Case reports

Recurrent Miller Fisher Syndrome with abnormal terminal axon dysfunction : a case report

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Abstract

Miller Fisher syndrome (MFS) is a localized variant of Guillain-Barré syndrome (GBS), characterized by ophthalmoplegia, areflexia, and ataxia. Recent neurophysiological studies have suggested that abnormal terminal axon dysfunction occurs in some cases of Miller Fisher syndrome and Guillain-Barré syndrome. We present a rare case report of recurrent MFS with abnormal terminal axon dysfunction. To the best of our knowledge, this is the first case report of recurrent MFS with terminal axon dysfunction that persisted up to nine months after the initial presentation of the second attack with positive antiganglioside antibodies and full clinical recovery.

Key words : Recurrent Miller Fisher syndrome ; neuromuscular transmission ; terminal axon dysfunction.

Introduction

Miller Fisher syndrome (MFS) is a variant of Guillain-Barré syndrome (GBS), characterized by ophthalmoplegia, areflexia, and ataxia. Recent case studies have demonstrated that pupillary abnormalities, ptosis, optic neuritis, and bulbar and facial palsy are components of the clinical presentation of MFS, often occurring in addition to the characteristic triad (Chan 2003). Antiganglioside (anti-GQ1b) antibodies are found very frequently (> 90% of cases). MFS is usually a monophasic illness of subacute onset. Recurrent MFS is extremely rare, with only a limited number of cases described in the literature (Battaglia *et al.*, 2005).

Recent neurophysiological studies suggest that abnormal neuromuscular transmission and terminal axon dysfunction occur in some cases of Miller Fisher syndrome and Guillain-Barré syndrome. Some experimental mouse models have demonstrated that presynaptic neuronal membranes and perisynaptic Schwann cells are targets for anti-GQ1b antibody attacks (Buchwald *et al.*, 1998; Halstead *et al.*, 2004; Overell and Willison, 2005).

In this study, we present a rare case report of recurrent MFS with abnormal terminal axon dysfunction.

Case report

A 30 year old male patient suffered from two episodes of MFS within a period of fourteen years. The first manifestation of MFS occurred in 1991. The patient developed typical signs of MFS (limb and gait ataxia, diplopia, paresthesias, and generalized hyporeflexia) after three days' duration of an apparent common cold. A cerebrospinal fluid (CSF) examination showed elevated protein levels (0.61 g/l, normal upper limit is 0.45 g/l). Neither an electrophysiological examination nor a brain MRI were performed at that time. A full clinical recovery was observed within three months. Borrelia and basic spectrum of neuroviruses (herpes simplex, zoster, virus of tick born encephalitis) in the serum and in the CSF were negative.

The second manifestation of MFS occurred in September 2005 after the patient had had a few days of flu-like symptoms. Within two days, the patient developed paresthesias of both hands and, forearms and both feet. At the same time, the patient started complaining of diplopia. The neurological status was as follows (two days after the onset of clinical complains) : marked bulbar symptomatology with dysarthria and paresis of the soft palate, both-sided paresis of the abducens nerve, limb and gait ataxia, and generalized hyporeflexia. The patient refered his problems identical as the problems in 1991. A head CT scan and brain MRI were both normal.

The patient underwent spinal taps. The first CSF analysis (two days after the onset of clinical symptomatology, on the first day of admission to the hospital) was normal (protein level 0.20 g/l, no signs of pleiocytosis). The second and third spinal taps (performed three and then five days after the onset of clinical symptomatology) revealed mild pleiocytosis (respectively 9 elements per µl at the second spinal tap, and 11 elements per µl at the third). The fourth CSF examination (two weeks after onset) revealed a tendency to protein level elevation (0.43 g/l); the CSF cell number was normal.

The first nerve conduction studies (NCS) and needle electromyography (EMG) revealed a borderline value of F-wave n. tibilias (56 ms). The control NCS and EMG, including the repetitive nerve stimulation (RNS) of the left ulnar nerve (six days after the onset of clinical manifestation; 10 stimuli were given; the measurement of the CMAP amplitudes was taken between the first and fourth stimuli) were performed at following frequencies : 2 Hz rest, 2 Hz post-exercise, 20 Hz rest, 20 Hz post-exercise, 50 Hz rest, and 50 Hz post-exercise. Exercise consisted of 20 seconds of maximal muscle contraction. RNS showed mild presynaptic neuromuscular transmission defect – a 17 and 19% increase of CMAP during the high frequency RNS (20, and 50 Hz respectively). The low frequency RNS (2 Hz) was normal. The area of CMAP was -8 and -9 % (for details, see Table 1). No other nerves were investigated beyond the ulnar nerve due to painful RNS.

Five series of plasmapheresis were performed. The oculomotor disturbances began to improve.

