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Letter to the editor

Progressive encephalomyelitis with rigidity and myoclonus, a diagnostic challenge

Progressive encephalomyelitis with rigidity and myoclonus (PERM), also known as 'stiff person plus syndrome', is an autoimmune central nervous system disorder belonging to the stiff man syndrome spectrum. PERM is characterized by rigidity, stimulus-sensitive spasm, myoclonus, hyperekplexia and autonomic disturbances with additional brain stem and/or spinal cord disorders [1]. It has also been associated with the presence of antibodies directed against the glycine receptor (anti-GlyR) [1,2], a ligand-gated chloride channel expressed in different parts of the brain and spinal cord. PERM is classified among the treatable autoimmune diseases and, as a consequence, despite its low incidence and variable clinical presentation [2,3], its diagnosis should not be missed. Our present report describes a case of acute PERM with respiratory failure and a severe evolution that illustrates how diagnostic difficulties may occur.

1. Case report

A 61-year-old man with no history of neurological disease developed, within a few days, right eyelid ptosis and diplopia. Brain magnetic resonance imaging (MRI) was normal (Fig. 1A). Myasthenia gravis was suspected and the patient was treated with pyridostigmine, then intravenous (IV) immunoglobulin (Ig). Two weeks later, he experienced widespread painful spasms, multifocal stimulus-sensitive myoclonus followed by hypertonic tetraparesis, swallowing difficulties, somnolence and respiratory failure, which eventually led to intubation and mechanical ventilation.

Cerebrospinal fluid (CSF) analysis showed 0.45 g/L of protein, 0.71 g/L of glucose and 12 lymphocytes/mm^3. Lyme disease serology was positive in both blood and CSF, resulting in 3-week treatment with ceftriaxone 2 g/day. A second brain MRI with diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) weighted sequences (WS) sequences showed left temporal and insular cortical hyperintensities without gadolinium enhancement (Fig. 1B, C). One month later, when the patient's clinical status was stable, CSF analysis found 90 lymphocytes/mm^3 with normal protein and glucose levels, which was negative for herpes simplex virus type 1 (HSV1) and type 2 (HSV2) on polymerase chain reaction (PCR) assay.

At this time, the patient was referred to our hospital, and neurological examination showed bilateral ptosis, global stiffness, stimulus-induced abdominal muscle spasm, hyperekplexia characterized by axial startle reflex following sensory or auditory stimulation, tetraparesis with increased reflexes and a right extensor plantar response. Brain MRI was normal (Fig. 1D). Electroencephalography (EEG) revealed intermittent slowing of background activity, whereas electromyography (EMG) was normal (with neither decremental nor continuous motor unit activity).

A third CSF analysis showed no pleocytosis, but there was an oligoclonal IgG distribution with a negative CSF/serum anti-*Borrelia* antibody index. Most of the patient's biological data were normal in blood, using the usual hematological and biochemical tests for: lactate; pyruvate; tumor markers; homocysteine; B12 vitamin; thyroid-stimulating hormone (TSH); angiotensin-converting enzyme; serology for syphilis, human immunodeficiency virus (HIV), tick-borne encephalitis (TBE), hepatitis and neurotropic viruses; Ig electrophoresis; anti-ganglioside, anti-acetylcholine receptor (AChR), anti-muscle-specific kinase (MuSK), anti-glutamic acid decarboxylase (GAD) and anti-onconeuronal antibodies; N-methyl-D-aspartate receptor (NMDAR); gamma-aminobutyric acid type B receptor (GABA BR); and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR) antibodies. Anti-glycine receptor (antiGlyR) antibodies (at very low rates on indirect immunofluorescence tests) and voltage-gated potassium channel (VGKC)-complex antibodies [33 pmol/L, but with no specificity for leucine-rich glioma inactivated 1 (LGI1) or contactin-associated protein 2 (CASPR2) antibodies] were present in blood.

PERM was therefore strongly suspected, and the patient was treated with a second course of IV Ig (0.4 g/kg/day for 5 days). A few days later, his neurological status improved and mechanical ventilation could be discontinued. Thoracoabdominal computed tomography (CT) was normal. When re-evaluated 3 months later, the patient remained stiff in all four limbs, but was nonetheless able to walk. EMG demonstrated continuous motor unit activity in the left biceps brachialis and

