



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

Clinical challenges

What did he eat?



Sara Rodrigo-Rey, MD^a, Consuelo Gutiérrez-Ortiz, PhD^{b,*},
Silvia Muñoz, MD^c, Jesús Vicente Ortiz-Castillo, MD^d,
R. Michael Siatkowski, MD^e

^a Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

^b Glaucoma and Neuro-ophthalmology Department, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

^c Ophthalmology Department, Hospital Universitari de Bellvitge, Barcelona, Spain

^d Strabismus Department, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

^e Department of Ophthalmology, Dean McGee Eye Institute, University of Oklahoma, Oklahoma City, OK, USA

ARTICLE INFO

(In keeping with the format of a clinical pathologic conference, the abstract and key words appear at the end of the article.)

Article history:

Received 20 September 2020

Available online 30 September 2020

Peter Savino and Helen
Danesh-Meyer, Editors

1. Case report

A 13-year-old boy was referred for acute horizontal binocular diplopia. His psychomotor development was normal, and his past medical history was unremarkable. He denied head trauma or exposure to toxins. Ten days before, he had experienced diarrhea and a low-grade fever, as well as asthenia. On admission, temperature was 99.3°F, and other vital signs were normal. Cardiopulmonary auscultation and abdominal examination were normal.

His visual acuity was 20/20 in each eye. Ocular examination revealed a dilated pupil that reacted poorly to light in the left eye. No relative afferent pupillary defect was observed. There was a complex pattern of extrinsic ocular motility abnormalities. He had an incomitant esophoria measuring 12 prism diopters at distance and 4 prism diopters at near associated

with limited abduction of both eyes. In addition, there was a left ptosis (Fig. 1). He did not relate diurnal variation. Slit lamp biomicroscopy, intraocular pressure, and funduscopy were normal in both eyes.

What is your initial diagnosis? What is the differential diagnosis at this point? What additional examinations and ancillary test would you order?

2. Comments by R. Michael Siatkowski, MD

This patient presents with acute onset of bilateral ophthalmoplegia after a presumed viral illness. The photo shows clear abduction deficits in each eye, as well as an adduction

* Corresponding author: Consuelo Gutiérrez-Ortiz, PhD, Glaucoma and Neuro-ophthalmology Department, Hospital Universitario Príncipe de Asturias, Carretera Alcalá-Meco, s/n, 28805, Alcalá de Henares, Madrid, Spain.

E-mail address: consuelogutierrez@gmail.com (C. Gutiérrez-Ortiz).

0039-6257/\$ – see front matter © 2020 Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.survophthal.2020.09.007>

deficit in the right eye. Left-sided ptosis and anisocoria are not easily appreciable in these pictures, but we are told that there is an efferent pupillary defect OS.

Bilateral diffuse ophthalmoplegia, whether complete or incomplete, may result from problems anywhere from the brainstem to the neuromuscular junction. From a topical diagnosis standpoint, these include intrinsic brainstem disease such as stroke or demyelination; infectious or noninfectious meningitis; ischemic, inflammatory, or autoimmune disorders of the cranial nerves; cavernous sinus or orbital lesions; and myasthenia gravis or botulism.

We are not told whether this patient has any motor or sensory problems that could occur with brainstem or autoimmune disease, but he has no evidence of optic neuropathy, proptosis, or other signs that would be expected with orbital involvement. The presence of anisocoria and/or abnormally reacting pupils is not consistent with myasthenia. Wernicke disease or other vitamin deficiency may present similarly, but this patient's history (or lack thereof) makes it unlikely. Diabetes mellitus has rarely been reported to cause bilateral simultaneous cranial neuropathies, but this is generally in type 2 patients who are several decades older than this patient.

Thus, the differential at this point is brainstem disease, some type of meningitis, a cavernous sinus mass, or inflammatory/autoimmune cranial neuropathies. In a previously healthy teenage boy, the most common entities would be a low-grade brainstem tumor, a parasellar mass (craniopharyngioma, pituitary adenoma) extending into the cavernous sinus, or parainfectious cranial nerve inflammation (idiopathic postviral, Miller Fisher syndrome [MFS] or variant thereof). The appropriate initial workup would consist of neurologic examination, magnetic resonance imaging of the brain and posterior fossa with and without gadolinium, and lumbar puncture. If there is any question that the anisocoria may be physiologic or the asymmetric pupillary reactivity is minimal, serum acetylcholine receptor antibodies should be drawn as well (or, alternatively, an edrophonium or

prostigmine test if available), as myasthenia is always a great masquerader.

3. Case report (continued)

The clinical diagnosis of incomplete left third nerve with pupillary involvement and bilateral abducens nerve and palsies was made.

