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LETTERS TO THE EDITOR

Miller-Fisher syndrome associated with acute motor axonal neuropathy: Clinic-immunological correlation☆

Síndrome de Miller-Fisher asociado a neuropatía axonal motora aguda: correlación clínico-inmunológica

Sir,

Miller-Fisher syndrome (MFS) is an extremely rare, autoimmune, axonal polyradiculoneuropathy which takes place during childhood. It is characterised by the clinical triad of ataxia, ophthalmoplegia and arreflexia.[1] The annual incidence of Miller-Fisher syndrome is 0.09 cases per 100 000 inhabitants. The few published series that exist with children account for approximately 9% of the total of acute polyradiculoneuropathy cases.[2] As in the case of Guillain—Barré syndrome, it is often triggered by certain strains of *Campylobacter jejuni* that induce the formation of anti-GQ1b antiganglioside, although there have also been cases described involving *Haemophilus influenzae* and *Mycoplasma pneumoniae*. Anti-GQ1b antibodies are elevated in 90—97% of Miller-Fisher syndrome cases. These antibodies recognise epitopes that are expressed specifically in the nodal regions of the oculomotor nerves, in the dorsal root ganglia and in the cerebellar neurons. All these structures are responsible for the symptoms of Miller-Fisher syndrome.[3]

Occasionally, Miller-Fisher syndrome and Guillain-Barré syndrome in its demyelinating, acute, motor axonal and acute sensorimotor variants may have an overlapping clinical spectrum, depending on the immunopathological cause. Moreover, motor axonal forms generally respect cranial nerves and present a predominantly distal involvement. Very few cases of this type of presentation have been studied in the light of current knowledge, improved antibody detection techniques and purification of new antigens from the nervous system. We present a study of a patient suffering from Miller-Fisher variant associated with an acute peripheral case of acute motor axonal neuropathy (AMAN). We analysed the antiganglioside antibody pattern and its correlation with the symptoms, as well as the evolution and response to treatment with intravenous immunoglobulin.

The patient was a boy aged 4 years and 9 months, who was admitted to our hospital due to generalised weakness with inability for ambulation, gait instability and palpebral oedema with right ptosis. These symptoms had a progressive clinical evolution of 2 weeks. The patient had suffered an episode of gastroenteritis of unknown aetiology 15 days earlier.

On examination at admission the patient was prostrate, with sensation of acute illness, highlighting a mild bilateral palpebral oedema with right ptosis. At the neurological level, he was conscious, alert, and responsive, with a clear sensory spectrum. He also presented ophthalmoplegia affecting the third, fourth and sixth cranial nerves, inability for vertical and horizontal visual tracking and bilateral facial paresis. In addition, he suffered generalised hypotonia with proximal predominance, inability to sit and walk, decreased strength which was especially marked in the lower limbs, and a slightly asymmetrical balance of the right leg over the left, 1/5 and 2/5, respectively. He also presented universal arreflexia, with seemingly preserved thermo-algesic and proprioceptive sensitivity. No cerebellar signs, tremor, dysmetria or dysdiadochokinesia were identified. There were no meningeal signs.

Complementary tests highlighted albumino-cytological dissociation in the cerebrospinal fluid with protein levels of 0.8 g/l and 5 mononuclear cells per mm^3. Neuroimaging tests (cervical and thoracolumbar MRI scans) showed no morphological changes or signal alterations in the brain, brainstem, spinal cord or cauda equina in T-1, T-2 or FLAIR weighted sequences.

In the initial neurophysiological study, the electromyograms of the upper limb (deltoid, biceps and extensor digitorum muscles) and lower limb (rectus femoris, anterior tibialis and gastrocnemius muscles) revealed a neurogenic pattern. There was spontaneous denervation activity with fibrillations and positive waves, highly deficient evoked motor conduction pathways that were more pronounced in the proximal muscles of the upper limb being examined, and motor unit potentials of long duration and great amplitude, with an increased proportion of polyphasic motor unit potentials. The electroneurogram presented impaired motor conduction with reduced amplitude. Distal latency and conduction velocity remained at normal parameters at the level of both facial nerves, right median nerve, right ulnar nerve and both peroneal nerves. Sensory conduction

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was within normal limits in both speed and amplitude and was, therefore, compatible with motor axonal polyradiculopathy.

