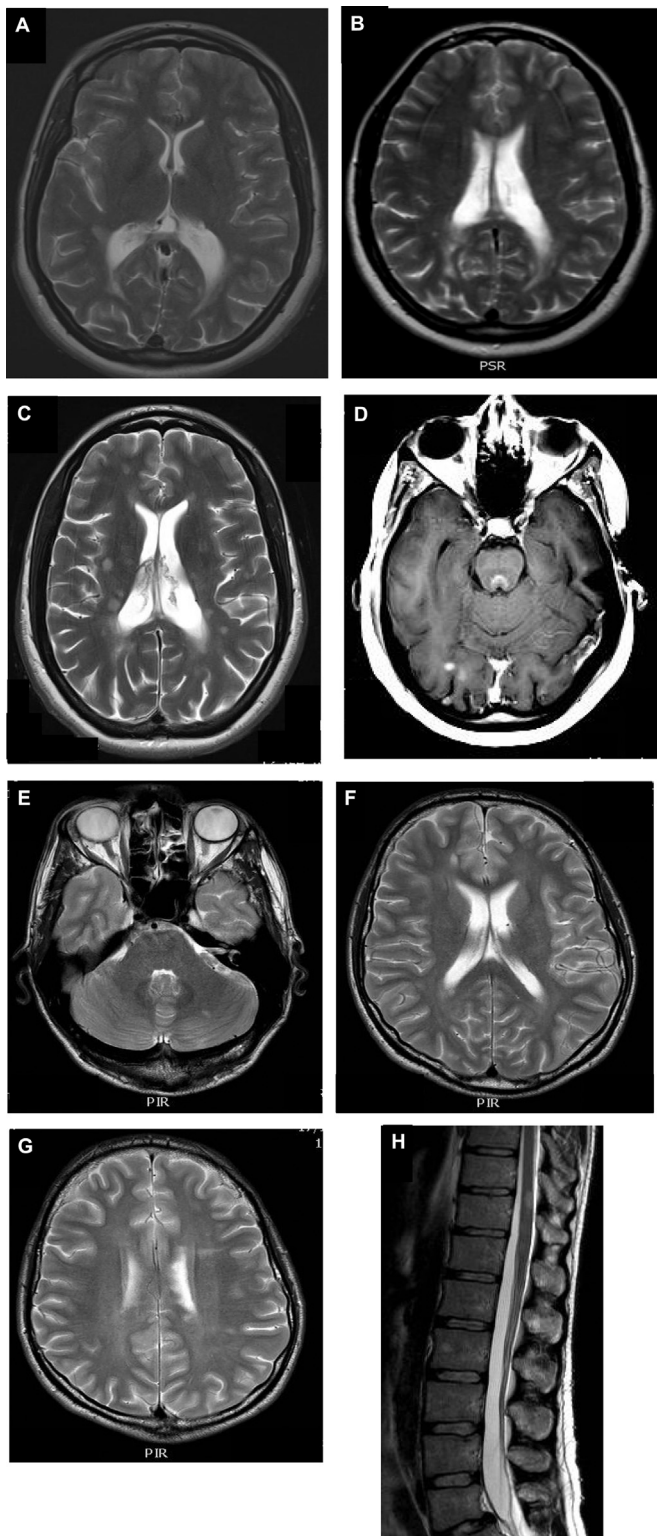
A cerebrospinal fluid (CSF) examination showed a mild lymphocytic pleocytosis (white cell count  $12 \times 10^6/L$ , protein 61 mg/dL) and unmatched oligoclonal bands not present in serum. Anti-NMDAR antibodies were positive in serum and not checked in CSF. A whole body CT-PET scan and pelvic ultrasound 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 (Fig. 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.

## 1.2. 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 (Fig. 1e–f) 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

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**Fig. 1.** Images A – C showing T2-weighted axial brain scans in May 2011 (A + B) and a follow up scan showing new lesions in September 2012 (C). Image D post-contrast T1-weighted image showing an enhancing lesion in the dorsal brainstem. Images E – G showing T2-weighted axial brain scans done at the time of the presenting illness in 2007 showing multiple T2 brain lesions. Image H T2-weighted sagittal image from December 2010 showing a cord lesion at T10.

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 (Fig. 1h). 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.

## 2. 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 (Uzawa et al., 2012; Ramberger et al., 2015; Fleischmann et al., 2015). 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 (Waschbisch et al., 2014). In contrast to MS, anti-NMDAR encephalitis may overlap much more frequently with NMOSD (Barry et al., 2015). 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 (Titulaer et al., 2014). In half of cases the demyelinating events were concurrent with the anti-NMDAR encephalitis and half were disseminated in time (Titulaer et al., 2014).

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 (Armangue et al., 2013, Apr). 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 MS (Ramberger et al., 2015).

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.

### Disclosures

Dr Chard has received honoraria (paid to his employer) from Ismar Healthcare NV, Swiss MS Society, Excemed (previously Sero Symposia International Foundation), Merck, Bayer and Teva for faculty-led education work; Teva for advisory board work; meeting expenses from Merck, Teva, Novartis, the MS Trust and National MS Society; and has previously held stock in GlaxoSmithKline. Dr Trip has received an honorarium from Teva for faculty-led education work and financial support to attend educational meetings from Teva, Novartis and Biogen.

### Acknowledgements

Dr Chard has received research support from the MS Society of Great Britain and Northern Ireland. Dr Chard and Dr Trip are both supported by the National Institute for Health Research University

College London Hospitals Biomedical Research Centre.

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