Acute oculomotor impairment with anti-GQ1b IgG due to central nervous system dysfunction

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Accepted for publication: September 28, 2005

Summary

We report the case of a patient with isolated central oculomotor impairment and anti-GQ1b antibody. The patient was referred to us with acute vertical diplopia. The neurological examination revealed right internuclear ophthalmoplegia (INO), skew deviation and mild gait ataxia. Extensive laboratory analyses, CSF study, multimodal evoked potentials and brain MRI were normal. Eye movement recording showed sac- cade dysmetria in addition to the INO. The subjective visual vertical was abnormally tilted to the left. The anti-GQ1b IgG antibody was detectable on serum DOT-BLOT. The brainstem and cerebellar features of the oculomo- tor impairment suggested that in our patient the anti- GQ1b IgG antibody showed a preferential cross-react- tion with central nervous system epitopes. This finding is at variance with previous reports on anti-GQ1b syn- drome with acute ophthalmoplegia, all of which argue for a localization of GQ1b epitopes within the peripher- al nervous system, even though, in the light of the de- scription of the ocular motor disorder, a central in- volvement might have co-occurred in this case.

KEY WORDS: acute ophthalmoplegia, anti-GQ1b IgG antibody, central nervous system, diplopia.

Introduction

In 2001, Odaka et al. (1) recognized an entity, termed “anti-GQ1b IgG antibody syndrome”, that covers a broad clinical spectrum ranging from isolated acute ophthalmoplegia (AO) or ataxia, to Miller-Fisher syndrome (MFS), Bickerstaff’s brainstem encephalitis (BBE), and to cases in which MFS, BBE and acute Guillain-Barré syndrome (GBS) overlap (1); they also suggested that all these various illnesses share a common autoimmune pathogenesis. In anti-GQ1b IgG antibody syndrome, AO is rare, presenting in 9% of patients in the largest reported series (1), and ophthalmoplegia may show a chronic or relaps- ing rather than an acute monophasic course (2,3).

In accordance with biochemical and immunohistochemical findings (4-6), it has been suggested that AO can be consid- ered a mild or atypical form of MFS (4,7), which usual- ly includes a “peripheral” oculomotor nerve dysfunction. However, central oculomotor impairment was reported in a few MFS patients (8,9), and probably occurred in AO patients as well (7,10,11).

Here, we report the first patient with anti-GQ1b IgG an- tibody and acute diplopia whose clinical and neurophys- iological features suggest central oculomotor impair- ment without peripheral nervous system involvement or consciousness disturbance.

Case report

A 26-year-old male complained of acute diplopia and slight unsteadiness in April 2001, a month after a brief febrile episode with diarrhoea. Upon admission, oculo- motor clinical examination revealed right internuclear ophthalmoplegia (INO) (on left gaze, horizontal left beating nystagmus in the left eye, and adduction deficit in the right eye, this latter feature not detectable during convergence), and a skew deviation (namely a comitant right hypertropia). Head-thrust and head-shaking nys- tagmus, hyperventilation, and positional nystagmus were normal. Otherwise, the neurological examination showed only minimal gait ataxia. Extensive laboratory analysis, which included CSF study and brain MRI, were normal except for anti-GQ1b IgG antibody on serum DOT-BLOT (Calbiochem, Darmstadt, Germany). This test result was not available until some weeks af- ter those of the other tests. Multimodal evoked poten- tials (BAEPs, VEPs, SSEPs and vestibular evoked myogenic potentials), EMG and ENG study gave nor- mal findings. Monocular horizontal saccades, recorded by means of the infrared reflection technique (IRIS sys- tem, Skalar, Delft), confirmed INO, but also revealed hypermetric rightward saccades (Fig. 1). The subjective visual vertical was abnormal (binocular vision: -10.5 deg; normal range ± 2.59 deg). The patient was treated with oral prednisone (1 mg/kg/day) on a tapering schedule for 2 weeks, and completely recovered within a few days.

Twenty-eight months later he was still well, brain MRI was normal, and anti-GQ1b IgG antibody was no longer detectable.