Neurological examination revealed no abnormalities in consciousness or corticospinal tract signs. There was no dysmetria, ataxia, limb muscles weakness, or sensory deficits. Deep tendon reflexes were diminished. Cranial nerve examination was normal except the previously described ocular motility disturbances.

Brain and orbit magnetic resonance imaging were unremarkable. Routine biochemistry and hemogram tests were also normal. Serologic tests for syphilis, tuberculosis, *Borrelia*, cytomegalovirus, Epstein-Barr virus, herpes simplex virus type 1 and 2, varicella-zoster virus, and adenovirus were negative. Edrophonium testing was also negative.

What supplemental testing would you order? What would be the final diagnosis? Is there any treatment available?

4. Comments by R. Michael Siatkowski ... (continued)

With normal neuroimaging and a negative edrophonium test, autoimmune/inflammatory cranial neuropathies rise to the top of the differential diagnosis. As the patient is systemically well, infectious meningitis is unlikely, but lumbar puncture is required to assess for noninfectious inflammation. The abnormal deep tendon reflexes in the setting of parainfectious multiple cranial neuropathies make the Miller Fisher variant of Guillain-Barre syndrome a



web 4C/FPO

Fig. 1 – Ocular motility examination. Limitation of abduction in both eyes with mild internal ophthalmoplegia and ptosis in the left eye.

likely diagnosis. This syndrome likely results from diffuse cross-reactivity of antimicrobial or antiviral antibodies with neural sheathes and/or axons. Although ataxia is present in the classic cases, it does not always occur or may be extremely subtle or short-lived; thus, the eponym's triad of ophthalmoplegia, areflexia or hyporeflexia, and ataxia are better considered as a spectrum of clinical findings rather than an obligate requisite diagnostic combination. Serum GQ1b antibodies are present in 80–90% of cases, but there are reports of antibodies to a number of other gangliosides, so a more comprehensive panel should be performed if the GQ1b testing is negative.

Although there are no clinical trials to support any treatment strategies, management is similar to that for classic Guillain-Barre syndrome, namely intravenous immunoglobulins or plasmapheresis. Steroids have not been proven to be useful in Guillain-Barre syndrome, so they would not be appropriate in this case. Fortunately, the prognosis for these patients is generally good, with improvement beginning a few weeks after symptom onset and complete or near-complete recovery within several months. Relapses occur only in 2–3% of patients.

5. Case report (continued)

A spinal tap was performed. The opening pressure was 11 cm of H₂O. Cerebrospinal fluid content revealed no cells, slightly elevated protein (54 mg/dl), glucose of 67 mg/dl, sterile cultures, and negative serologies. Full ganglioside antibodies serum test was performed (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and antisulfatide antibodies). The patient had IgM antibodies against GM1. Electromyography did not show nerve conduction abnormalities.

The patient was diagnosed with acute ophthalmoparesis without ataxia, a variant of MFS. Our patient had bilateral abducens nerve palsy plus an incomplete third cranial nerve palsy with pupillary involvement presumably related to a prior gastrointestinal infection, associated with anti-GM1 autoantibody.

Intravenous immunoglobulin therapy was started, 400 mg/kg daily for 5 days. He experienced progressive and complete recovery of ocular motility deficits and deep tendon reflexes (Fig. 2).

6. Discussion

The clinical spectrum of the anti-GQ1b antibody syndrome encompasses a broad group of polyneuropathies with overlapping clinical features. The acute onset of the triad of extrinsic ophthalmoplegia, ataxia, and hyporeflexia or areflexia characterizes MFS.⁵ Clinical variants of anti-GQ1b antibody syndrome include MFS—complete and atypical forms—Guillain-Barré syndrome, Bickerstaff brainstem encephalitis, or polyneuritis cranialis.^{14,21,25} These conditions are uncommon during childhood.^{18,19} Nearly 90% of the reported cases have serum anti-GQ1b antibody titers, which seems to be closely related to ophthalmoplegia.^{3,6}

Polyneuropathies are preceded by upper respiratory tract infection in 75% of patients and gastrointestinal infection in only the 4%.^{17,20,22} The most common pathogen related to MFS is *Campylobacter jejuni*.^{13,28,30} Other infectious agents also related are cytomegalovirus, parvovirus,¹ and *Haemophilus influenzae*.²⁶ Recently severe acute respiratory syndrome coronavirus-2 infection has been reported to produce an acute Miller Fisher-like syndrome.⁸

Acute ophthalmoplegia accounts for an incomplete form of MFS that might also be associated with hyporeflexia or areflexia.^{17,29} Diagnosis is generally based on clinical features, lack of abnormalities in consciousness or corticospinal tract signs, absence of limb weakness, monophasic illness pattern, and the absence of any identifiable alternative diagnosis. Moreover, there may be supportive findings such as cerebrospinal fluid albumin-cytological dissociation, electrophysiological abnormalities, and serum anti-GQ1b autoantibodies.²⁵ Just few cases have been previously reported in adults,²⁹ even less in childhood.^{7,10,11,15,23,24,27} There were serum anti-GQ1b antibodies in all the cases, and occasionally antibodies against ganglioside complex.



