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Development of anti-NMDA receptor encephalitis in a patient with multiple sclerosis

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SUMMARY

Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis is a rare subtype of autoimmune encephalitis, often presenting with early-onset, disease-specific neuropsychiatric symptoms. This case report describes a female patient with relapsing-remitting multiple sclerosis (RRMS) who developed anti-NMDA receptor encephalitis while receiving disease-modifying treatment. She exhibited neurocognitive symptoms and atypical magnetic resonance findings. Clinical and laboratory findings, including lumbar puncture, confirmed the presence of IgG antibodies against the GluN1 subunit of the NMDA receptor, establishing the diagnosis. First-line therapy with methylprednisolone and plasma exchange proved refractory, and immunoglobulin therapy yielded only a suboptimal response. Rituximab achieved the optimal therapeutic effect; however, therapy was followed by recurrent COVID-19 infection in this previously unvaccinated patient. This report highlights the complexities of diagnosis, differential considerations, therapeutic strategies and the detrimental impact of anti-NMDA receptor encephalitis and RRMS on the patient's quality of life.

BACKGROUND

Autoimmune encephalitis is an immune-mediated central nervous system (CNS) disease with a wide range of clinical presentations and unique disease-specific serology.[1] Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis is the most studied type, with a progressive clinical course and highly characteristic early neuropsychiatric features.[2] In contrast, multiple sclerosis (MS) is a chronic autoimmune, inflammatory, demyelinating and neurodegenerative disease of the CNS characterised by the dissemination of demyelinating lesions in time and space. There are several clinical forms of MS, with the most common being relapsing-remitting MS (RRMS).

A few cases of coexisting MS and anti-NMDA receptor encephalitis have been reported worldwide.[3–5] To the best of our knowledge, only one case report has described isolated neurocognitive impairment in a patient with anti-NMDA receptor encephalitis and MS, which resulted in a poor outcome.[6] Gaining a clinical understanding of superimposed anti-NMDA receptor encephalitis is crucial for timely recognition in patients with MS and for implementing effective diagnostic and personalised therapeutic strategies to optimise patient outcomes. This case report described the unique presentation of anti-NMDA receptor encephalitis in a female patient with a history of RRMS who developed prominent neurocognitive symptoms that were refractory to first-line immunosuppressive therapies.

CASE PRESENTATION

A woman in her late 30s with an 11-year history of RRMS, managed with teriflunomide, was admitted to the hospital. Over the past month, she had experienced double vision, decreased visual acuity, forgetfulness, gait and coordination disturbances and impaired urination and defecation. For the previous 10 years, her RRMS had remained in remission, with a functional disability score of 1.0 on the Expanded Disability Status Scale. Her medical history was notable for latent tuberculosis, for which she had completed a 4-month course of rifampin; she had no other chronic illnesses. Her family history was unremarkable. On admission, the patient exhibited significant cognitive impairments, including slowed information processing, delayed reaction time, working memory deficits, reduced sustained attention and verbal decline. Physical examination revealed conjugate gaze palsy in horizontal directions with reduced visual acuity in both eyes, while colour and contour perception remained intact. Muscle strength was mildly reduced (4/5) in the left leg and normal (5/5) in the other extremities per the Medical Research Council Muscle Strength Scale. Deep tendon reflexes were normal (2+) in the upper extremities but brisk (3+) in the lower extremities, with bilateral Babinski signs present. Sensation to touch, pain and temperature was preserved. Both arm and leg ataxia required hands-on assistance, and truncal ataxia was observed. Acute urinary retention necessitated catheterisation. The patient was initially started with intravenous methylprednisolone (1 g daily for 5 days) for a presumed MS relapse. However, owing to ongoing clinical deterioration and persistent cognitive and functional decline, five courses of acute plasmapheresis were initiated alongside further diagnostic evaluations.

