Case Report
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AQP4-IgG-Seropositive Patient Who Silently Carried Anti-NMDAR Antibodies Developed Encephalitis During A Relapse

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ABSTRACT

The association of autoimmune diseases is relatively common. Comorbidity anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis and Neuromyelitis Optica Spectrum Disorder (NMOSD) is an unusual and rare overlapping syndrome. We report the case of an AQP4-IgG-seropositive NMOSD patient who developed anti-NMDAR encephalitis during corticosteroid treatment for a relapse of Longitudinal Extensive Transverse Myelitis (LETM), with the presence of anti-NMDAR antibodies in the serum two years earlier. The patient showed significant improvement in both clinical syndromes with a good response to steroid and immunosuppressive therapy. Conclusion Early diagnosis and treatment of overlapping autoimmune syndromes, such as AQP4+IgG seropositive NMOSD with anti-NMDAR encephalitis, are key factors for ensuring early and better recovery outcomes.
Keywords: *Encephalitis, Anti-N-Methyl-D-Aspartate Receptor, Neuromyelitis Optica Spectrum Disorders (NMOSD), Overlap Demyelinating Syndrome, AQP4, NMDA*

Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an antibody-mediated disorder of the central nervous system with three cardinal manifestations: transverse myelitis, optic neuritis, and area-postrema syndrome. In 2005, a protein that acts as a water channel, aquaporin 4 (AQP4), at the feet of an astrocyte was identified as the target of the anti-AQP4 antibody. Further studies demonstrated that anti-AQP4 activated the classical complement system and, together with interleukin-6, increased the permeability of

the blood–brain barrier. Moreover, it is a chemoattractant, signalling eosinophils and neutrophils to enter the evolving lesion and degranulate. Astrocyte injury occurs due to the effects of the complement membrane-attack complex. Demyelination is a secondary consequence of myelinolysis and oligodendrocyte injury (Sechi, 2024)

N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disease associated with cerebrospinal fluid (CSF) antibodies against the NR1 subunit of NMDAR. It is postulated that the antigen NMDAR, which may be expressed in nervous tissue-counting tumors (typically ovarian teratoma) or released by viral-induced neuronal disruption, is directly transported to local lymph nodes, resulting in the generation of memory B cells. With CD4+ T cells, naive B cells exposed to NMDAR become activated and cross the blood-brain barrier via the choroid plexus. It usually generates a picture of psychosis, working memory deficits, seizures, language disorders, catatonia, movement disorders, and dysautonomia in the later stages (Irani, 2024).

Here, we report the case of an AQP4-IgG-seropositive NMOSD patient who developed anti-NMDAR encephalitis during corticosteroid treatment for a relapse on Longitudinal Extensive Transverse Myelitis (LETM), with the presence of anti-NMDAR antibodies in the serum two years earlier.

Case Presentation

A 42-year-old male with a 19 year-history of AQP4+ NMOSD was admitted for relapse. The patient was treated with azathioprine alone at a dose of 225 mg/day.

His neurological history involved several hospitalizations due to disease relapse, presenting as sequelae of amaurosis of the right eye and moderate reduction in visual acuity of the left eye.

He was admitted to Ramos Mejia Hospital, Buenos Aires City, Argentina, with weakness in both lower limbs for two weeks that progressed to difficult in standing. Subsequently, patient had loss of sphincter control and decreased visual acuity in the left eye.

Neurological examination revealed amaurosis in the right eye, light perception in the left eye, sensory level with hypoesthesia from T2 with paraplegia, and urine retention.

It was interpreted as a relapse of his underlying pathology, and treatment was started with intravenous methylprednisolone at a dose of 1 g once daily for five days, with tapering of prednisone to 1 mg/kg weight plus his previous treatment of 225 mg/day of azathioprine.

