

# CLINICAL CHALLENGES

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## The Double Vision Decision

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**Comments by Nicholas T. Monsul, MD, and Neil R. Miller, MD**

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

*Case Report.* A 50-year-old man noted binocular horizontal diplopia and ptosis in both eyes (OU). He has also noted an “unsteady” gait, which he ascribed to the diplopia. He had gastroenteritis for 1 day at the time of the diplopia and a sinus infection 1 week prior. He denied consuming inadequately prepared or canned food and has had no history of tick bites. He took no medications and had no past medical problems except for a right rotator cuff tear 8 months before.

Neuro-ophthalmologic examination 4 days after the onset of diplopia revealed visual acuity of 20/25 OU with color vision of 10 of 14 OU using the Ishihara pseudo-isochromatic plates. Kinetic perimetry revealed full visual fields OU. The pupils were 5 mm in the right eye (OD) and 6 mm in the left eye (OS), reacted briskly to light bilaterally, and there was no relative afferent pupillary defect (RAPD). There was nearly complete bilateral ophthalmoplegia with minimal infraduction OU (Fig. 1). Trigeminal, facial function, and exophthalmometry were normal. Slit-lamp biomicroscopy was normal and retinal examination was normal OU. Muscle strength and tone, coordination, position sense, and sensation to pin prick and light touch were intact in all extremities. He was areflexic in all extremities and his gait was wide-based and ataxic; he had no Romberg sign or pronator drift.

*What are the diagnostic possibilities? How would you proceed?*

### Comments

*Comments by Nicholas Monsul, MD, Department of Neurology, Johns Hopkins Hospital, and Neil R. Miller, MD, Wilmer Eye Institute, Baltimore, Maryland, USA*

A 50-year-old man presents with an acute bilateral ophthalmoplegia and ptosis in the setting of a gastroenteritis and sinusitis 1 week earlier. The pupils are briskly reactive without an RAPD; there is no evidence of an optic neuropathy and the patient’s general neurologic examination is remarkable for decreased deep-tendon reflexes and a wide-based ataxic gait. In evaluating any patient with acquired strabismus, one must consider three main etiologies: myopathic, neuromuscular, and neurologic. In this patient, the presence of areflexia (a lower motor neuron sign), with normal strength and an ataxic gait eliminate both a myopathic and a neuromuscular etiology. The evaluation should therefore focus on a neurologic cause.

Neurologic causes of ophthalmoparesis may result from lesions of the ocular motor nuclei, fascicles, or nerves. Thus, they may be intrinsic or extrinsic processes, such as tumors, vascular lesions, inflamma-



*Fig. 1.* Extraocular movements showing nearly complete ophthalmoplegia with only minimal infraduction OU.

tions, and infections. It is hard to imagine a single intraxial lesion that could produce a bilateral generalized ophthalmoplegia, ataxia, and hyporeflexia. Such a lesion would have to extend from the mesencephalon to the pons and involve the corticospinal and cerebellar tracts as well and would leave the patient much more neurologically impaired than he is. Although a single lesion such as a pituitary adenoma could produce bilateral ophthalmoplegia from extension into both cavernous sinuses, the pupils would almost certainly be affected in such a case. In addition, such a lesion could not produce either hyporeflexia or ataxia. Thus, the process in this patient must be a more generalized one.

There are several generalized processes that need to be considered given the constellation of findings. The dominantly inherited spinocerebellar ataxias (SCA) are a group of disorders that, in addition to the affecting the cerebellum, can also affect the spinal cord, retina, optic nerve, and ocular motility.<sup>40</sup> The ophthalmoplegia is secondary to defective supranuclear input as oculocephalic testing can overcome the limitation of the ocular motility. We are not given this patient's response to oculocephalic testing, but patients with one of the SCAs usually have deep-tendon reflexes that are brisk or normal early in the course of the disease and that only become lost as the disease progresses. Typically, it is a combination of clinical findings, family history, electromyographic studies showing reduced sensory action potentials,<sup>39</sup> magnetic resonance (MR) imaging demonstrating atrophy of the cerebellum or pons,<sup>27</sup> and genetic testing that allows the diagnosis of SCA to be made. In this case, the rapidity of the development of the ophthalmoplegia, the lack of family history, and the areflexia make SCA an unlikely diagnosis.