INVESTIGATIONS

Blood test results

Complete blood count, coagulogram, C reactive protein level, comprehensive metabolic panel and thyroid function were normal. Infections were screened using a modified two-tiered test for Lyme disease, which detected positive IgG antibodies against *B. burgdorferi* but negative IgM *B. burgdorferi* antibodies, indicating a past Lyme disease infection. Latent tuberculosis was confirmed employing the QuantiFERON-Tuberculosis Gold Plus test. The

remaining tests were negative for the HIV-1 antigen, HIV-½ antibodies, hepatitis C and B virus antibodies, syphilis antibody, *Candida* and *Aspergillus* antigens. The rheumatological profile, including antinuclear antibody, dsDNA, c-ANCA, p-ANCA, ENA, lupus anticoagulant, anticardiolipin and anti-beta-2 glycoprotein-1 antibodies, was negative. Tumour markers, such as CA 125, CA 19–9, CA 15–3 and beta-2 microglobulin, M protein, remained negative. Serum AQP4 IgG antibodies were not detected.

Cerebrospinal fluid analysis

Cerebrospinal fluid analysis (CSF) was clear and transparent. The total count of mononuclear cells (25 cells/µL, 100%) indicated lymphocytic pleocytosis. Protein 0.33 g/L (normal range 0.23–0.38 g/L), glucose 3.17 mmol/L (normal range 2.77–4.44 mmol/L) and lactate level 2.03 mmol/L (normal range 0.6–3.1 mmol/L) remained within normal ranges. However, IgG was slightly elevated at 31.5 mg/L (normal range 10–30 mg/L), and oligoclonal bands were positive.

The infection profile of the CSF was negative for *B. burgdorferi* IgM and IgG antibodies (ELISA), cytomegalovirus (PCR), *Epstein-Barr virus* (PCR), *herpes simplex virus type* 1 and 2 (PCR), *Varicella Zoster* virus (PCR), *M. tuberculosis* (PCR) and *Toxoplasma gondii* (PCR). CSF culture did not reveal pathogen growth. Paraneoplastic antibodies in the CSF—including anti-amphiphysin, anti-CV2, anti-PNMA2, anti-SOX1, anti-RI, anti-Yo, anti-Hu, anti-Recoverin, anti-Titin, anti-Zic4, anti-GAD65 and anti-Tr—were all negative. Flow cytometry and cytological analyses did not detect any tumour markers in the CSF. Anti-MOG antibodies were absent in the CSF; however, intrathecal IgG anti-GluN1 antibodies were detected at a titre of 1:3.2 using the standard immunofluorescence test (IFT), confirming the diagnosis of anti-NMDA encephalitis.

Imaging studies

Routine CT of the head, chest, abdomen and pelvis were unremarkable. Transvaginal ultrasonography revealed a uterine myoma. Brain MRI was compared with the baseline images, revealing new demyelinating lesions in the temporal lobes, brainstem, cerebral peduncle and pons (figure 1). MRI of the brain before and after gadolinium contrast revealed patchy enhancement of the contrast along the optic chiasm and trigeminal nerves bilaterally (figures 2 and 3).

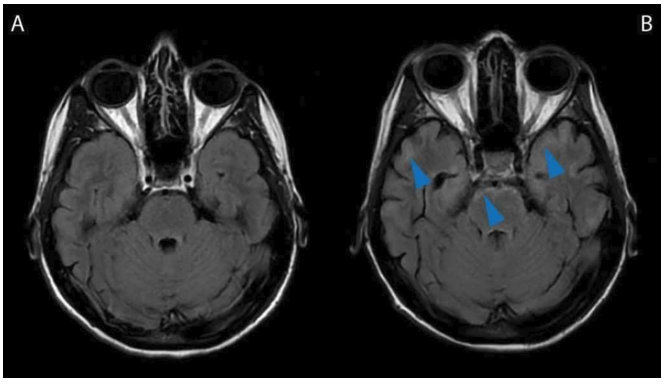

Figure 1 (A) Axial fluid-attenuated inversion recovery MRI of the head at baseline, showing no abnormalities. (B) Axial fluid-attenuated inversion recovery MRI at admission showing bilateral subcortical hyperintensity in the temporal lobes and a thin-rimmed hyperintensity in the pons (blue arrowheads).

