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GQ1b ganglioside antibody-related disorders: a case with a complex phenotype

Y.-M Pers[1], G. Taïeb[1], X. Ayrignac[1], G. Castelnovo[1], A. M Hubert[2], J. Boucraut[2] and P. Labauge[1]

[1]Department of Neurology, Caremeau Hospital, CHU Nîmes, France; [2]Immunology Laboratory, Conception Hospital, AP-HM, 13005 and CNR2M, UMR CRNS 6231, Faculté de Médecine, 13015, Marseille, France

Abstract

We described an overlap syndrome associating Miller Fisher syndrome (MFS) and acute inflammatory demyelinating polyradiculoneuropathy (AIDP). Furthermore, the patient presented unusual neurological manifestations including headache, T10 sensory level, urinary urgency, and gadolinium enhancement of the spinal roots. One year follow-up was characterized by clinical recovery and persistent high rates of anti-GQ1b, -GD1b and -GT1b antibodies. Our case suggests broad phenotype of persistent antigangliosides antibodies.

Key words: Antigangliosides antibodies; micturitional disturbances; spine cord, MRI; headache; acute inflammatory demyelinating polyradiculoneuropathy.

Introduction

Gangliosides are important carbohydrate determinants for autoimmune activity. Several studies suggested that serum antibodies against gangliosides are responsible for some forms of acute and chronic neuropathy syndromes. Indeed, anti-GQ1b gangliosides antibodies are associated with 4 acute syndromes: Miller Fisher syndrome (MFS), Bickerstaff brainstem encephalitis (BBE), acute inflammatory demyelinating polyradiculoneuropathy (AIDP) with ophtalmoplegia and isolated acute ophtalmoparesis. MFS has been classified as a variant of Guillain-Barre syndrome (GBS) (1). The pathophysiology of MFS involves immunologically mediated central and peripheral processes. We report a patient who had MFS criteria with unusual neurological manifestations and spinal cord roots Magnetic Resonance (MR) findings. This observation extends the anti-GQ1b antibody phenotype.

Case report

A 40 year-old woman, with a medical history of Hashimoto disease treated by thyroid hormones, presented headache six days after a viral rhinitis. One week later, she described paraesthesias in the four extremities and transient horizontal diplopia. Initial clinical examination was normal. Symptoms progressively worsened during the following four days, with occurrence of proximal (3/5, according to the Medical Research Council scale) and distal (4/5) legs weakness, sensory ataxia, generalized areflexia, hypoesthesia, and painful dysesthesia inferior to T10 level, associated with urinary dysfunction including urgency and incontinence. Cerebral MR imaging was normal but T1-weighted spinal cord MR examination showed gadolinium-enhancement of dorsal, lumbar and cauda equina roots inferior to T10 level (Fig. 1) in absence of spinal cord abnormalities. Lumbar puncture indicated normal opening pressure and the cerebrospinal fluid (CSF) analysis only revealed increased albumin (0.78 g/l). Electromyogram (EMG) showed all criteria for a demyelinating form of Guillain-Barré syndrome. Sural nerve potential amplitudes were decreased. Measure of antigangliosides antibodies showed high elevated rates of anti-GQ1b (1080), -GD1b (270) and -GT1b IgG antibodies (1650), low levels of anti-GT1a IgG antibodies (100) whereas anti-GM1, -GD1a and -GM2 IgG and anti-gangliosides IgM antibodies measurement were negative (the presence of antigangliosides antibodies was tested by using ELISA methods, the titer corresponded to the calculated dilution value crossing the threshold, normal values inferior to 20). Based on these findings, a diagnosis of AIDP associated with anti-GQ1b antibody was made. Standard biological parameters were normal. *Borrelia burgdorferi*, *Campylobacter jejuni, Hemophilus influenzae, Mycoplasma pneumoniae*, *Syphilis*, HIV, CMV, HTLV-1 and B/C hepatitis serologies were negative. Research of monoclonal gammopathy and cold agglutinins was negative. Intravenous immunoglobulins treatment (0,4 g/kilo/d during 5 days) was followed by a favourable evolution of muscle

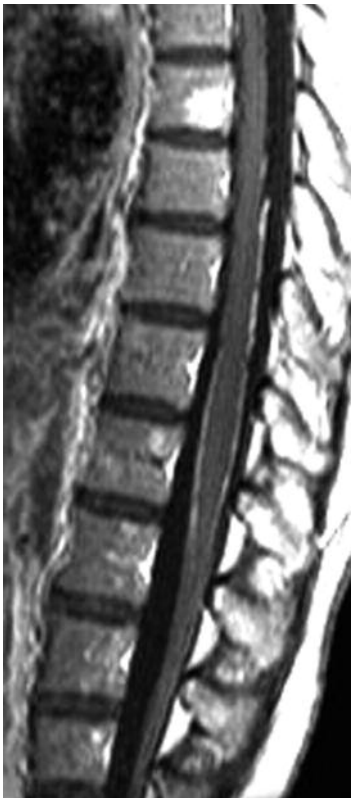

FIG. 1. — Spinal cord MRI (T1 weighted sequences with gadolinium injection) Gadolinium-enhanced high signal intensity lesions in spinal roots below T10 with a normal appearing spinal cord.

weakness and pain. Unaided walking and normality of urinary function appeared 20 days after, although diffuse areflexia persisted. One year follow up was characterised by absence of clinical symptoms and normal neurological examination with reappearance of deep tendon reflexes. Spinal cord MR and EMG study were normal. However, high rates of anti-GQ1b and -GD1b antibodies persisted.

