CASE REPORT

Periventricular white matter lesion and incomplete MRZ reaction in a male patient with anti-*N*-methyl-D-aspartate receptor encephalitis presenting with dysphoric mania

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SUMMARY

Several findings suggest that there may be an overlap of anti-*N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis with neuromyelitis optica spectrum disorders or acute demyelinating encephalomyelitis (ADEM)-like demyelination. We present a case of a patient with anti-NMDAR antibody encephalitis, who on MRI featured a single prominent T2-hyperintensive white matter lesion in the periventricular region, adjacent to the anterior horn of the left lateral ventricle. In view of the lesion location and the cerebrospinal fluid (CSF) findings (incomplete MRZ (measles, rubella and varicella zoster) reaction, lymphocytic pleocytosis, intrathecal IgG and IgM synthesis; absence of aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibodies), the presence of a multiple sclerosis-like immune response was discussed. This case appears to add evidence to the hypothesis of an overlap between anti-NMDAR antibody encephalitis and other inflammatory central nervous system diseases.

BACKGROUND

In anti-*N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis, the cerebrospinal fluid (CSF) shows inflammatory changes in most patients whereas brain MRI shows abnormalities in less than 50% of patients.[1] Generally, an intrathecal synthesis of NMDAR IgG is detected.[2]

Although often transient, white matter lesions have been observed in anti-NMDAR antibody encephalitis.[3] Recently, even extensive and clinically relevant demyelination has been described. In the majority of these patients, antibodies against either aquaporin 4 (AQP4) or myelin oligendrocyte glycoprotein (MOG) were detected, suggesting an overlap of neuromyelitis optica (NMO) spectrum or acute demyelinating encephalomyelitis (ADEM)-like demyelination with anti-NMDAR antibody encephalitis.[4 5] An association of NMDAR antibody encephalitis with multiple sclerosis (MS) was not found, despite MS being by far the most common demyelinating central nervous system (CNS) disorder. MS is associated with intrathecal production of IgG directed against multiple infectious agents, often measles, rubella and varicella zoster (MRZ).[6] The so-called MRZ reaction has been claimed to predict MS with a high degree of specificity.[7]

We present a case of a patient with anti-NMDAR antibody encephalitis with CSF findings suggesting a MS-like immune response. We believe that this case adds a new aspect to the accumulating evidence indicating a possible overlap between NMDAR antibody encephalitis and demyelinating diseases.

CASE PRESENTATION

A 34-year-old man was brought to our psychiatric ward by the police following aggressive and disorganised behaviour in public. The patient's colleagues reported that behavioural problems (primarily impulsivity, aggressiveness and hostility) had been present for approximately 1 week. Clinically, the patient had a dysphoric mania with psychotic symptoms (logorrhoea, increased drive with violent outbursts, agitation, accelerated and partly incoherent thinking, paranoid ideation with hyper-religiosity and slight persecutory delusion, dysphoric mood and disturbed sleep–wake cycle with reduced need to sleep). Apart from slightly increased distractibility and reduced attention/concentration, there was no cognitive or mnestic dysfunction. The physical (including neurological) examination was completely normal. The patient's family history was inconspicuous with regard to neurological or psychiatric disorders. Pharmacotherapy with olanzapine (20 mg/day) and lorazepam (up to 8 mg/day) was established resulting in reduction of impulsivity, aggressiveness and agitation, whereas psychotic symptoms persisted. An MRI of the brain (performed approximately 9 days after onset of symptoms) demonstrated a T2-hyperintensive white matter lesion immediately adjacent to the anterior horn of the left lateral ventricle as well as a slight hippocampal asymmetry (left>right); gadolinium could not be applied due to the patient's behavioural disturbance. Analysis of the CSF (approximately 11 days after onset of clinical symptoms) showed a lymphocytic pleocytosis (33 leucocytes/μL (normal <5/μL), 97% lymphocytes, 2% monocytes, 1% plasma cells), a mild blood–CSF barrier dysfunction (total protein 584 mg/mL, CSF/serum albumin ratio 7.2×10^{-3}, normal $<6.3\times10^{-3}$) and intrathecal immunoglobulin synthesis (IgG 29%, IgM 74%, isolated oligoclonal IgG bands in the CSF). Consequently, treatment with methylprednisolone (500 mg per day intravenously for five days), ceftriaxone (2 g intravenously) and aciclovir (750 mg