Fig. 2 – After treatment, there was complete recovery of extraocular motility.

Antiganglioside antibodies are strongly related to MFS, being present in approximately 80% of patients.³ They induce an autoimmune cross-reaction due to a molecular similarity between host ganglioside protein and surface pathogen epitopes.^{9,30} Clinical manifestations of spectrum anti-GQ1b syndrome depend on the different expression sites of the target molecules in the nervous system. GQ1b and GT1a antigens are mainly located in paranodal regions of the extramedullary portion of the oculomotor, trochlear, and abducens cranial nerves.^{2,6} Fukami and coworkers described a significant association between anti-GQ1b or anti-GT1a titers and ophthalmoplegia, but it can also appear related to other ganglioside autoantibodies, as in the present case.⁶ On the other hand, anti-GM1, anti-GM1b, and anti-GD1 have been related to limb weakness.⁶ MFS and its variants are usually self-limiting, and spontaneous recovery without residual deficits occurs in most cases; however, medical supportive care may be necessary. Corticosteroids, intravenous immunoglobulin, or plasmapheresis are recommended to speed up the recovery of symptoms.

Acute ophthalmoplegia in childhood is a mayor diagnostic challenge for clinicians. The most frequent clinical picture is bilateral abducens nerve palsy.^{17,29} It also may present as pure horizontal, pure vertical, or with mixed palsy pattern, as intrinsic ophthalmoplegia, or ptosis without limited eyed movements. Anti-GQ1b or anti-GT1a have been identified in all cases. In addition, serum anti-GM1 was also detected in two cases.^{1,4} Our patient would be the first described one associated with isolated anti-GM1 positive titers.

Some potentially dangerous diseases may present with multiple or bilateral acute nerve palsies. Therefore, pituitary apoplexy, mesencephalic ischemia, neuromuscular junction disorders, cavernous sinus disease, trauma, drug toxicity, infections, metastatic or paraneoplastic diseases, and autoimmune diffuse polyneuropathies should be ruled out.^{12,16}

To conclude, MFS and especially its atypical forms may be potentially severe and challenging to diagnosis, so a high clinical suspicion is needed. This case underlines the relevance of a complete screening of all the antiganglioside antibody complex.

7. Method of literature search

PubMed literature search was performed for relevant articles related to bilateral abducens palsy and Miller Fisher spectrum disorders, using the following terms: Miller Fisher syndrome, acute ophthalmoparesis without ataxia, anti-GQ1b antibody syndromes, and antiganglioside antibodies. Additional articles were collected from the reference list of articles previously obtained from the original PubMed literature search.

8. Disclosure

Declaration of conflicting interests.

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Author contributions: R.-R.S. and G.-O.C. contributed to conceptualization, supervision, validation, writing the original draft, and reviewing and editing the same. M.S., O.-C.J.V., and S.R.M. contributed to supervision, validation, and reviewing and editing the article.

REFERENCES

- Canavese C, Mancini S, Tocchet A, et al. Acute unilateral ophthalmoparesis associated with anti-GQ1b and GM1 antibodies after parvovirus infection in a 10-year-old girl. *Eur J Paediatr Neurol.* 2018;22(1):213–4
- Chiba A, Kusunoki S, Obata H, et al. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. *Neurology.* 1993;43(10):1911–7
- Chiba A, Kusunoki S, Shimizu T, et al. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome. *Ann Neurol.* 1992;31(6):677–9
- De Bruyn A, Poesen K, Bossuyt X, et al. Clinical spectrum of the anti-GQ1b antibody syndrome: a case series of eight patients. *Acta Neurol Belg.* 2019;119(1):29–36
- Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N Engl J Med.* 1956;255(2):57–65
- Fukami Y, Wong AH, Funakoshi K, et al. Anti-GQ1b antibody syndrome: anti-ganglioside complex reactivity determines clinical spectrum. *Eur J Neurol.* 2016;23(2):320–6
- Guisset F, Ferreiro C, Voets S, et al. Anti-GQ1b antibody syndrome presenting as acute isolated bilateral ophthalmoplegia: report on two patients and review of the literature. *Eur J Paediatr Neurol.* 2016;20(3):439–43
- Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology.* 2020;95(5):e601–5
- Jacobs B, Endtz H, van der Meché F, et al. Serum anti-GQ1b IgG antibodies recognize surface epitopes on *Campylobacter jejuni* from patients with Miller Fisher syndrome. *Ann Neurol.* 1995;37(2):260–4
- Jindal G, Parmar VR, Gupta VK. Isolated ptosis as acute ophthalmoplegia without ataxia, positive for anti-GQ1b immunoglobulin G. *Pediatr Neurol.* 2009;41(6):451–2
- Kauser H, Jain P, Sharma S, Aneja S. Complete bilateral ophthalmoplegia with unilateral facial palsy in a child with anti-GQ1b syndrome. *Indian J Pediatr.* 2015;82(2):192–4
- Keane JR. Bilateral ocular paralysis. *Arch Neurol.* 2007;64(2):178
- Koga M, Gilbert M, Li J, et al. Antecedent infections in Fisher syndrome: A common pathogenesis of molecular mimicry. *Neurology.* 2005;64(9):1605–11
- Koga M, Kishi M, Fukusako T, et al. Antecedent infections in Fisher syndrome: sources of variation in clinical characteristics. *J Neurol.* 2019;266(7):1655–62
- Kuroki S, Saida T, Nukina M, et al. Three patients with ophthalmoplegia associated with *Campylobacter jejuni*. *Pediatr Neurol.* 2001;25(1):71–4
- Lee MS, Galetta SL, Volpe NJ, Liu GT. Sixth nerve palsies in children. *Pediatr Neurol.* 1999;20(1):49–52
- Lee SH, Lim GH, Kim JS, et al. Acute ophthalmoplegia (without ataxia) associated with anti-GQ1b antibody. *Neurology.* 2008;71(6):426–9