During the hospitalization, a week after admission, the patient presented with generalized tonic/clonic seizures. He developed psychomotor excitement, disorganized speech, catatonia, and involuntary movements. Concomitant autoimmune encephalitis was to be ruled out. Routine blood tests, infectious disease screening, electroencephalogram (EEG), and CSF tests were all negative. Brain magnetic resonance imaging (MRI) showed hyperintense lesions on T2 and DWI hyperintense imaging in the right temporal lobe without enhanced gadolinium contrast (Fig. 1). Autoimmune encephalitis antibodies were further examined, and anti-NMDAR antibodies were detected in the CSF and serum (Fig. 2). Serum and CSF were negative for anti-CASPR2, AMPAR, LGI1, GABAB, and DPPX antibodies. Anti-AQP4 IgG was detected in the serum and CSF samples (Fig. 2). All antibody determination was performed using a cell-based indirect immunofluorescence assay (Euroimmun, Lubeck, Germany). A serum sample from a determination made for anti-AQP4 IgG two years ago was reviewed to identify anti-NMDAR antibodies and was found to be positive.

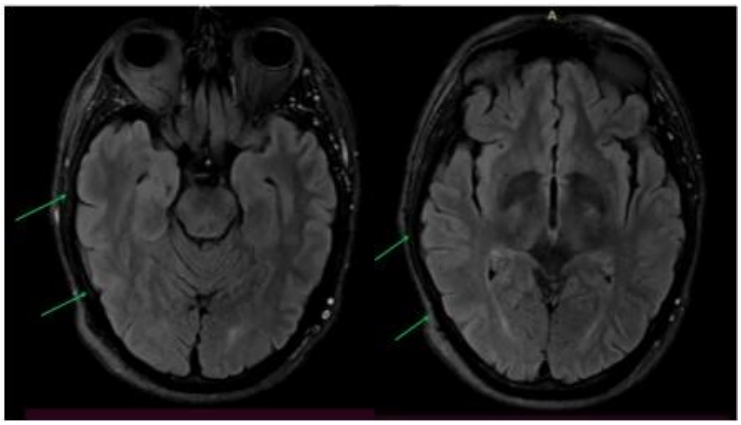

Figure 1: Brain magnetic resonance imaging (MRI) showed hyperintense lesions on T2 and DWI hyperintense imaging in the right temporal lobe without enhanced gadolinium contrast.

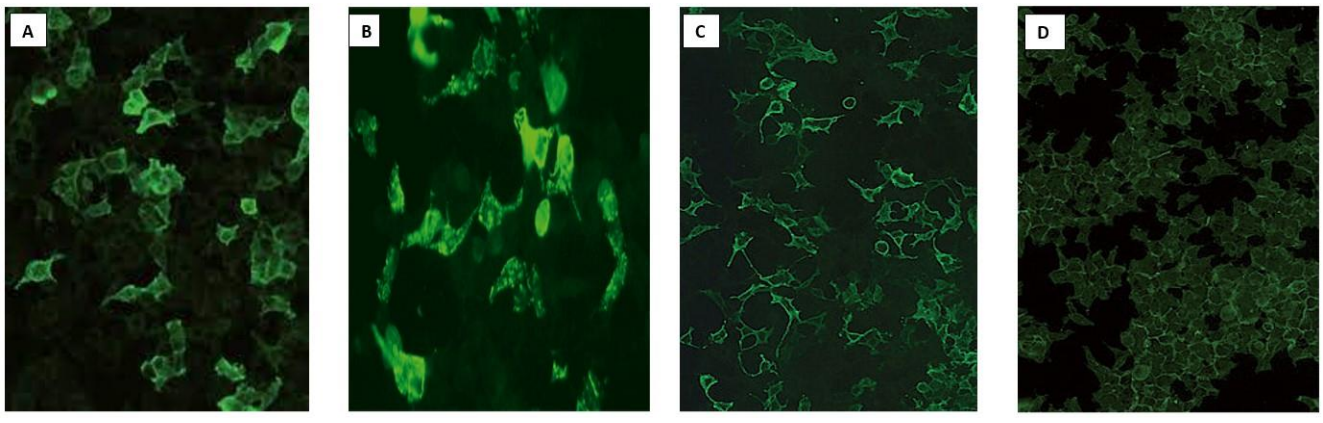

Figure 1: Demonstration of co-occurrence of NMDAR antibodies with aquaporin 4 antibodies in HEK293 cells transfected. (A), NMDAR-IgG serum, (B) NMDAR-IgG CSF, (C) AQP4-IgG serum, (D) AQP4-IgG CSF. A–D: magnification ×400.