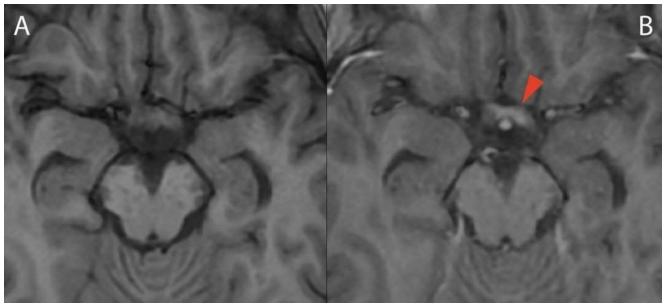

Figure 2 (A) Axial T1-weighted MRI of the head without contrast. (B) Axial T1-weighted contrast-enhanced MRI revealing patchy enhancement along the optic chiasm (red arrowhead).

On day 9 of hospitalisation, the patient's level of consciousness became stuporous, with a Glasgow Coma Scale score of 6 despite receiving first-line treatment. Generalised hypotonia and roving eye movements were observed. The patient was immediately intubated to initiate invasive mechanical ventilation. Electroencephalography revealed no epileptic activity. Consequently, chest radiography was warranted owing to abrupt changes in the patient's oxygen saturation and arterial blood gas, which revealed a ventilator-associated pneumothorax of the right lung that was successfully drained using a catheter with a vacuum bottle.

Repeated head MRI revealed a subacute stroke of presumed undetermined aetiology in the left superior cerebellar artery (SCA) (figure 4). Routine stroke evaluations, including electrocardiography, transthoracic echocardiography and transcranial and carotid duplex ultrasound, did not reveal structural or functional aberrations. Brachiocephalic CT and digital subtraction angiography did not reveal signs of vasculitis or stenosis. However, an MRI of the spinal cord showed mostly marginally localised multiple short chronic demyelinating lesions in the cervical and thoracic segments, reflecting a diagnosis of MS. Pelvic MRI showed no sign of a teratoma. Follow-up body positron emission tomography (PET) was performed to exclude oncological processes, and no atypical metabolic activity was observed.

DIFFERENTIAL DIAGNOSIS

A presumptive diagnosis of acute MS relapse was initially made; however, resistance to first-line therapies and the rapidly progressive clinical course made this diagnosis unlikely. Infectious encephalitis was ruled out based on the rapid disease progression and a negative CSF profile (PCR, serology and culture), despite the bilateral temporal lobe involvement, typical of HSV encephalitis.

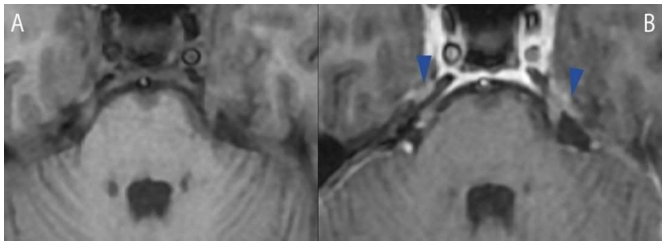

Figure 3 (A) Axial T1-weighted MRI without contrast. (B) Axial T1-weighted contrast-enhanced MRI showing slight bilateral enhancement along the trigeminal nerves (blue arrowheads).

Progressive multifocal leucoencephalopathy (PML) was included in the differential diagnosis owing to its progressive nature and refractory response to first-line therapies. It could be acquired through opportunistic John Cunningham virus (JCV) infection owing to disease-modifying therapy for MS, though it is more commonly associated with natalizumab use.[7] Teriflunomide is unlikely to cause PML. JCV testing was not performed owing to the low clinical suspicion for the disease. Furthermore, no typical white matter lesions were observed on the head MRI.

Another diagnosis that overlaps with this clinical presentation is posterior reversible encephalopathy syndrome (PRES). It is characterised by sudden changes in mental state, decreased visual acuity and other focal neurologic signs. MRI findings of subcortical hyperintensities in the bilateral temporal lobes and pons support this diagnosis; however, the posterior and occipital lobes tend to be affected more frequently.[8] The condition is reversible once arterial hypertension, a known triggering factor, is managed.[9] A diagnosis of PRES is unlikely because of changes in mental status, psychiatric symptoms, cranial nerve involvement, disease course and laboratory and MRI findings.