Repeated NCS, including EMG studies and antiganglioside antibodies, were investigated. RNS of the ulnar nerve still showed an increased response to high-frequency stimulation - the increase was by 18 and 19% respectively (for details, see Table 1). Stimulated single-fibre electromyography (SFEMG) of the frontalis muscle was performed 9 months after the first clinical complaints, and was abnormal : mean value of consecutive differences (MCD) was 61 μs (normal < 32 μs). In 9 of 20 fibre pairs, there was excessive jitter > 55 μs (normal < 10%). To avoid inadequate axon stimulation, we raised the stimulus strength by 15% beyond the value at which no further blocking was seen (Trontelj and Stalberg 1992). Antiganglioside antibodies (anti-GQ1b IgG) were strongly positive (unfortunately the anti-GQ1b titer cannot be performed in the reference lab). A full clinical recovery was apparent within three months after first symptoms had appeared. As of May 2007, the patient is still in good clinical condition without any clinical symptoms of MFS. The control antiganglioside antibodies (anti-GQ1b IgG) continued to be positive, and the RNS was persistently abnormal- with a CMAP increase of 20% (Table 1).

Discussion

This paper presents an unusual case of recurrent MFS. The recurrence rate in GBS is about 1 to 6% (Wijdicks and Ropper, 1990). There are just a few case reports of recurrent MFS in the literature (Dewarrat et al., 1995; Riche et al., 1998). Riche et al reported a case of a patient with three recurrences of MFS within a sixteen year period (Riche et al., 1998). It is widely accepted that serum anti-GQIb IgG is associated with ophthalmoplegia in patients with MFS. The anti-GQIb antibody titers have been found to be elevated during an episode, gradually decreasing and vanishing two years later (Dewarrat et al., 1995). In the case presented here, the positivity of anti-GQIb IgG persisted for nine months despite an otherwise complete clinical recovery. We did not examine the patient´s serological HLA typing; HLA-DR2 is possibly associated with recurrence (Chida et al., 1999).

Recent neurophysiological studies suggest that abnormal neuromuscular transmission occurs in some cases of Miller Fisher syndrome and Guillain-Barré syndrome (Lo et al., 2006). Presynaptic disorders of neuromuscular transmission are generally characterized by low CMAP amplitudes, but the CMAP amplitudes in our patient were normal. These findings have been observed in other cases of Miller-Fisher syndrome (Lo et al., 2006).

Table 1

Prospective ulnar nerve conduction studies

	CMAP, mV	2 Hz, %	20 Hz, %	50 Hz, %
September 2005	11.2	+1, +1	+17 (-8), +19 (-9)	+19 (-10), +16 (-8)
November 2005	11.1	0	+19, (-10), +22 (-14)	+18 (-9), +19 (-10)
May 2006	10.8	+1, +2	+20, (-11), +34 (-19)	+15 (-7), +25 (-14)

Prospective ulnar repetitive nerve stimulation (RNS) during and after the course of the illness.

The first value is the amplitude change at rest; the second value is the amplitude change after 20 seconds of maximal muscle contraction.

Values in parentheses denote area changes.

For low and high frequency RNS : Number of stimuli given = 10. The measurements of the CMAP done between the first and the fourth stimuli.

Positive signs denote increment and negative signs denote decrement in percentages (%).

(Normal lab data < 8%).

CMAP Compound muscle action potential.

RNS showed a 20% increment, which is insufficient to demonstrate a clear neuromuscular transmission abnormality. But this abnormality sustained nine months after onset, when the clinical neurological exam was otherwise back to normal. That this finding may represent subclinical phenomena in muscles that are no longer clinically affected has suggested by some authors (Lo *et al.*, 2006). Lo et al provided electrophysiological support for an abnormality of neuromuscular transmission in anti-GQ1b-positive patients with acute ophthalmoparesis (Lo *et al.*, 2004). Halstead et al have demonstrated in mouse models that both presynaptic neuronal membranes and perisynaptic Schwann cells are targets for mouse antidisialoside antibodies of a similar specificity to those found in cases of MFS (Halstead *et al.*, 2004). Patch clamp studies show that IgG from MFS patients also has postsynaptic effects (Buchwald *et al.*, 1998). However, single-fibre electromyography (SFEMG) in our patient detected abnormal jitter and impulse blocking, suggesting terminal axon dysfunction. Concomitant axonal blocking is the electrophysiological signature of conduction block at a distal, preterminal axon branch. Indeed, Lange *et al.* recently reported that the target of some immune neuropathies may be in the terminal axon, outside of the neuromuscular junction (Lange *et al.*, 2006).

To the best of our knowledge, this is the first case report of recurrent MFS with a terminal axon dysfunction that persisted up to nine months from the initial presentation of the second attack with positive antiganglioside antibodies and a full clinical recovery. Our findings could indicate that terminal axon block is not completely reversible. The clinical relevance of neurophysiological abnormalities has not yet been thoroughly studied and deserves further investigation, although Uncini and Lugaresi recommended the performance of serial motor conduction studies, repetitive stimulation, and SFEMG in MFS patients in order to better understand the pathophysiology of weakness (Uncini and Lugaresi, 1999). These authors suggested that weakness in MFS might be due to a block of acetylcholine release from motor terminals, mediated by antiGQ1b antibodies (Uncini and Lugaresi, 1999).

Acknowledgement

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