Discussion

This is the first report of acute isolated central oculomotor impairment with anti-GQ1b antibody. The patient, presenting neither a consciousness disturbance nor long tract signs, did not fulfill the diagnostic criteria for typical or atypical MFS, or the BBE diagnostic criteria as proposed by Odaka et al. (1). The patient instead presented brainstem and cerebellar oculomotor impairment without clinical or neurophysiological peripheral nervous system involvement.

The oculomotor abnormalities detected in our patient are in keeping with the hypothesis of a brainstem and, possibly, cerebellar dysfunction. The patient presented an abnormal subjective visual vertical, which suggests an imbalance along the otolith and/or the vertical semicircular canal pathways. This imbalance may be located somewhere between the vestibular nerve and the vestibular cortex (12). It seemed likely that our patient's dysfunction was located within the brainstem: he presented, as mentioned, an abnormal subjective visual vertical without rotary vertigo, but with both skew deviation and INO. Internuclear ophthalmoplegia is a classic brainstem sign caused by a medial longitudinal fasciculus lesion; moreover, our patient also showed saccade hypermetria, which is attributable to cerebellar vermis dysfunction.

The literature contains few descriptions of similar patients (10,11), but before the first report of anti-GQ1b antibody (13), Abad and Wolintz (10) reported a single case of post-infectious isolated gaze palsy. Slavin (11) described two patients presenting gaze palsy, without long tract signs or changes in mental status, that followed a viral disease. These patients recovered completely. The clinical features, unilateral gaze paresis and gaze-evoked nystagmus in one patient, and Parinaud's syndrome in the other, suggested brainstem involvement.

The presence of anti-GQ1b antibody was reported in patients presenting with acute isolated post-infectious ophthalmoparesis (4,7,14). The ophthalmoparesis was peripheral in all of them, with the exception of two patients described by Yuki et al. in whom an additional central component might have superimposed (7).

Recently, Lyu and Chen (15) described three patients with multiple cranial neuropathy associated with anti-GQ1b antibody; all these patients presented with an oculomotor disorder, the description of which, in two of them, does not rule out possible CNS involvement. Finally, Hamaguchi et al. (2) reported a patient with anti-GQ1b syndrome who suffered three different relapses with different scenarios of central and peripheral nervous system involvement.

How the same antibody can produce a variety of clinical signs involving central and peripheral targets remains to be determined.
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be clarified. It has been shown in animal models that anti-GQ1b IgG antibody induces a massive increase in spontaneous quantal acetylcholine release by means of a complement-mediated alpha-latrotoxin-like effect (16). This results in a blocking of neuromuscular transmission and in a subsequent complement-dependent destruction of the motor nerve terminal.

In anti-GQ1b antibody syndrome with AO, single fibre electromyography showed that the neuromuscular transmission improvement paralleled the clinical recovery (17). Latrotoxin, a potent neurotoxin from black widow spider venom, stimulates a massive release of neurotransmitters both at peripheral and at central nervous system level (18). Subtypes of calcium-independent receptor for alpha-latrotoxin (CIRL1 and CIRL3) are predominantly expressed in the brain (19). The fine specificity of anti-GQ1b IgG antibody in the peripheral nervous system (20) may also apply for preferential cross-reaction with structurally differing gangliosides in the central nervous system. In rats, GQ1b ganglioside is localized in cerebellar glomeruli (21), and anti-GQ1b IgG antibodies in sera from MFS patients bind to the molecular layer of the human cerebellum (22).

Accordingly, the clinical picture of our patient could be explained by the blocking of neural transmission and subsequent tissue damage that probably occur preferentially at a central synapse level. Moreover, the biological features of anti-GQ1b IgG antibody may not only explain the variability, but also indicate a different pathophysiology of the clinical signs. More specifically, our patient presented with brainstem and cerebellar rather than with peripheral oculomotor signs; this finding is at variance with most of previous reports and it broadens the spectrum of anti-GQ1b associated syndrome with prevalent or isolated oculomotor signs.

Generally this syndrome has a benign prognosis and the most appropriate treatment is yet to be established. Intravenous high-dose immunoglobulin and plasmapheresis has been claimed to be effective (23,24) and steroid treatment is not recommended, as in GBS and in MFS (1,7). The favourable course of our patient might be due to a spontaneous remission. In conclusion, testing for anti-GQ1b IgG should be performed even in patients presenting with isolated acute central oculomotor impairment without clinical or instrumental data suggesting other diagnoses.

References

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