Neurosarcoidosis can present with systemic involvement or as isolated CNS sarcoidosis. The diagnosis of this condition is particularly challenging because of its non-specific clinical manifestations and laboratory findings. Perineural enhancement of the optic chiasm and bilateral trigeminal nerves on contrast-enhanced head MRI (figures 2 and 3) was suggestive of neurosarcoidosis, given that optic nerve involvement is the second most common finding among all cranial neuropathies.[10] Follow-up body PET was performed with head MRI to aid differentiation, but no atypical metabolic activity was observed. Neurosarcoidosis has been considered a last-resort diagnosis because a definitive diagnosis can only be made with a positive tissue biopsy. In this case, our patient did not undergo brain biopsy, and the diagnosis of neurosarcoidosis was excluded based on laboratory results, clinical manifestations and MRI findings. However, isolated neurosarcoidosis was the main differential diagnosis that needed to be ruled out in this case.

Cranial nerve involvement should also prompt consideration of CNS lymphoma, which can affect the CNS parenchyma, dura, leptomeninges, cranial nerves, spinal cord,[11] frontal lobe and basal ganglia.[12] However, CNS lymphoma typically presents on MRI with multiple enhancing[13] lesions or a single homogeneously enhancing parenchymal mass.[14] In our case, the patient did not have multiple enhancing lesions with necrotic regions but exhibited subcortical hyperintensities with cranial nerve involvement. Additionally, the CSF cytology and flow cytometry of the CSF were negative. Li *et al* described a case in which primary CNS lymphoma was misdiagnosed in a patient with NMDA receptor antibody-positive blood and CSF. The patient's condition deteriorated without appropriate treatment.[15] However, in our case, the patient improved without lymphoma-specific therapy and has remained stable during long-term follow-up.

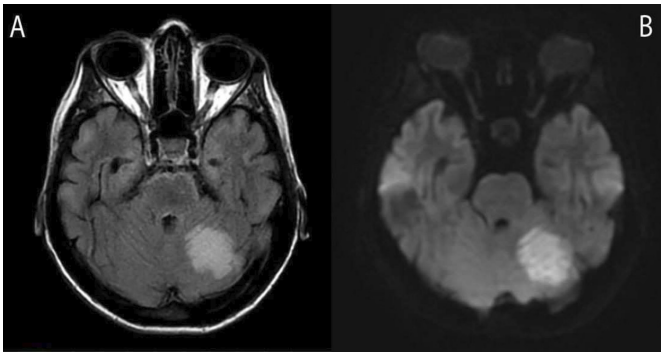

Figure 4 (A) Axial fluid-attenuated inversion recovery MRI demonstrating an ischaemic lesion in the left superior cerebellar artery territory. (B) Axial diffuse-weighted MRI revealing typical diffusion restriction in the same region.

Myelin oligodendrocyte glycoprotein antibody-associated disorder (MOGAD) is a rare CNS inflammatory disease characterised by optic neuritis, transverse myelitis, acute disseminated encephalomyelitis and cortical encephalitis with typical MRI features, including lesions affecting the brainstem, deep white matter, cortical areas, bilateral optic neuritis and extensive longitudinal spinal cord lesions.[16] In our case, anti-MOG antibodies were negative in the CSF, and serum testing was not performed, as recent studies suggest that MOG-IgG can be present in the CSF of seronegative MOGAD patients.[17] Therefore, a diagnosis of MOGAD was excluded.

Anti-NMDA encephalitis was considered the leading diagnosis, despite the absence of hallmark psychiatric features, owing to the presence of cognitive impairment. The presence of cerebrospinal pleocytosis or oligoclonal bands, along with cognitive symptoms (impaired memory formation and slow mental processing), speech dysfunction (reduced verbal output) and rapid decline in consciousness, was insufficient to meet the clinical criteria for anti-NMDA receptor encephalitis.[2] However, a definitive diagnosis was established once IgG antibodies against GluN1, a major subunit of the NMDA-type glutamate receptor, were detected in CSF. Radiological criteria for anti-NMDA receptor encephalitis are yet to be universally accepted because of the wide range of MRI findings. However, it remains useful for ruling out other differential diagnoses. In most cases, head MRI appears normal; however, in this case, involvement of the medial temporal lobe was marked, making it the second most common lesion after the hippocampal region.[18] In our case, the patient met the diagnostic criteria for definite anti-NMDA receptor encephalitis, presenting with at least one major symptom (decreased level of consciousness, speech dysfunction or cognitive dysfunction) and positive IgG GluN1 antibodies in the CSF,[2] while other causes of encephalitis were excluded.