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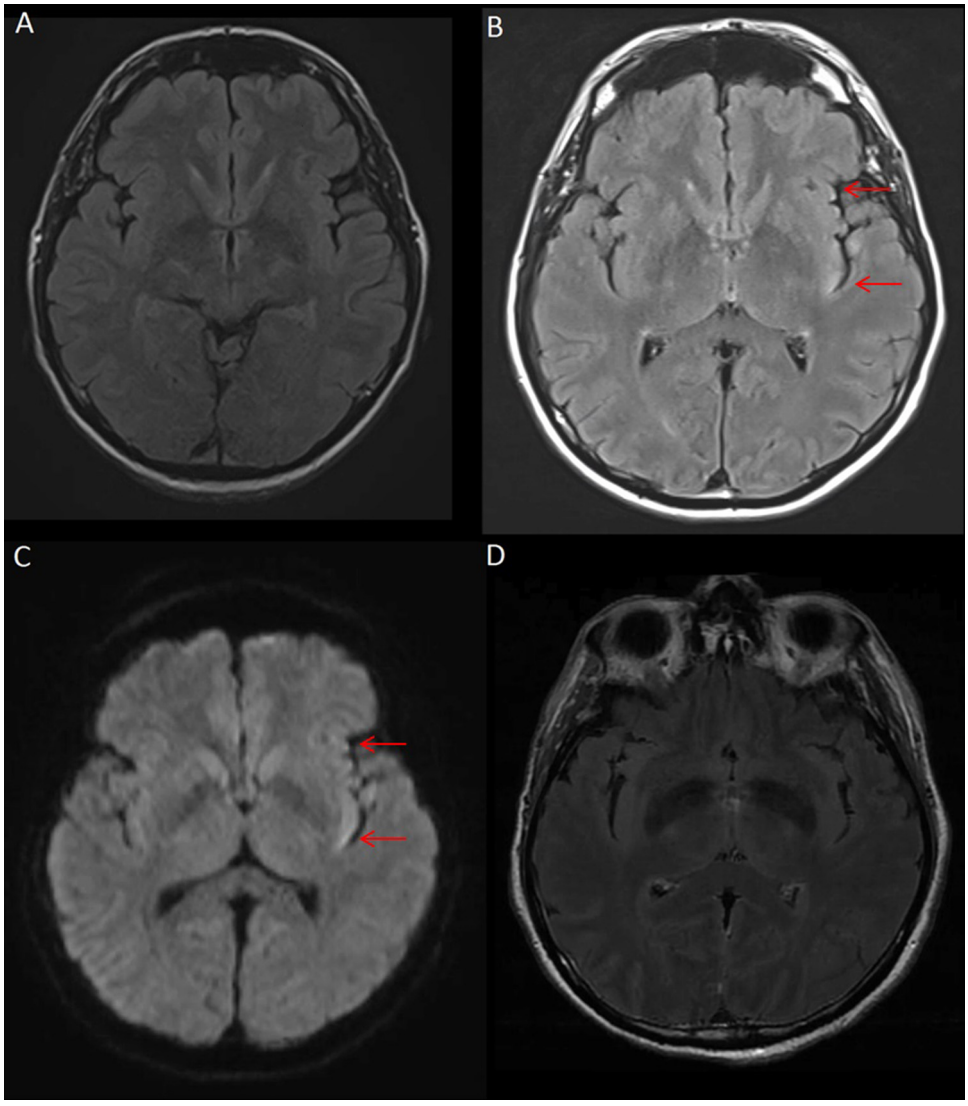

Fig. 1 – Brain magnetic resonance imaging (MRI) performed at the beginning of symptoms with fluid-attenuated inversion recovery (FLAIR) sequences shows normal appearances (A) whereas, 2 weeks after symptom onset with FLAIR (B) and diffusion-weighted sequences (C), there are left temporal and insular cortex hypersignals (red arrows). However, 2 months later (FLAIR), there are no abnormalities (D).

right triceps surae muscles (Fig. 2). The patient also presented with persistent and severe bladder involvement requiring suprapubic catheter implantation. An oral steroid course was initiated and, 2 months later, anti-GlyR antibodies were positive in both blood and CSF which, in association with the slow gradual evolution, led to initiation of monthly IV cyclophosphamide treatment. At the same time, botulinum toxin injections were given bilaterally in both hypertonic biceps brachialis and triceps surae muscles. Diazepam and baclofen were also started, and resulted in mild improvement of both stiffness and spasm.

2. Discussion

This case shows that, when faced with subacute or acute progressive diplopia with or without bulbar signs, PERM should be considered and sought in addition to brain stem lesions, neuromuscular junction disorders or other auto-immune diseases (Bickerstaff's encephalitis, Miller Fisher syndrome). Excessive startle and cortical reflex myoclonus are also common and rather specific symptoms of PERM [2]. Spasms (often painful) and stiffness of the neck, trunk and/or limb muscles are found in 60% of cases, but can be misdiagnosed as pyramidal signs [2], and should therefore prompt EMG to detect spontaneous or stimulus-induced continuous motor unit activity [2]. Brain MRI is normal in 70% of cases, but may show, as in our present case, temporal cortical T2 hyperintensities [2]. Spinal cord MRI, however, rarely shows patchy or extensive hyperintensities on T2 WS imaging [2]. EEG may reveal focal epileptic or cortical disturbances [2].

The association between PERM and anti-GlyR antibodies is present in only half the reported cases [2,3], although our present findings emphasize that repeat searches in blood and CSF for anti-GlyR should be recommended, particularly in

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