CASE REPORT

The Role of Botulinum Toxin in the Management of Ophthalmoplegia Secondary to Miller Fisher Syndrome

Siegfried K. Wagner, Nabil Uddin, and Saurabh Jain

Department of Ophthalmology, Royal Free Hospital NHS Foundation Trust, London, UK

ABSTRACT

Miller Fisher syndrome is an acute demyelinating polyneuropathy classically presenting with ataxia, areflexia, and ophthalmoplegia. The authors report the case of a 27-year-old female, who presented with limb weakness and double vision following a prodromal pharyngitis. Ophthalmic examination revealed fluctuant ophthalmoplegia eventually consistent with bilateral sixth cranial nerve palsies, prompting investigation for anti-ganglioside antibodies, which returned positive. Due to disabling diplopia, the patient was treated with botulinum toxin, with a resulting favourable reduction in the size of strabismus. Four months following her presentation, the patient was orthophoric and resumed normal activities.

ARTICLE HISTORY

Received 28 June 2017
Accepted 12 July 2017

KEYWORDS

Anti-ganglioside antibodies;
botulinum toxin; Miller
Fisher syndrome;
ophthalmoplegia

Introduction

Miller Fisher syndrome (MFS) describes a rare variant of Guillain-Barré syndrome (GBS) typically characterised by a triad of areflexia, ataxia and ophthalmoplegia.¹ We report a case where a patient with MFS presented with complex ophthalmoplegia eventually consistent with bilateral sixth cranial nerve palsies. Due to a persistent stable esotropia and prism intolerance, the patient was treated with a single dose of botulinum toxin resulting in orthophoria and resumption of their occupation.

Case report

A 27-year-old female construction manager presented to the emergency department with evolving limb numbness, difficulty walking, droopy eyelids, and double vision. She had a preceding viral illness marked by sore throat and fever. Two days ago, she awoke with a numb left arm, which had progressed to involve both legs. Additionally, she had left facial numbness and a drooping left eyelid. She also reported horizontal double vision. She had no past ocular history and no relevant past medical history. Her admitting examination revealed a broad-based uncoordinated gait, global

hyporeflexia, and decreased sensation in both lower limbs. She was afebrile (36.7°C) and normotensive (118/61 mm Hg) but tachycardic (104 beats per minute). Initial blood investigations were unremarkable with normal biochemical parameters and haematology. Erythrocyte sedimentation rate (ESR) was 1 mm/h and C-reactive protein 1 mg/L.

Following admission for neurological investigations, she underwent magnetic resonance imaging of the head and spine, which was within normal limits. Lumbar puncture showed normal parameters (glucose 3.8 mmol/L, protein 0.26 g/L, white cells $<1 \times 10^6/L$), and no microorganisms or oligoclonal bands were isolated. She was discharged 7 days following her admission with a diagnosis of possible non-organic illness having demonstrated mild improvement in her symptomatology. Outpatient follow-up to ophthalmology was arranged due to persistent double vision.

On the day of her discharge, she was seen in the orthoptic/ophthalmology clinic. Visual acuities were 20/15 OU. She had preserved colour vision (13/13 Ishihara plates) and normal pupillary reflexes. Bilateral ptosis (left greater than right) was present but demonstrated no fatigability or

CONTACT Siegfried K. Wagner ✉ saurabh.jain@nhs.net Department of Ophthalmology, Royal Free Hospital NHS Foundation Trust, Pond Street, London, NW3 2QG, UK.

This work has been accepted as an electronic poster at the British Isles Paediatric, Ophthalmology and Strabismus Association (BIPOSA) Annual Meeting 2016 and at the American Association of Pediatric Ophthalmology and Strabismus (AAPOS)/Strabismus and Pediatric Ophthalmological Society of India (SPOSI) Annual Meeting 2016.

