Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Subacute motor axonal neuropathy associated with the IgG anti-GalNAc-GD1a antibody

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Summary

A 14-year-old boy developed a distinct asymmetrical muscle atrophy and weakness with no sensory disturbance in the lower extremities after enteritis. He had an elevated titre of the IgG antibody against GalNAc-GD1a, but none of the others. A nerve conduction study revealed motor axonopathy. Intravenous immunoglobulin therapy improved the status gradually, with low titres of IgG anti-GalNAc-GD1a.

BACKGROUND

The antibody to the ganglioside N-acetylgalactosaminyl GD1a (GalNAc-GD1a) is an anti-ganglioside antibody mainly associated with Guillain-Barré syndrome (GBS).¹⁻⁴ Several authors, however, have reported cases of non-GBS type neuropathy with this antibody, including chronic motor axonal neuropathy.⁵⁻¹¹ We report on a patient with subacute motor axonal neuropathy presenting itself as mononeuropathy multiplex with elevated titres of the IgG anti-GalNAc-GD1a antibody. Intravenous immunoglobulin (IVIG) therapy improved the status gradually, with low titres of IgG anti-GalNAc-GD1a. We recommended an investigation of IgG anti-GalNAc-GD1a in cases of motor axonal neuropathy including mononeuropathy multiplex.

CASE PRESENTATION

A 14-year-old boy noticed difficulty in running 2 weeks after a case of acute enteritis. Proximal muscle atrophy of the left lower extremity and weakness of the right foot developed over the 1–2 months thereafter. He visited our hospital 2 months later from the onset of neurological symptoms. He had no medical history and the family history was unremarkable.

His general physical examination was normal. Upon neurological examination, he had intact cognition and normal cranial nerve function. The muscle bulk was normal in the bilateral upper extremities and the right lower extremity, but proximal muscles of the left lower extremity showed atrophy. The muscle strength, assessed by the Medical Research Council (MRC) scale, of the bilateral upper extremities, proximal of the right lower extremity and distal of the left lower extremity was normal. The left quadriceps femoris, the right tibialis anterior, extensor digitorum longus, extensor hallucis longus, triceps surae, flexor digitorum longus and flexor hallucis longus were weak (MRC 3). Tendon reflexes of the bilateral upper extremities were normal, but those of the lower extremities were

brisk. Plantar responses were flexor. An examination of the sensory system revealed a normal response to a pinprick, light touch, warm and cold stimulation, vibration and joint position. Coordination and the urinary system were normal.

INVESTIGATIONS

Results of the routine laboratory examination were normal. Testing included creatine kinase, erythrocyte sedimentation rate, C reactive protein and glycated haemoglobin. Serum anti-nuclear antibody, proteinase 3-anti-neutrophil cytoplasmic antibody (ANCA), myeloperoxidase-ANCA, anti-SS-A anti-SS-B and the anti-hepatitis C virus (HCV) antibody were negative. Cerebrospinal fluid (CSF) revealed a mild elevation of protein concentration (56 mg/dl) with normal cell counts. A nerve conduction study revealed normal motor conduction velocities (MCVs) in the right median and ulnar nerve, and normal compound muscle action potentials (CMAPs) in the right abductor pollicis brevis and abductor digiti quinti. MCVs in the right deep peroneal and posterior tibial nerve were normal, however, the CMAPs in the right extensor digitorum brevis (0.15 mV) and abductor hallucis (0.74 mV) were decreased. Sensory nerve conduction velocities and sensory nerve action potentials were normal in the right median, ulnar and sural nerves. A needle electromyographic examination demonstrated fibrillation potential and reduced the interference pattern in the left vastus medialis. MRI of the proximal lower extremities disclosed the muscle atrophy of the left quadriceps femoris, adductor magnus and adductor longus. High-intensity lesions on a T2-weighted and short inversion-time inversion-recovery image were illustrated in the left vastus lateralis, vastus intermedius, vastus medialis and the bilateral biceps femoris (figure 1A,B). A biopsy taken from the left vastus medialis revealed small angular fibres and group atrophy. Anti-ganglioside antibody testing, using ELISA,¹ demonstrated that the IgG anti-GalNAc-GD1a antibody was strongly positive (the optical density