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three times per day intravenously) was initiated and the patient was transferred to the department of neurology. Further work up of the CSF revealed increased CSF/serum antibody indices for both VZV and rubella (6.1 and 1.7, respectively, normal ≤1.4) indicating an autoimmune origin of the inflammatory CSF changes. CSF CXCL13 was moderately increased (65 pg/mL, normal ≤10 pg/mL) within a range also seen in other autoimmune diseases, such as MS.[8] Anti-NMDAR IgG was positive in serum and CSF at equal titres of 1:100, indicating intrathecal synthesis of anti-NMDAR IgG. Anti-AQP4 and anti-MOG antibodies (both measured by a cell-based assay)[4] in serum were negative (blood specimen taken approximately 11 days after symptom onset). Subsequently, the antiviral and antibiotic therapy was stopped. Steroid treatment was reduced to oral prednisolone 100 mg once daily and then tapered out. The patient received 30 g of immunoglobulins intravenously on five consecutive days. A second MRI, performed after treatment, provided no further information (application of gadolinium was planned; however, due to the patient's behavioural abnormalities the examination had to be stopped). Repeat CSF analysis (performed 23 days after the first lumbar puncture) showed 8 leucocytes/μL; CSF CXCL13 had dropped below detection level (<7.8 pg/mL). No abnormalities were revealed with whole-body F-fluorodeoxyglucose-positron-emission tomography (FDG-PET) CT, CT of the abdomen and thorax, and sonography of the testicles. Serum α-fetoprotein and β-human chorionic gonadotropin were negative. The patient was found to suffer from hepatitis C, genotype 3a, but a relation to the current affection was not apparent.

OUTCOME AND FOLLOW-UP

Despite complete recovery, the patient was constantly worried and wished for further in-patient monitoring in his home country. Therefore, he was transferred to a hospital in his home country. A personal correspondence via email (ZU) 6 months after the discharge of the patient was completely in line with the assumption of a stable recovery.

DISCUSSION

Our case showed one prominent periventricular white matter lesion on MRI (however, it was unspecific and without application of gadolinium), and lymphocytic CSF pleocytosis associated with prominent intrathecal IgG and IgM synthesis approximately on day 11 after onset of symptoms. Although the absolute numbers were low (6 of 44 patients), Irani *et al*[3] reported that subcortical white matter lesions were more likely to be detected during the later course of the disease. As NMDARs are predominantly expressed in neurons, the pathophysiology of white matter lesions in anti-NMDAR antibody encephalitis has remained unknown until an association of anti-NMDAR antibody encephalitis with NMO and demyelination of ADEM-like aetiology, as judged by the presence of anti-AQP4 and anti-MOG antibodies, respectively, was published.[4] In our patient's serum, both antibodies were lacking. In contrast, CSF analysis showed increased CSF/serum antibody indices for rubella and for VZV. This polyspecific antiviral intrathecal immune response, also called MRZ reaction (incomplete in our case), has been judged to be strongly indicative of (autoimmune) inflammation and for the presence of tertiary lymphoid organs within the CNS compartment.[9] The MRZ reaction may represent one of the most specific laboratory findings in MS,[6] a much more common demyelinating disease compared with NMO or ADEM. A positive MRZ reaction in the CSF has not been reported in association with anti-NMDAR antibody encephalitis. The MRZ reaction only rarely occurs in NMO[10] and its presence allows to differentiate MS from ADEM.[11] CXCL13 is a B-lymphocyte-attractant chemokine that has been shown to correlate with the clinical course of MS, and with the presence of intrathecal IgG synthesis and of a positive MRZ reaction.[8] The rapid drop of CXCL13 levels after immunomodulatory treatment was associated with excellent long-term recovery in our patient. This is in line with previous results indicating that normal CXCL13 levels at 2–6 months after disease onset are associated with a favourable outcome.[12] However, the value of short-term CSF CXCL13 measurement to assess treatment response in anti-NMDAR antibody encephalitis needs further investigation.

Learning points

- Anti-*N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis occasionally occurs with white matter lesions.
- There might be an overlap between anti-NMDAR antibody encephalitis and certain inflammatory (demyelinating) central nervous system diseases.
- The value of short-term cerebrospinal fluid CXCL13 measurement to predict response to first-line treatment in anti-NMDAR antibody encephalitis needs further investigation.

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