© 2018 Taylor & Francis

Cogan twitch. She had a small left divergent squint (1^Δ base-in [BI]) for near and an alternating convergent squint (12^Δ base-out [BO]) for distance. She had globally reduced extraocular movements, particularly in abduction and adduction with hypometric horizontal saccades. Furthermore, she exhibited bilateral abducting nystagmus. Given the presence of acute ophthalmoplegia, gait disturbance, and areflexia in conjunction with a preceding illness, serological testing for anti-ganglioside antibodies was arranged and a prism prescribed.

Follow-up 1 week later showed an alternating convergent squint at both near (12^Δ BO) and distance (20^Δ BO) with much improved extraocular movements. Her findings were now isolated to bilateral abduction deficits suggestive of mild sixth cranial nerve palsies. Similar findings were seen 2 weeks later (near: 14^Δ BO, distance: 20^Δ BO). Given the patient's inability to work, she was keen on interventions, which might mitigate the diplopia. Unable to tolerate prisms and not pleased with a patch, she was offered botulinum toxin (1.25 units of Botox® to the left medial rectus). Two weeks after toxin administration, the patient reported a return to work and an improvement in double vision (near: esophoria, distance: 12^Δ BO). Additionally, serological results revealed positive anti-GQ1b immunoglobulin G antibodies consistent with a diagnosis of MFS. At last follow-up, 4 months after her initial presentation, the patient reported a return to baseline with orthophoric findings at both 1 foot and 6 feet on examination, full eye movements, resolved ptosis, and good control (prism fusion range 30^Δ BO to 12^Δ BI at 1 foot).

Discussion

The acute demyelinating polyneuropathy MFS describes a rare variant of Guillain-Barré syndrome (GBS) typically characterised by areflexia, ataxia, and ophthalmoplegia¹ and a rare incidence (1/100,000 per year).¹ However, the term MFS has grown to encompass a spectrum of disorders ranging from the classic MFS triad to acute ophthalmoparesis (ophthalmoplegia alone) to Bickerstaff brainstem encephalitis (ophthalmoplegia, ataxia, and hypersomnolence).² All conditions generally share the features of preceding infection, a monophasic time course, and cerebrospinal fluid (CSF)

albuminocytological dissociation. Further evidence comes from serological testing, where anti-ganglioside antibodies reinforce the view that these conditions have similar pathophysiology. Anti-GQ1b IgG antibodies are present in approximately 90% of cases of MFS, believed to result from the inflammatory insult to the cranial nerves.³ Notably, there is a dearth of GQ1b, GT1A, and GD1b in the neuromuscular junctions of human limb and axial muscles, whereas the motor endplates of the extraocular muscles demonstrate an abundance.⁴

Our patient presented with features of classic MFS. She described a preceding systemic upset consistent with antecedent infection. Neurological features generally follow around 8 days after prodromal symptoms⁵ (9 days in our patient), and most frequently *Campylobacter jejuni* is identified.⁶ However, a plethora of microorganisms have been implicated including *Haemophilus influenzae*, Epstein-Barr virus, and group A streptococcus.^{6,7} It is likely, given the upper respiratory tract complaints, that our patient suffered one of the latter infections. Although albuminocytological dissociation is typical in MFS, this generally develops 1–3 weeks following the initial symptoms and is entirely normal in half of patients,⁸ as in our case.

Ophthalmoplegia is the most frequent feature of MFS, being present in approximately 90% of anti-GQ1b disease. Typically, it is bilateral and moderately symmetrical, with the most common deficit being seen in abduction; however, mixed horizontal-vertical patterns and vertical gaze palsies are also reported.^{9,10} In a series of anti-GQ1b antibody-positive patients,¹⁰ all five patients exhibited evidence of sixth cranial nerve palsies. Although our patient ultimately demonstrated features consistent with bilateral sixth cranial nerve palsies, her initial orthoptic assessment showed a symmetrical generalised incomplete external ophthalmoplegia. It may be that acutely presenting patients manifest such gross features before mild convalescence unmasks an isolated cranial neuropathy. A comprehensive orthoptic assessment demonstrating such features in the presence of recent illness should trigger suspicion of MFS.