TREATMENT

Therapeutic resistance to methylprednisolone and five courses of plasmapheresis led to the initiation of empirical treatment for HSV encephalitis with acyclovir, alongside anti-tuberculosis therapy for previously detected latent tuberculosis. Acyclovir was administered three times per day at 10 mg/kg body weight. The anti-tuberculosis regimen consisted of isoniazid (300 mg), rifampicin (600 mg), pyrazinamide (2000 mg), moxifloxacin (400 mg), linezolid (600 mg) and dexamethasone (12 mg). Additionally, antifungal treatment with intravenous fluconazole (800 mg) was started while awaiting CSF test results. All antimicrobial therapies were discontinued once the CSF infection profile returned negative. For secondary stroke prevention, daily oral aspirin (100 mg) was initiated. On detecting specific IgG antibodies against GluN1 in the CSF, a 5-day course of intravenous immunoglobulin (0.4 g/kg body weight) was administered. Despite regaining spontaneous breathing, the patient continued to experience cognitive deficits, limb and truncal ataxia and urinary retention, prompting treatment with intravenous rituximab (1000 mg). A second dose was administered 6 weeks later owing to purulent cystitis.

OUTCOME AND FOLLOW-UP

At discharge, the patient's consciousness had fully recovered (GCS 15), and horizontal eye movements were restored. She could reposition herself independently but remained dependent on an indwelling urinary catheter, and persistent ataxic gait required walking aids and rehabilitation. She recognised family members again, though deficits in information processing speed and working memory persisted, per follow-up neuropsychological evaluation.

Within 3 months of discharge, she contracted COVID-19 twice. The second episode led to severe viral pneumonia with secondary bacterial infection, successfully treated with remdesivir, imipenem and ciprofloxacin.

Over the next 3 months, considerable improvements in gait and urinary control were observed. Enhancements in executive function, verbal fluency and mental flexibility allowed her to resume daily activities and return to work.

Follow-up MRI revealed post-encephalitic atrophic changes in the bilateral temporal lobes and post-ischaemic encephalomalacia in the left cerebellar lobe (figure 5).

At the 2 year follow-up, the patient remains relapse-free on ponesimod, with an Expanded Disability Status Scale score of 2.0.