18. Lin JJ, Hsia SH, Wang HS, et al. Clinical variants of Guillain-Barré syndrome in children. *Pediatr Neurol.* 2012;47(2):91–6
19. Lo YL. Clinical and immunological spectrum of the Miller Fisher syndrome. *Muscle Nerve.* 2007;36(5):615–27
20. Mori M, Kuwabara S, Fukutake T, et al. Clinical features and prognosis of Miller Fisher syndrome. *Neurology.* 2001;56(8):1104–6
21. Odaka M, Yuki N, Hirata K. Anti-GQ1b IgG antibody syndrome: clinical and immunological range. *J Neurol Neurosurg Psychiatry.* 2001;70(1):50–5
22. Pellegrini F, Prodocimo G, Barton JJ. The pescatorial sixth. *Surv Ophthalmol.* 2016;61(2):248–54
23. Sato K, Yoshikawa H. Bilateral abducens nerve paresis associated with anti-GQ1b IgG antibody. *Am J Ophthalmol.* 2001;131(6):816–8
24. Vanden Eijnden S, Borza D, Caudron V, Cavatorta E. Isolated 6th nerve palsy in a child associated with asymptomatic Chlamydia pneumoniae infection and elevated anti-GQ1b antibody. *Eur J Pediatr.* 2001;160(6):400
25. Wakerley BR, Uncini A, Yuki N. Guillain-Barré and miller fisher syndromes - New diagnostic classification. *Nat Rev Neurol.* 2014;10(9):537–44
26. Wakerley BR, Yuki N. Polyneuritis cranialis—subtype of Guillain-Barré syndrome? *Nat Rev Neurol.* 2015; 11:664
27. Weber P, Regeniter A, Kaiser H. Acute ophthalmoparesis in a child with anti-GQ1 b IgG antibody. *Neuropediatrics.* 2003;34(5):274–5
28. Yuki N, Koga M. Bacterial infections in Guillain-Barré and Fisher syndromes. *Curr Opin Neurol.* 2006;19(5):451–7
29. Yuki N, Odaka M, Hirata K. Acute ophthalmoparesis (without ataxia) associated with anti-GQ1b IgG antibody: Clinical features. *Ophthalmology.* 2001;108(1): 196–200
30. Yuki N, Taki T, Takahashi K, et al. Molecular mimicry between GQ1b ganglioside and lipopolysaccharides of *Campylobacter jejuni* isolated from patients with Fisher's syndrome. *Ann Neurol.* 1994;36(5):791–3

A B S T R A C T

Keywords:

acute ophthalmoparesis
 Miller Fisher syndrome
 anti-GQ1b antibody syndromes
 antiganglioside antibodies
 bilateral sixth nerve palsy
 childhood diplopia

A 13-year-old boy reported acute horizontal binocular diplopia and headache. Ten days before these symptoms he suffered from a gastrointestinal infection. Ophthalmological examination revealed bilateral ophthalmoparesis and diffuse hyporeflexia. Magnetic resonance imaging of the brain was normal. Lumbar puncture revealed albuminocytological dissociation. There were no anti-GQ1b antibodies, but serum anti-GM1 antibodies were detected. He received intravenous immunoglobulins and had fully recovered two weeks later. Miller Fisher syndrome and its atypical variants are uncommon in childhood; nevertheless, they should be considered in the differential diagnosis of bilateral acute ophthalmoparesis.

© 2020 Elsevier Inc. All rights reserved.