Figure 1 MRI before IVIG therapy revealed the muscle atrophy of the left quadriceps femoris, adductor magnus and adductor longus (A and B). High-intensity lesions on a T2-weighted (A) and short inversion-time inversion-recovery image (B) were demonstrated in the left vastus lateralis, vastus intermedius, vastus medialis and the bilateral biceps femoris. Twelve months following IVIG therapy, MRI demonstrated recovery of muscle volume and the disappearance of the high-intensity lesions (C and D).

was 0.704, normal <0.1). The IgM anti-GalNAc-GD1a antibody, IgG and IgM anti-GM1, anti-GM2, anti-GM3, anti-GD1a, anti-GD1b, anti-GD3, anti-GT1b, anti-GQ1b, anti-GA1 and anti-Gal-C antibodies were all found to be negative.

TREATMENT

As a result of the tests, he was placed on IVIG therapy for 5 days.

OUTCOME AND FOLLOW-UP

Twelve months after the IVIG therapy, the muscle strength of the left quadriceps femoris, the right triceps surae, flexor digitorum longus and flexor hallucis longus improved to normal. However, the right tibialis anterior, extensor digitorum longus and extensor hallucis longus were still weak (MRC 4). MRI of the proximal lower extremities demonstrated the improvement of muscle atrophy and the disappearance of high-intensity lesions (figure 1C,D). The optical densities of the IgG anti-GalNAc-GD1a antibody tested by ELISA, 6 and 12 months after the IVIG therapy were 0.174 and 0.188, respectively.

DISCUSSION

A 14-year-old boy developed subacute muscle atrophy and weakness with hyperreflexia, without sensory disturbance, in the lower extremities after acute enteritis. A CSF revealed albuminocytologic dissociation, whereas a nerve conduction study showed axonopathy. Although the clinical course alongside some neurological features of the patient resembled acute motor axonal neuropathy (AMAN),^{12 13} a subtype of GBS, the patient's features showed remarkable asymmetry in motor dysfunction, which progressed over 2 months. Low titre of IgG anti-GalNAc-GD1a antibody remained in sera at 12 months after the IVIG therapy. We therefore considered the clinical features of the patient, not as AMAN, but as a subacute motor axonal neuropathy presenting itself as mononeuropathy multiplex.

Results of the blood tests suggested that the neuropathy of the patient differed from diabetic neuropathy, vasculitic neuropathy, peripheral neuropathy with primary Sjögren's syndrome and HCV-associated neuropathy. Because of the anti-ganglioside antibody, serum testing only detected the IgG anti-GalNAc-GD1a antibody with a high titre, which lowered after treatment, we believe this antibody may be associated with the neuropathy.

The anti-GalNAc-GD1a antibody might function as the pathogenesis of GBS by binding to an inner part of the compact myelin and a periaxonal-axolemma-related protein in the ventral roots or intramuscular nerves, where the GalNAc-GD1a was detected by an immunohistochemical study.¹⁴ Several investigators reported that IgG anti-GalNAc-GD1a antibodies were associated with GBS variant with the sparing of cranial nerves, predominant distal motor weakness and an axonal neuropathy, or pure motor and axonal variants of GBS.^{2 3} Anti-GalNAc-GD1a antibodies have otherwise been reported to be associated with non-GBS type neuropathy, but the titres were not as high as these found in GBS, where most of the antibodies against the other gangliosides were concomitantly detected.^{5 6 8–11} Therefore, the role of the anti-GalNAc-GD1a antibody in such cases remains uncertain. Also case studies reported by Kaji *et al*⁷ only had the IgG anti-GalNAc-GD1a antibody as did our patient. The common clinical feature among these cases was the chronic motor axonal neuropathy presenting as mononeuropathy multiplex. We considered that the IgG anti-GalNAc-GD1a antibody may be associated with both subacute and chronic asymmetrical motor axonal neuropathy.

