• Letter to the Editor •

# Anti-GQ1b antibody syndrome presenting as acute ophthalmoplegia with pupillary involvement and blepharoptosis: a case report and literature review

*Meng-Mei He, Si-Wei You, Chang-Mei Guo*

Department of Ophthalmology, Eye Institute of Chinese PLA, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi Province, China

**Correspondence to:** Chang-Mei Guo. Department of Ophthalmology, Eye Institute of Chinese PLA, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi Province, China. gcm2@163.com

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**Dear Editor,**

Anti-GQ1b antibody syndrome represents a spectrum of autoimmune disorders affecting both the peripheral and central nervous systems, characterized by diverse and complex clinical manifestations. The syndrome is primarily defined by the clinical trial of ataxia, ophthalmoplegia, and areflexia. However, isolated completely bilateral ophthalmoplegia without ataxia or other neurological symptoms has rarely been reported.

Rare cases of anti-GQ1b antibody syndrome presenting as acute ophthalmoplegia without ataxia or areflexia have been described recently, mostly in adult populations. In the present study, we report a novel case of a 13-year-old boy who presented with acute complete bilateral ophthalmoplegia with pupillary involvement and mild blepharoptosis. Furthermore, we provide a comprehensive review of the current research landscape regarding anti-GQ1b antibody syndrome, with particular emphasis on its atypical presentations in pediatric patients. Informed consent was obtained from the patient's parents. The process was conducted in accordance with the principles of the Declaration of Helsinki.

**Case Presentation** The clinical course and diagnostic findings of this case are presented in Figure 1. A previously healthy 13-year-old boy was admitted to our inpatient department with a two-week history of acute diplopia. The patient reported prodromal upper respiratory symptoms, including headache and rhinorrhea, preceding the onset of ocular symptoms. Notably, the patient denied visual acuity loss or conjunctival injection. Medical and family histories were unremarkable. Prior to admission at our institution, the patient had undergone a 10-day hospitalization in the neurology department of a local hospital. Comprehensive neuroimaging studies, including magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the orbits, brain, and brainstem, revealed no structural abnormalities. Diagnostic lumbar puncture performed 5d post-symptom onset demonstrated normal intracranial pressure (170 mm $H_2O$) and revealed clear, colorless cerebrospinal fluid (CSF) without coagulation. CSF analysis showed normal cytochemical parameters: nucleated cell count ($2.0\times10^6$/L), protein concentration (16.0 mg/dL), glucose level (3.5 mmol/L), and chloride level (125.9 mmol/L). The clinical symptoms were not improved by the intravenous administration of dexamethasone according to the diagnosis of "painful ophthalmoplegia", so the boy was referred to our hospital for further management.

Ophthalmological examination: Best-corrected visual acuity was 6/6 in both eyes. Intraocular pressure measurements and visual field testing were within normal range. Mild bilateral blepharoptosis was observed, with the upper eyelids covering 3 mm of the corneal surface. Ocular motility assessment demonstrated complete limitation of eye movements in all directions, including adduction, abduction, elevation, and depression bilaterally (Figure 2A–2I). Pupillary examination showed bilateral mydriasis (5 mm in diameter) with markedly sluggish direct and indirect light reflexes (Figure 2J–2L). Fundoscopic examination revealed normal optic disc morphology and retinal architecture without pathological findings.

Eurological examination: the patient demonstrated preserved muscle strength and intact sensory function throughout all extremities. Cranial nerve assessment showed normal facial sensation with symmetrical bilateral forehead wrinkles