The seroimmunological study of antiglycolipid antibodies conducted by enzyme immunoassay (ELISA) detected the presence of IgM antibodies against ganglioside GQ1b at a titre of 1/1500 and IgG positivity against ganglioside GM1 at a titre of 1/500 and IgM against antigen GM2 at a titre of 1/3000. Determination of the remaining antiglycolipid antibodies against GM3, asialo GM1, GD1a, GD1b, GD3, GT1b, sulphatide and globoside were negative.

We performed stool culture for *Campylobacter jejuni*, which resulted negative. CRP in blood for herpes group viruses was negative. The patient was diagnosed with Miller-Fisher syndrome and associated acute motor axonal neuropathy.

The patient was treated with intravenous immunoglobulin at doses of 2 g/kg (400 mg/kg/day for 5 days) and early motor rehabilitation, with good clinical and neurophysiological response. One month after starting treatment, the clinical examination revealed partial recovery of oculomotor and facial reflexes, unaided sitting, aided standing and paraparetic walking with some aid. In the control neurophysiological study conducted 3 months later, the electromyograms of the orbicularis oculi and the right deltoid revealed an absence of spontaneous activity. Furthermore, voluntary movements at maximum effort were slightly deficient in the orbicularis oculi and without significant deficit in the deltoid. Motor unit potentials were normal. The control electroneurogram showed motor conduction involvement of the right and left facial nerves, with decreased amplitude in both evoked potentials, but predominantly on the left. The only finding in connection with the initial neurophysiological examination was peripheral neuropathy of the facial nerves, predominantly on the left side, possibly at the level of the intrapetrous pathway. However, this had a lesser degree than in the initial examination and the remainder of the neurophysiological study was normal.

Current knowledge of acute polyradiculoneuropathies indicates that these entities are acquired as the result of an aberrant immune response secondary to a triggering event. This event could be infection, vaccination, malignancy or some other autoimmune stimulus. The variety of antibodies formed determines the subsequent pathological outcome.[4,5] Thus, the presence of anti-GQ1b leads to the involvement of oculomotor nerves since antigen GQb1 is specifically expressed in the nodal regions of the oculomotor nerves, the dorsal root ganglia and the cerebellar neurons. Furthermore, acute neuropathy characterised by cervical—pharyngeal—brachial paralysis or bulbar dysfunction has been recognised as a variant of Guillain—Barré syndrome. In addition, a recent clinical study has shown that cervical—pharyngeal—brachial paralysis, Miller-Fisher syndrome and Bickerstaff encephalitis form a continuous clinical spectrum.[6] A specific anti-GT1a antibody without GQ1b reactivity is essential for the development of bulbar paralysis in patients with Guillain-Barré syndrome. The glossopharyngeal nerve and vagus nerve contain GQ1b and GT1a,[7] but the presence of GT1a has not been demonstrated in human peripheral nerves. It is likely that specific anti-GD1b antibodies cause ataxia in Guillain—Barré syndrome.[8]

Antigens GM1, GM1b, GD1a, and GalNAc-GD1a are also typical of peripheral motor nerve axolemma at the level of the Ranvier nodes (in animal models). Consequently, the development of their respective antibodies leads to AMAN.[9]

Antibodies against GM2 have been described in cases of cranial nerve paralysis, as well as in cases of sensory involvement associated with herpes group virus infections.[10] A frequent association between the presence of anti-GM2 and facial paralysis has also been reported.[11]

The clinical characteristics of our patient (oculomotor cranial nerve involvement, facial involvement and motor axonal neuropathy without demyelination) had a consistent correlation with his immunophenotype, namely anti-GQb1 with ophthalmoplegia, anti-GM1 with motor axonal involvement and anti-GM2 with facial paresis. However, previous publications have reported greater variability in the behaviour of the latter antibody, since it has also been associated with demyelinating and high cranial nerve symptoms, always with facial involvement. This antigen is located both in the axon and in the myelin around Ranvier nodes.[12]