Discussion

In addition to the classic triad described by Fisher in 1956, a variety of other signs and symptoms have been reported in MFS. However, headache is a symptom which is not commonly associated with MFS or AIDP. After excluding usual acute headache causes, AIDP was evocated in our patient. There are several plausible explanations for the headache: increased intracranial pressure or hypertensive arterial pressure secondary to autonomic disturbances as previously described in the literature. Friedman raises the hypothesis of an activation of the trigeminovascular pain pathway mediated by anti-GD1b antibodies (2). Mechanism of headache in MFS patients remained uncertain. In our case, intracranial pressure was normal. Interestingly, headache resolved exactly simultaneously with the other neurological symptoms after 1 month.

Anti-GQ1b antibodies are always associated with MFS, BBE, GBS with ophtalmoplegia or acute ophtalmoparesis (3). In one of the largest series, MFS criteria were based on ataxia, areflexia and ophtalmoplegia. Severe weakness excluded this diagnosis (4, 5). Our case is atypical, since it is associated with severe weakness, micturitional disturbance, and sensory dorsal level with gadolinum enhancement of spinal roots.

Both sensory level and urinary retention strongly suggest spinal cord involvement. Optic neuritis, myelitis, and BBE have been rarely described as central nervous system feature associated with GBS. In our case, MRI showed spinal nerve roots inflammatory process without spinal cord injury. Byun and coll (6) have reported MRI findings in 8 patients with GBS. All had enhancement of the anterior spinal nerve roots and 2 patients had also enhancement of the posterior spinal nerve roots. Only those two last patients had clinical sensory and electromyography disorders. Although the enhancement of the intrathecal spinal nerve roots is not specific, MRI could help clinicians to strengthen GBS diagnosis. In our case, micturitional symptoms and sensory level were probably related to spinal roots involvement (7) although normal spinal cord MRI does not exclude spinal involvement.

Anti-GQ1b IgG antibodies are very specific of MFS, BBE, AIDP with ophtalmoplegia and acute ophtalmoparesis. Some authors suggest that anti-GQ1b IgG antibodies have a role in the development of the variety of clinical signs seen in MFS, BBE and GBS (8). They described various anti-ganglioside profiles corresponding to immuno-clinical variants of GBS and showed five anti-gangliosides antibodies cross reacting with anti-GQ1b antibodies: GT1a, GD1b, GT1b, GD1a, and GM1. In our report, anti-GQ1b IgG antibodies were associated with anti-GT1a, -GD1b and -GT1b IgG antibodies. Anti-GM1 or -GD1a antibodies were absent. The most frequent pattern is the cross-reaction between anti-GQ1b and -GT1a, with a frequency close to 70% (9, 10). It is always associated with ophtalmoplegia in MFS or GBS (11). Suzuki and coll (9) suggest that the cross-reactivity of anti-GQ1b IgG with -GD1b is involved in the development of impaired proprioception in MFS and GBS. Anti-GD1b with-GQ1b antibodies are frequently associated with acute sensory ataxic neuropathy (ASAN) (12). In a large series of 194 patients with anti-GQ1b IgG antibody positivity, Odaka and coll (3) found more anti-GT1b and

-GD1b antibodies in the overlap MFS/GBS than in patients with MFS. Furthermore, limb weakness appears more frequently with anti-GT1b IgG. However, they did not precise the axonal or demyelinating mechanism. In our case, EMG patterns consist of a demyelinating process. Interestingly, like in our case, cross-reacting anti-GQ1b, -GD1b, and -GT1b antibodies seems predictive of this overlap AIDP with ophthalmoplegia (3).

The origin of ataxia (proprioceptive or cerebellar dysfunction) in MFS has not been fully explained (4). In our case, clinical findings, added to EMG and MRI findings, with enhancement of posterior spinal roots, are in favour of sensory ataxia.

High levels of anti-GQ1b antibodies were found in AIDP with ophtalmoplegia, returning to normal levels 6 months after disease onset (4). Here, high rate of antibodies remained stable one year after the first symptoms with normal neurological examination and no relapse.

Autoimmunity context could interfere in antibodies maintenance. This case raises the question of the direct pathogenic role of the anti-gangliosides autoantibodies.

Conclusion

This observation describes a patient with a complex phenotype of anti-GQ1b antibody syndrome with MFS, AIDP, headache, T10 sensory level, urinary urgency, roots gadolinium enhancement, and persistent anti-gangliosides one year after disease onset.

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Prof. Pierre Labauge, M.D., Ph.D.,
DPT of Neurology,
CHU de Nimes,
30029 Nimes Cedex (France).
E-mail: labauge@yahoo.fr