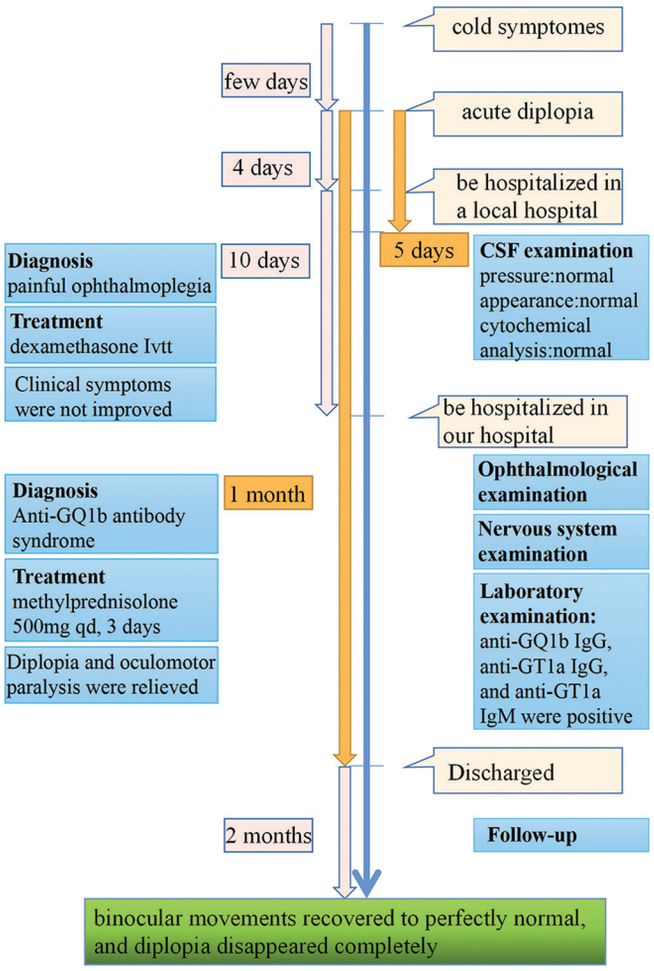


**Figure 1 The timeline of case details** CSF: Colorless cerebrospinal fluid; IgG: Immunoglobulin G.

and nasolabial folds. Both Kernig's and Brudzinski's signs were negative. Deep tendon reflexes were normoactive and symmetrical bilaterally. Cerebellar function tests, including finger-to-nose and heel-to-shin maneuvers, were performed with normal coordination, and gait assessment revealed no evidence of ataxia. Findings for all other cranial nerves were normal. Electrophysiological studies showed normal repetitive nerve stimulation test results in the bilateral median, ulnar, accessory, and axillary nerves. Pharmacological testing with neostigmine administration yielded negative results, ruling out neuromuscular junction disorders.

Laboratory investigations: comprehensive hematological and biochemical profiles, including thyroid function tests, fasting blood glucose, erythrocyte sedimentation rate, C-reactive protein, viral serology, immunoglobulin panels, complement studies, and auto-antibody screening, were within normal reference ranges. One month following symptom onset, radioimmunoassay analysis demonstrated undetectable levels of both anti-acetylcholine receptor (AChR) and anti-muscle-specific kinase (MuSK) antibodies (<0.001 nmol/L). Enzyme-linked immunosorbent assay (ELISA) revealed normal anti-titin antibody levels (0.425 U/mL). Serological analysis using

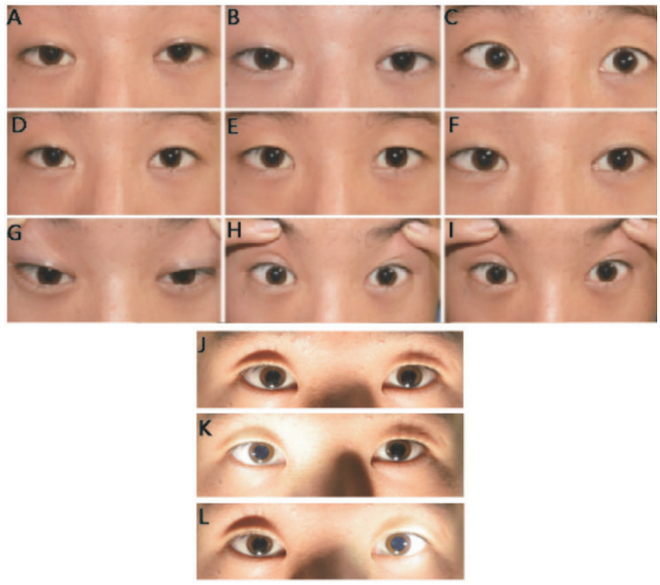


**Figure 2 Clinical examination reveals dysfunction of bilateral oculomotor, trochlear and abducent nerve** A–I: Bilateral ocular movements were paralyzed in four directions. D, F: Bilateral ocular adduction, abduction. B, H: Elevation, and depression; J–L: The binocular pupils were round, 5 mm in diameter, and direct and indirect reactive to light was very slow. J: The light shines on both eyes. K: The light shines on the right eye. L: The light shines on the left eye.