Antiganglioside antibodies play an important role in the pathophysiology of AMAN-type polyneuropathy and Miller-Fisher syndrome. Antiganglioside antibodies cause nerve damage through complement activation or function impairment of voltage-dependent calcium and sodium channels. The grouped (clustered) epitopes from the complexes of 2 gangliosides in the cell membrane can be recognised by serum antibodies in Guillain-Barré syndrome and Miller-Fisher syndrome and may regulate the accessibility and avidity of antiganglioside antibodies. The glycolipid configuration or specific distribution of ganglioside receptors in the peripheral nervous system may also influence the pathogenic effect in Guillain—Barré syndrome and Miller-Fisher syndrome.[5] Theoretically, involvement of the type of immunoglobulin elicited by the previous autoimmune stimulus is connected with the development of IgM in initial stages. In addition, the possibility exists of triggering ''membrane attack complex'' via complement activation. This would lead to more severe and difficult to control damage than that caused by IgG affecting sodium and calcium channels. It is possible and reasonable that treatment with immunoglobulins in early stages would improve prognosis and long-term evolution by preventing progression of autoimmune activation, as in the case of our patient.[13]

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Levodopa-responsive parkinsonism-dystonia due to a traumatic injury of the substantia nigra☆

Parkinsonismo-distonía unilateral sensible a levodopa por lesión traumática de la sustancia negra

Sir,

The relationship between traumatic brain injury (TBI) and parkinsonism has been established for a long time.[1,2] However, in exceptionally rare cases there have been reports of parkinsonism secondary to traumatic lesions of the substantia nigra (SN).[3] Case reports of parkinsonism due to SN lesions of vascular origin, either by lacunar stroke[4—7] or by small mesencephalic haemorrhages,[8] are better known, but also exceptional. Bhatt published a series of 3 patients who developed parkinsonism several months after a severe TBI with SN lesions. As characteristic data, there was a delay between the trauma and the onset of parkinsonism. The latter developed quickly and aggressively, with all patients responding to therapy with levodopa.[3] A possible pathophysiological mechanism which was postulated to justify the delay in the onset of parkinsonism with respect to trauma, was iron deposition from the degradation products of the haemorrhagic lesion. This deposition would trigger the cascade of events typical of dopaminergic degeneration observed in idiopathic Parkinson's disease (IPD), thus explaining the response to dopaminergic therapy in these cases. When the SN is affected, the resulting parkinsonism is strictly unilateral, unless the injury is more extensive and affects other structures. We found very few references in the literature regarding the usefulness of computed tomography or positron emission tomography in this entity, and they mainly referred to cases with a vascular aetiology.[9,10] Recently, a case of parkinsonism secondary to trauma with SN lesion was published in which the transcranial duplex study had not registered hyperechogenicity in the SN, unlike the characteristic pattern in IPD.[11]

We report a case of unilateral parkinsonism-dystonia secondary to traumatic injury of the SN and partially responsive to levodopa. We present the DaTSCAN study, which shows a notable decrease in radioisotope uptake in the striatum ipsilateral to the lesion.

The patient was a 62-year-old male. At the age of 45 he suffered a TBI with loss of consciousness of 30—60 min duration due to a fall from a second storey, with no apparent immediate neurological sequelae. One year later, he started to suffer uncontrolled and involuntary movements of the left limbs, which were more pronounced in the foot. The examination revealed hemidystonia, without any other significant signs. Two months later, in addition to hemidystonia, he suffered akinetic-rigid syndrome characterised by resting tremor, significant cogwheel rigidity and bradykinesia in the affected side of the body. These symptoms had a relatively rapid onset, with severe worsening of parkinsonism within a few weeks. A cranial MRI scan (Fig. 1) conducted at that time showed a right mesencephalic lesion at the level of the SN, with a hyperintense signal on T2-weighted sequences and a hypointense signal

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