To the best of our knowledge, this is the first documented case of ophthalmoplegia secondary to MFS being treated with botulinum toxin. Use of this neurotoxin was prompted by the patient's

persistent stable esotropia and prism intolerance. She reported subjective improvement with a demonstrable benefit on orthoptic testing even with a modest dose (1.25 units) and was able to resume employment. Given the time course of MFS, one might consider botulinum toxin to “tide over” a patient during the acute phase, akin to a vascular sixth cranial nerve palsy.

In conclusion, MFS is a rare condition, but thorough orthoptic evaluation highlighting an acute ophthalmoplegia in the context of a preceding infective illness can guide diagnosis. The persistent strabismus, which often accompanies the convalescent phase of MFS, is amenable to botulinum toxin and should be considered to mitigate a patient’s disabling symptoms.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

- [1] Snyder LA, Rismondo V, Miller NR. The fisher variant of Guillain-Barré syndrome (Fisher syndrome). *J Neuro-Ophthalmol* 2009;29:312–324. doi: [10.1097/WNO.0b013e3181c2514b](https://doi.org/10.1097/WNO.0b013e3181c2514b).
- [2] Wakerley BR, Uncini A, Yuki N, GBS Classification Group. Guillain-Barré and Miller Fisher syndromes—new diagnostic classification. *Nat Rev Neurol* 2014;10:537–544. doi: [10.1038/nrneurol.2014.138](https://doi.org/10.1038/nrneurol.2014.138).
- [3] Spatola M, Du Pasquier R, Schlupe M, Regeniter A. Serum and CSF GQ1b antibodies in isolated ophthalmologic syndromes. *Neurology* 2016;86:1780–1784. doi: [10.1212/WNL.0000000000002558](https://doi.org/10.1212/WNL.0000000000002558).
- [4] Liu JX, Willison HJ, Pedrosa-Domellöf F. Immunolocalization of GQ1b and related gangliosides in human extraocular neuromuscular junctions and muscle spindles. *Invest Ophthalmol Vis Sci* 2009;50:3226–3232. doi: [10.1167/iovs.08-3333](https://doi.org/10.1167/iovs.08-3333).
- [5] Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher syndrome. *Neurology* 2001;56:1104–1106. doi: [10.1212/WNL.56.8.1104](https://doi.org/10.1212/WNL.56.8.1104).
- [6] Koga M, Gilber M, Li J, Koike S, Takahashi M, Furukawa K, Hirata K, Yuki N. Antecedent infections in Fisher syndrome: a common pathogenesis of molecular mimicry. *Neurology* 2005;64:1605–1611. doi: [10.1212/01.WNL.0000160399.08456.7C](https://doi.org/10.1212/01.WNL.0000160399.08456.7C).
- [7] Yuki N, Hirata K. Fisher’s syndrome and group A streptococcal infection. *J Neurol Sci* 1998;160:64–66. doi: [10.1016/S0022-510X\(98\)00220-2](https://doi.org/10.1016/S0022-510X(98)00220-2).
- [8] Nishimoto Y, Odaka M, Hirata K, Yuki N. Usefulness of anti-GQ1b IgG antibody testing in Fisher syndrome compared with cerebrospinal fluid examination. *J Neuroimmunol* 2004;148:200–205. doi: [10.1016/j.jneuroim.2003.11.017](https://doi.org/10.1016/j.jneuroim.2003.11.017).
- [9] Yuki N, Odaka M, Hirata K. Acute ophthalmoparesis (without ataxia) associated with anti-GQ1b IgG antibody: clinical features. *Ophthalmology* 2001;108:196–200. doi: [10.1016/S0161-6420\(00\)00420-6](https://doi.org/10.1016/S0161-6420(00)00420-6).
- [10] Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. *Neurology* 1993;43:1911–1911. doi: [10.1212/WNL.43.10.1911](https://doi.org/10.1212/WNL.43.10.1911).