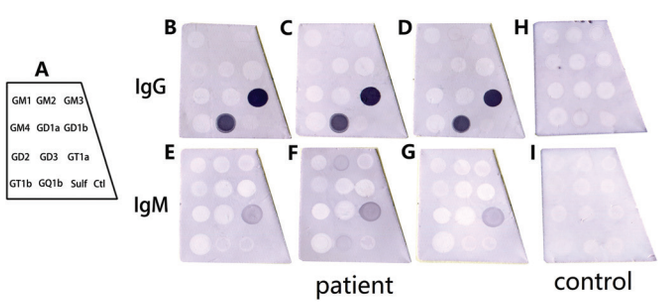


**Figure 3 The IgG and IgM antibodies to gangliosides (GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b) and to sulfatide in serum were detected qualitatively by immunospot assay** A: Distribution of gangliosides and sulfatide on immunospot assay panel; B–D: Results of IgG antibodies to gangliosides and to sulfatide in three parallel trials of patients; E–G: Results of IgM antibodies to gangliosides and to sulfatide in three parallel trials of patients; H: Results of IgG antibodies to gangliosides and to sulfatide in the control trial. I: Results of IgM antibodies to gangliosides and to sulfatide in the control trial. IgG: Immunoglobulin G; IgM: Immunoglobulin M.

immunodot assay for ganglioside and sulfatide antibodies demonstrated the following specific findings: Positive results were obtained for anti-GQ1b immunoglobulin G (IgG), anti-GT1a IgG, and anti-GT1a immunoglobulin M (IgM) antibodies (Figure 3). All other tested anti-ganglioside antibodies, including anti-GM1, anti-GM2, anti-GM3, anti-GM4, anti-GD1a, anti-GD1b, anti-GD2, anti-GD3, anti-GT1b,

and anti-sulfatide antibodies, were undetectable.

Based on the comprehensive clinical evaluation and diagnostic findings, the patient was diagnosed with anti-GQ1b antibody syndrome manifesting as acute complete bilateral ophthalmoplegia accompanied by pupillary involvement and mild blepharoptosis. The patient received intravenous methylprednisolone therapy (500 mg daily) for three consecutive days, resulting in significant improvement of diplopia and oculomotor paralysis. Following clinical stabilization, the patient was discharged with outpatient follow-up recommendations. At the two-month follow-up evaluation, complete restoration of binocular ocular motility was observed, with resolution of diplopia and normalization of all extraocular movements. The patient demonstrated full functional recovery without residual neurological deficits.

## DISCUSSION

Studies have shown that almost all patients with anti-GQlb antibody syndrome exhibit a history of preceding infections, predominantly with *Campylobacter Jejuni* or *Haemophilus* influenzae, which typically manifest as gastrointestinal or upper respiratory tract symptoms[1]. Gangliosides, particularly GQ1b, GD1a, GT1a, and GM1, represent a class of structurally diverse membrane glycolipids that are predominantly localized in neural tissues. These molecules play crucial roles in various neurophysiological processes, including neuronal development, signal transduction, and synaptic plasticity[2]. The pathogenesis of this syndrome is primarily attributed to molecular mimicry, wherein structural homology between GQ1b gangliosides and lipo-oligosaccharides derived from *Campylobacter Jejuni* and *Haemophilus* influenzae induces cross-reactive immune responses. This immunological cross-reactivity subsequently triggers the production of anti-GQ1b antibodies, leading to autoimmune-mediated neurological dysfunction.

The precise pathophysiological mechanisms underlying the phenotypic variability in anti-GQ1b antibody syndrome remain incompletely understood. Current evidence suggests that the heterogeneous clinical manifestations may be attributed to the differential distribution of GQ1b and GQ1b-like ganglioside epitopes within the nervous system. Immunohistochemical studies have demonstrated high-density expression of these epitopes at critical anatomical sites, including the nodes of Ranvier in cranial nerves III, IV, and VI, as well as presynaptic neuromuscular junctions, which are particularly vulnerable due to the absence of a blood-nerve barrier. The binding of anti-GQ1b antibodies to these neural structures induces a pathophysiological cascade characterized by conduction blockade at motor end-plates. This immunological interaction triggers excessive quantal release of acetylcholine, potentially explaining the characteristic extraocular muscle paralysis observed in affected patients.