DISCUSSION

Anti-NMDA receptor encephalitis is mediated by immunoglobulin G antibodies targeting the GluN1 subunit of the glutamate NMDA receptor. It is primarily associated with ovarian teratomas and sporadic herpes simplex encephalitis.[2] However, the underlying neuroimmunological mechanisms linking autoimmune encephalitis to demyelinating diseases remain unclear. Proposed theories include T-cell autoreactivity, genetic predisposition, pro-inflammatory cytokines and microbiota influences, which may help explain the pathogenic overlap of these distinct disorders in the future.[19] Several cases of anti-NMDA receptor encephalitis have been reported in association with MOGAD and neuromyelitis optica spectrum disorder.[20] While MS is no exception, only a handful of documented cases support the growing recognition of anti-NMDA receptor encephalitis coexisting with MS. A study by Zhang *et al* identified only 15 MS cases among 79 demyelinating disease patients with anti-NMDA receptor encephalitis in a PubMed database review.[21] Psychiatric symptoms are key to early recognition, especially in MS patients, as demonstrated in case studies by Suleman and Javed,[3] Gulec *et al*[4] and Chahal *et al*.[5] These symptoms appear in 83% of anti-NMDA encephalitis cases and often accompany cognitive dysfunction.[18] However, cognitive dysfunction alone may be misinterpreted as MS progression or relapse, delaying proper diagnosis and treatment. Fleischmann *et al* described a woman with RRMS initially misdiagnosed with an MS relapse owing to cognitive impairment and refractory therapeutic response. Her correct diagnosis of anti-NMDA receptor encephalitis was only made years after progressive cognitive decline and re-examination of previously obtained CSF samples, resulting in a poor prognosis despite temporary stabilisation with immunosuppressive therapy.[22] According to Dalmau *et al*, a definitive diagnosis of anti-NMDA receptor encephalitis necessitates IgG GluN1 antibodies and at least one major symptom.[2] In our case, diagnosis was confirmed through the presence of IgG GluN1 antibodies in the CSF—known to be more sensitive than serum testing[23] along with cognitive dysfunction, speech reduction and a subsequent decline in consciousness, meeting the criteria for definite anti-NMDA receptor encephalitis. Hummert *et al* found a correlation between IgG GluN1 titers and clinical severity;[24] however, despite severe symptoms, our patient exhibited a low IgG GluN1 titre, likely owing to prior first-line therapy administration. CSF NMDA receptor antibodies demonstrate high specificity for anti-NMDA receptor encephalitis. A study involving 431 patients (including 412 with paired serum and CSF samples) found no cases where antibodies were exclusively present in serum.[25] However, diagnosis should not rely solely on antibody presence; fulfilling clinical criteria remains essential. The IgG subclass is highly specific compared with less reliable IgA or IgM antibodies.[26] In a study of 240 patients with conditions such as stroke, dementia and schizophrenia, 11 had IgA, IgM or both, but none had serum IgG NMDA receptor antibodies.[26] Live neuron cultures showed that all 40 serum samples with IgG NMDA receptor antibodies exhibited cell surface reactivity, compared with only three samples with IgM and one with IgA, underscoring IgG's pathognomonic role.[26] Experimental studies further suggest that while IgG NMDA receptor 1 antibodies do not induce brain inflammation, they can trigger psychosis-like symptoms.[27] Although anti-NMDA receptor antibodies can be detected in both serum and CSF, CSF testing is crucial to avoid false-positive and false-negative results. Low serum titres have been reported in individuals without anti-NMDA receptor encephalitis or immune-mediated CNS disorders.[28] Many laboratories use commercially available HEK cell-based assays that co-express GluN1/GluN2 subunits, which can yield inaccurate results.[29] For instance, patients with systemic lupus erythematosus and neurocognitive impairment may produce antibodies against the GluN2 subunit, leading to false positives.[29] An indirect immunofluorescence assay targeting the GluN1 subunit in CSF is recommended, though indeterminate results may still occur.[30] In uncertain cases, specialised in-house cell-based assays provide greater specificity but require expertise for accurate interpretation.[30] The breakdown of blood-brain barrier integrity, a known feature of MS demonstrated in experimental autoimmune encephalomyelitis models,[31] may explain how GluN1 antibodies infiltrate the CNS. Acting as NMDA receptor antagonists, these antibodies contribute to the characteristic clinical features of anti-NMDA receptor encephalitis.[32] Given the high mortality rate of anti-NMDA receptor encephalitis, clinicians should emphasise the importance of recognising severe cognitive symptoms in patients with MS, particularly those with fulminant disease that remains refractory to treatment. Above all, fluctuations in mental status, rapid cognitive decline, verbal reduction and dysautonomia should be considered atypical for MS relapse. These indications can facilitate the timely identification of anti-NMDA receptor encephalitis.[33]

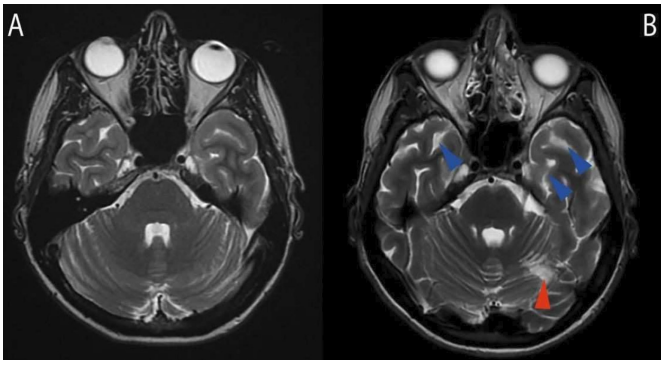

Figure 5 (A) Axial T2-weighted MRI at baseline, showing no structural changes. (B) Follow-up axial T2-weighted MRI demonstrating bilateral temporal lobe atrophy (blue arrowhead) and post-ischaemic encephalomalacia in the left cerebellar lobe (red arrowhead).