Motor axonal neuropathy has been found to occur in several diseases, most of which rarely respond to treatment. IVIG therapy, or other immunomodulation treatment, appeared to be effective for the neuropathy associated with the anti-GalNAc-GD1a antibody. Hence, we propose that screening for the IgG anti-GalNAc-GD1a antibody should be carried out on patients with asymmetrical motor axonal neuropathy, to find out this potentially treatable disease.

Learning points

- ▶ The IgG antibody to GalNAc-GD1a is usually associated with GBS.
- ▶ Our case suggests that the IgG anti-GalNAc-GD1a antibody is also associated with chronic or subacute motor axonal neuropathy presenting as mononeuropathy multiplex.
- ▶ IVIG therapy seems effective for the neuropathy caused by the IgG anti-GalNAc-GD1a antibody.
- ▶ The IgG anti-GalNAc-GD1a antibody should be investigated in cases of motor axonal neuropathy including mononeuropathy multiplex.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Kusunoki S**, Chiba A, Kon K, *et al*. N-acetylgalactosaminyl GD1a is a target molecule for serum antibody in Guillain-Barré syndrome. *Ann Neurol* 1994;**35**:570–6.
2. **Hao Q**, Saida T, Yoshino H, *et al*. Anti-GalNAc-GD1a antibody-associated Guillain-Barré syndrome with a predominantly distal weakness without cranial nerve impairment and sensory disturbance. *Ann Neurol* 1999;**45**:758–68.
3. **Kaida K**, Kusunoki S, Kamakura K, *et al*. Guillain-Barré syndrome with antibody to a ganglioside, N-acetylgalactosaminyl GD1a. *Brain* 2000;**123**:116–24.
4. **Willison HJ**, Yuki N. Peripheral neuropathies and anti-glycolipid antibodies. *Brain* 2002;**125**:2591–625.
5. **Tsukaguchi M**, Yamada A, Deguchi K, *et al*. A case of chronic inflammatory demyelinating neuropathy associated with antibodies to gangliosides GM1 and GalNAc-GD1a. *Rinsho Shinkeigaku* 1997;**37**:228–32.
6. **Sugie K**, Murata K, Ikoma K, *et al*. A case of acute multifocal motor neuropathy with conduction block after Campylobacter jejuni enteritis. *Rinsho Shinkeigaku* 1998;**38**:42–5.
7. **Kaji R**, Kusunoki S, Mizutani K, *et al*. Chronic motor axonal neuropathy associated with antibodies monospecific for N-acetylgalactosaminyl GD1a. *Muscle Nerve* 2000;**23**:702–6.
8. **Ortiz N**, Rosa R, Gallardo E, *et al*. IgM monoclonal antibody against terminal moiety of GM2, GalNAc-GD1a and GalNAc-GM1b from a pure motor chronic demyelinating polyneuropathy patient: effects on neurotransmitter release. *J Neuroimmunol* 2001;**119**:114–23.
9. **Lopate G**, Choksi R, Pestronk A. Severe sensory ataxia and demyelinating polyneuropathy with IgM anti-GM2 and GalNAc-GD1A antibodies. *Muscle Nerve* 2002;**25**:828–36.
10. **Kanzaki A**, Endo S, Kusunoki S, *et al*. A case of chronic pure motor neuropathy associated with anti-GalNAc-GD1a-IgM antibody. *No To Shinkei* 2003;**55**:609–12.
11. **Chikakiyo H**, Kunishige M, Yoshino H, *et al*. Delayed motor and sensory neuropathy in a patient with brainstem encephalitis. *J Neurol Sci* 2005;**234**:105–8.
12. **McKhann GM**, Cornblath DR, Griffin JW, *et al*. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. *Ann Neurol* 1993;**33**:333–42.
13. **Kuwabara S**, Ogawara K, Koga M, *et al*. Hyperreflexia in Guillain-Barré syndrome: relation with acute motor axonal neuropathy and anti-GM1 antibody. *J Neurol Neurosurg Psychiatr* 1999;**67**:180–4.
14. **Kaida K**, Kusunoki S, Kamakura K, *et al*. GalNAc-GD1a in human peripheral nerve: target sites of anti-ganglioside antibody. *Neurology* 2003;**61**:465–70.

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