The clinical heterogeneity of anti-GQ1b antibody syndrome is further influenced by variations in anti-GQ1b and anti-GT1a antibody responses. These variations are modulated by heteromeric complexes of gangliosides, which create novel epitopes that alter autoantibody recognition[3]. Furthermore, the clinical presentations of anti-GQ1b antibody syndrome vary with age. Acute ophthalmoplegia is the predominant phenotype in children, in contrast to the higher incidence of Miller Fisher syndrome in adults[4]. This distinction may underlie the lower GQ1b expression in juvenile peripheral nerves and its preferential localization to oculomotor nerve paranodes. Moreover, studies implicate GQ1b-related mechanisms even in seronegative cases. Uchibori *et al*[5] detected calcium-dependent IgG antibodies against GQ1b-containing complexes in seronegative patients, suggesting the pathological role of GQ1b may extend beyond seropositive results.

In this case report, we present a pediatric case of anti-GQ1b antibody syndrome, confirmed by seropositivity for anti-GQ1b antibodies, presenting as acute complete bilateral ophthalmoplegia with pupillary involvement following an upper respiratory infection. Although albumino-cytologic dissociation typically peaks weeks 2–3, our patient's CSF analysis, performed early on day 5, was normal, potentially explaining this discrepancy.

To our knowledge, this represents the first pediatric case of anti-GQ1b antibody syndrome presenting with acute complete bilateral ophthalmoplegia, pupillary involvement, and blepharoptosis. Unlike typical reports of isolated nerve palsy[6-7], this case demonstrates simultaneous III, IV, and VI cranial nerve involvement. The pronounced susceptibility may stem from developmental factors, including rich GQ1b expression and increased blood-nerve barrier permeability in ocular motor nerves.

The present case exhibited isolated ocular manifestations, including ophthalmoplegia, blepharoptosis, and mydriasis, without sensory ataxia or impaired consciousness. This clinical presentation poses significant diagnostic challenges, as it requires differentiation from myasthenia gravis, painful ophthalmoplegia, and cavernous sinus syndrome in ophthalmic practice. Key distinguishing features were as follows: Myasthenia gravis was ruled out by the rapid, non-fluctuating progression without fatigability, supported by negative anti-AChR antibodies, normal repetitive nerve stimulation, and unremarkable thymic imaging. Painful ophthalmoplegia was considered unlikely due to the absence of characteristic unilateral periocular pain preceding the palsy, the patient's pediatric age, and lack of trigeminal nerve involvement or venous congestion signs (*e.g.*, periorbital edema, conjunctival injection)[8]. Cavernous sinus syndrome was excluded by the bilateral symmetry of findings and the lack of trigeminal

nerve (ophthalmic/maxillary divisions) dysfunction or venous outflow obstruction[9].

Anti-GQ1b antibody syndrome generally carries a favorable prognosis and may resolve spontaneously. However, rare severe complications like brainstem encephalitis can occur[10]. Current therapeutic strategies for anti-GQ1b antibody syndrome and its variants primarily include intravenous immunoglobulin (IVIG), plasma exchange, and corticosteroid therapy[11]. First-line immunotherapies include IVIG and plasma exchange, which work by neutralizing pathogenic antibodies and removing them from circulation, respectively[12]. The efficacy of corticosteroids, while established in Guillain-Barré syndrome, remains controversial in anti-GQ1b antibody syndrome[13]. Emerging therapeutic strategies target underlying inflammatory and complement-mediated pathways. Cyclooxygenase-2 (COX-2) inhibitors, particularly celecoxib and meloxicam inhibitors may offer neuroprotection[14], while complement C5 inhibitors represent a promising approach by blocking the formation of the membrane attack complex and preventing antibody-mediated neural injury[15].

In conclusion, Anti-GQ1b antibody syndrome presents a diagnostic challenge due to its heterogeneous clinical manifestations, often leading to misdiagnosis in clinical practice. In cases lacking typical features, comprehensive diagnostic evaluation should include meticulous history-taking, detailed neurological examination, and targeted auxiliary examinations, particularly CSF analysis and anti-GQ1b antibody serology. The present case illustrates the diagnostic complexity of this syndrome, where the patient manifested isolated ocular symptoms-ophthalmoplegia, mydriasis, and blepharoptosis-without accompanying sensory ataxia or impaired consciousness. This atypical presentation necessitates careful differentiation from other neuro-ophthalmological conditions, including myasthenia gravis, painful ophthalmoplegia, and cavernous sinus syndrome. The definitive diagnosis of anti-GQ1b antibody syndrome ultimately relies on the identification of elevated anti-GQ1b antibody titers, underscoring the importance of specific serological testing in the diagnostic workup of patients presenting with acute ophthalmoplegia, particularly when accompanied by pupillary abnormalities.

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