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Antineuronal antibodies: Anti-recoverin in neurological syndromes without retinopathy. SARS-CoV2 infection as a trigger☆

Anticuerpos antineuronales: anti-recoverina en síndromes neurológicos sin retinopatía. Infección por SARS-CoV2 como desencadenante

Dear Editor:

Central and peripheral nervous system diseases associated with presence of antibodies against neuronal epitopes are increasingly frequent. Researchers first identified autoantibodies targeting intracellular antigens, and subsequently autoantibodies targeting synaptic and cell surface proteins. These autoantibodies may appear in the context of tumours, as part of an indirect immune-mediated response,[1,2] or in the context of central nervous system infection.[2]

We present the cases of 3 patients with varying levels of neurological involvement who tested positive for anti-recoverin autoantibodies.

The first patient was a 77-year-old man who was admitted due to diplopia, lower limb weakness, and constitutional symptoms progressing over the course of one month. He also reported episodes of disorientation and sleep-wake cycle alterations. The examination revealed left fourth cranial nerve palsy, proximal paresis of the left lower limb, fasciculations in the quadriceps muscle, and hyperreflexia.

A brain MRI scan detected no alterations. A chest radiography revealed a solid mass in the right upper lobe. Core needle biopsy diagnosed squamous cell carcinoma, and a CT scan ruled out metastasis. Assessment by the ophthalmology department detected no signs of retinopathy.

Symptoms progressed, with the patient presenting more severe weakness, complex ophthalmoplegia, and hypophonia. CSF analysis yielded normal results. Antineuronal antibody testing detected anti-recoverin, anti-Ki67, and anti-GAD65 antibodies. A neurophysiological study showed signs compatible with left polyradiculopathy or left lumbosacral plexopathy. Treatment with immunoglobulins and steroids was ineffective.

The second patient was a 45-year-old man who was admitted due to bilateral pneumonia secondary to SARS-CoV-2 infection and pulmonary thromboembolism, requiring ventilatory support at the intensive care unit. From admission, he presented altered level of consciousness, with alternating episodes of psychomotor agitation and low level of consciousness. A brain MRI scan with contrast detected no alterations, and CSF analysis yielded normal results. EEG revealed desynchronisation and generalised background slowing, with no interhemispheric asymmetry. A 5-day cycle of immunoglobulins failed to achieve a clinical improvement. Ten days later, in view of the impossibility of extubating the patient due to agitation, we administered methylprednisolone dosed at 500 mg/day for 5 days. A subsequent CSF analysis revealed mildly elevated protein levels (61 mg/dL) and presence of leukocytes (31 cells/μL: 68% neutrophils, 29% lymphocytes) and erythrocytes (16 900 cells/μL). The patient improved progressively several days after finishing corticosteroid therapy; sedatives were withdrawn and he was transferred to a ward bed. Antineuronal antibody testing detected anti-recoverin and anti-titin antibodies in the blood. At discharge, the patient presented normal mental state and EEG activity. A PET-CT scan detected no signs of malignancy, an ophthalmologic examination detected no signs of retinopathy, and antibody testing yielded negative results.

The third patient was an 82-year-old man who had recently undergone surgery for a bladder tumour; he was admitted due to status epilepticus consisting of focal clonic seizures affecting the right side of the body, progressing to

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generalised tonic-clonic status. Seizures resolved 48 hours after administration of antiepileptic treatment, but alterations in the level of consciousness persisted. CSF analysis yielded normal results. Brain MRI detected postictal signal alterations in the cortex of the left hemisphere.

Onconeuronal antibody testing detected anti-recoverin antibodies in the blood. Despite pharmacological treatment, the patient died during hospitalisation due to infection.

Our 3 patients tested positive for anti-recoverin antibodies in the blood, manifesting with altered mental status, status epilepticus, and multiple cranial neuropathy and plexopathy; 2 cases were associated with neoplasia (lung and bladder tumours) and one was associated with SARS-CoV-2 infection.

Recoverin is a protein expressed in rod photoreceptors, involved in Ca^{2+} signalling in phototransduction. Anti-recoverin antibodies play a significant role in the pathogenesis of immune-mediated retinal degeneration and cancer-associated retinopathy, mainly in patients with small-cell lung cancer.[3] Cases have been reported of patients testing positive for anti-recoverin antibodies and presenting no visual symptoms, most of whom were diagnosed with cancer; cancer cells in these patients displayed abnormal recoverin expression.[4–6] Anti-recoverin antibodies have also been identified in patients with systemic lupus erythematosus[7] and individuals with early signs of psychosis.[8]

The association between anti-recoverin antibodies and COVID-19 had not previously been described. Cases have been reported of retinal blood vessel alterations associated with SARS-CoV-2 infection and severe COVID-19.[9,10] Tropism for retinal cells may explain the presence of anti-recoverin antibodies.

The pathophysiology of neurological involvement associated with anti-recoverin antibodies remains to be understood, as the protein is only known to be expressed in the retina. As onconeural antibody batteries become increasingly accessible, the clinical spectrum associated with a wide range of antibodies will surely expand in the coming years.

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Conflicts of interest

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