The role of pro-inflammatory cytokines in the pathogenesis of anti-NMDA receptor encephalitis has been extensively studied. In particular, high intrathecal levels of CXCL13, IL-6 and IL-17A have been associated with treatment resistance, disease severity and poor clinical outcomes.[6] Local inflammatory processes have also been implicated in thrombotic events, though the precise mechanism remains unclear.[34] Ischaemic stroke in the context of anti-NMDA receptor encephalitis is rare. However, individuals seropositive for NMDA receptor 1 antibodies have been shown to exhibit an elevated cardiovascular risk within 3 years following their first mild-to-moderate ischaemic stroke, independent of other risk factors.[35] One notable case involved a 12-year-old girl who developed acute ischaemia in the left frontoparietal lobe following a diarrhoeal illness, as confirmed by MRI and magnetic resonance angiography.[36] A large study found that NMDA receptor antibodies are associated with greater ischaemic injury in APOE4 allele carriers owing to blood-brain barrier disruption. Conversely, in individuals with an intact blood-brain barrier, anti-NMDA antibodies provided protection and led to better clinical outcomes.[37] In our case, it is plausible that NMDA receptor antibodies exacerbated the ischaemic lesion size. The stroke was not attributed to genetic vasculopathies like cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), a commonly overlooked cause of stroke in this clinical context. Although the patient had no family history of stroke, dementia or vascular encephalopathy, her young age and bilateral subcortical hyperintensities, particularly in the temporal lobes, raised suspicion. However, typical MRI findings of CADASIL, such as lacunar infarctions, cerebral microbleeds and hyperintensities in the external capsule and corpus callosum, were absent.[38–40] Given the possibility of an underlying genetic vasculopathy, NOTCH3 gene testing should be considered. The ischaemic pattern in our patient was consistent with an embolic stroke, though no thrombus was directly visualised in the left SCA on CT angiography. It was presumed to be located deeper within the smaller SCA branches. A comprehensive evaluation ruled out well-established thromboembolic sources, including cardiac and hypercoagulable states. As the most typical causes of stroke in young individuals have been ruled out, the aetiology is attributed to NMDA receptor encephalitis, likely owing to in situ thrombosis resulting from immunothrombotic dysregulation.

Titulaer *et al* found that anti-NMDA receptor encephalitis is more severe in patients under 45 years of age, but early diagnosis and treatment lead to better functional outcomes.[41] Despite complications following discharge, our patient achieved a favourable prognosis and fully recovered after 169 days of illness. The use of rituximab as second-line therapy was necessary, even though the patient was unvaccinated against COVID-19 and contracted the infection twice. Nevertheless, when considering rituximab in clinical practice, precautions should include reviewing vaccination records and conducting an individual risk-benefit assessment. Screening for hepatitis virus is also mandatory before initiating rituximab therapy.

The heterogeneous presentation of anti-NMDA receptor encephalitis, which may mimic MS relapse, poses a global challenge for healthcare professionals in ensuring early recognition and timely intervention. Given our limited understanding of its coexistence with MS, recognising dysexecutive cognitive impairment at an early stage is crucial. This underscores the need for interdisciplinary collaboration and patient-centred care coordination to optimise outcomes.

Learning points

- Patients with relapsing-remitting multiple sclerosis may concurrently develop autoimmune central nervous system disorders.
- Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis can manifest as isolated neurocognitive dysfunction, ranging from mild to severe cognitive impairment.
- Immunothrombotic dysregulation in anti-NMDA receptor encephalitis may trigger an ischaemic cerebrovascular event.
- Rituximab is an effective treatment for anti-NMDA receptor encephalitis but carries a risk of severe infection; therefore, a risk-benefit assessment should be performed before initiating therapy.

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