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Further investigations, including paraneoplastic and vasculitis panels, yielded negative results. He was also examined using testicular ultrasonography and computed tomography (CT) of the chest, abdomen, and pelvis, which excluded teratomas and other tumours.

Treatment was started with levetiracetam 500 mg every 12 h along with continued azathioprine and prednisone 1 mg/kg orally. Patient had good clinical course, with slight recovery from his lower limb weakness and LE vision as well as remission of seizures and psychotic symptoms.

Discussion

We present the case of a patient who had a relapse of AQP4-IgG-seropositive NMOSD and developed anti-NMDAR encephalitis during immunosuppressive treatment with corticosteroids.

The association of autoimmune diseases is a relatively common occurrence, secondary to the systemic loss of immunological tolerance, and sometimes not limited to only one tissue or organ. Patients who are AQP4-IgG-seropositive often have coexisting autoimmune disorders, including Sjögren's syndrome, systemic lupus erythematosus, Hashimoto's disease, and myasthenia gravis (Villa *et al*., 2023; Nan *et al*., 2021). Additionally, anti-NMDAR encephalitis is associated with demyelinating diseases of the central nervous system, such as acute disseminated encephalomyelitis, myelitis, NMOSD, and MOG antibody-associated diseases (Tao *et al*., 2019). The co-morbidity of anti-NMDAR encephalitis and AQP4-IgG-seropositivity NMOSD has been less frequently reported (Tao *et al*., 2019).

Recent reviews have described AQP4-IgG-seropositive and anti-NMDAR encephalitis overlapping mainly in young women, averaging 33 years of age, who present with delayed encephalitis and NMOSD manifestations, with a low prevalence of ovarian teratoma. It is very rare in men. In general, the severity of clinical symptoms and signs in patients with overlapping syndromes indicates a worse prognosis than in patients with classic NMDAR encephalitis (Sinani *et al*., 2020). Our patient, a 42-year-old man, presented with encephalitis during treatment for a relapse of his underlying disease, AQP4-IgG-seropositive NMOSD, and had good recovery. The presence of anti-NMDAR antibodies in CSF confirmed this diagnosis. It is interesting to highlight the presence of anti-NMDAR antibodies detected in a sample stored in our serum library two years ago, at the time of diagnosis of NMOSD AQP4-IgG-seropositivity.

Although some studies have suggested a relationship between both antibodies (anti-AQP4 and anti-NMDAR), their correlation in patients with this comorbidity is limited. It has been postulated that AQP4 deficiency may lead to excessive glutamate discharge into the synaptic gap, generating excessive

reactivation of NMDA receptors and triggering a complement-dependent cytotoxicity mediated by AQP4 antibodies. However, immune complexes can form between AQP4 and NR3a subunits of NMDA receptors, suggesting that AQP4 may be involved in NMDA receptor attacks. Hence, AQP4 and NMDA may share functionality although the specific mechanisms require further investigation (Tao *et al*., 2019).

The presence of anti-NMDAR antibodies two years earlier suggests a potential mechanism for developing encephalitis whenever these antibodies are activated during a relapse.

It is necessary to have a high index of suspicion in patients diagnosed with NMOSD AQP4+ who present with atypical manifestations such as seizures, psychiatric disorders, and alterations in behaviour or memory to further investigate presence of other autoimmune diseases.

Further studies should determine whether the presence of anti-NMDAR autoantibodies previously in patients who are AQP4-IgG-seropositive could predict overlapping syndromes. Early diagnosis and treatment of overlapping autoimmune syndromes, such as AQP4+IgG seropositive NMOSD with anti-NMDAR encephalitis, are key factors for ensuring early and better recovery outcomes.

Conclusion / Highlights

Early diagnosis and treatment of overlapping autoimmune syndromes, such as NMOSD with anti-NMDA receptor encephalitis, are key factors in ensuring early and better recovery outcomes.

Conflict of Interest: The authors declare no conflicts of interest associated with this manuscript.

Consent: Informed consent for publication of clinical details, test results, and radiological images was obtained from all patients.

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