Systemic lupus erythematosus (SLE) is a chronic, multi-system inflammatory disease of the connective tissues that frequently has neuro-ophthalmologic findings. Although the most common ocular manifestation of SLE is retinal vascular occlusive phenomena, the frequency with which cranial nerves are affected is about 15%.<sup>41</sup> The facial nerve is most often affected, but the trigeminal and ocular motor nerves may also be damaged<sup>14</sup> from ischemia secondary to occlusion of the vasa nervorum or by demyelination that can clinically mimic Guillain-Barré syndrome (GBS).<sup>7</sup> The pathologic process may affect one or more of the ocular motor nerves, or the brainstem where it may produce an ocular motor nerve palsy, a unilateral or bilateral internuclear ophthalmoplegia, a vertical or horizontal gaze paresis.<sup>9</sup> It may even be within the orbit, in which case it typically is associated with proptosis and other signs of orbital inflammation.<sup>11</sup> However, we are unaware of any cases of SLE producing the combination of neurologic and ocular manifestations such as described in this patient.

Paraneoplastic syndromes that affect the visual sensory and ocular motor pathways are becoming increasingly recognized. Paraneoplastic visual sensory disorders include cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and optic neuropathy. Paraneoplastic optic neuropathy is frequently associated with other neurologic deficits, particularly ataxia, peripheral neuropathy, and autonomic neuropathy.<sup>4,21</sup> Other paraneoplastic syndromes that affect the ocular motor pathways include the Lambert-Eaton syndrome, the opsoclonus-myoclonus syndrome and brainstem encephalopathies. This patient has no clinical evidence of either Lambert-Eaton syndrome or the opsoclonus-myoclonus syndrome, but he cer-

tainly could have a paraneoplastic brainstem/cerebellar paraneoplastic encephalopathy. Patients with paraneoplastic brainstem/cerebellar encephalopathy may have single or multiple ocular motor nerve paresis as well as evidence of cerebellar dysfunction. Such patients do not, however, have hyporeflexia. Typically, the underlying cancer is a small-cell carcinoma of the lung, a thymoma or ovarian carcinoma, and patients with this condition frequently have one of several autoantibodies in their serum, including anti-Yo, anti-Hu, anti-Ri, or CRMP-5.<sup>2,15,21,33,47</sup>

The combination of ptosis and ophthalmoparesis is a common manifestation of one of the most common mitochondrialopathies, chronic progressive external ophthalmoplegia (CPEO). CPEO may occur as an isolated phenomenon, or it may be associated with pigmentary retinopathy and heart block, in which the triad is called the Kearns-Sayre syndrome (KSS).<sup>46</sup> Some patients with KSS also have cerebellar ataxia and sensorineural deafness. Typically, however, more than half the patients with CPEO have proximal muscle weakness and exercise intolerance that is not noted in this patient.

Ptosis and complete external ophthalmoplegia frequently occur in patients with myotonic dystrophy. These patients have myotonia, however, not areflexia (as in this patient). In addition, iridescent cataracts are present in nearly 100% of patients with myotonic dystrophy.<sup>45</sup>

The rare inherited disorder abetalipoproteinemia (Bassen-Kornzweig syndrome) thought to be secondary to malabsorption of vitamin E, is characterized by demyelination of peripheral nerves. Patients with this condition usually have decreased deep-tendon reflexes, and they may develop cerebellar ataxia and pigmentary retinopathy. Signs of ocular motor dysfunction in such patients include progressive gaze restriction and a posterior internuclear ophthalmoplegia of Lutz.<sup>46</sup> We are unaware of bilateral external ophthalmoplegia occurring in such patients, who almost always have muscle weakness and onset of symptoms starting between the ages of 6 and 12 years old.

Myasthenia gravis should always be considered in a patient with an external ophthalmoplegia; however, as noted above, the presence of hyporeflexia and ataxia in this patient makes a diagnosis of myasthenia gravis untenable.

Toxins elaborated by the organism *Clostridium botulinum* impair neuromuscular transmission by interfering with the release of acetylcholine at the presynaptic side of the neuromuscular junction. The neuro-ophthalmologic findings typically include ophthalmoplegia and ptosis following either ingestion of contaminated food or exposure to the organism. Although this patient did have an antecedent gastroenteritis, there is no

evidence of generalized proximal motor weakness, and his pupils are not dilated and non-reactive or even weakly reactive, findings that typically occur with botulism.

In 1881, Carl Wernicke described a syndrome primarily found in alcoholics characterized by nystagmus usually preceding complete or incomplete ophthalmoplegia, gait ataxia, and mental confusion that may develop acutely or subacutely. Many of these patients are hyporeflexic. Although most patients with the so-called Wernicke syndrome have significant mental confusion, confabulation, or amnesia, in which case the condition is called the Wernicke-Korsakoff syndrome, mentation is normal in 10% of patients.<sup>34</sup> Although Wernicke syndrome is typically associated with a nutritional deficiency of thiamine and usually found in alcoholics, it can also occur in patients on fad diets or under other circumstances. Lesions of the medial thalami, inferomedial portions of the temporal lobe, third ventricular tumors or herpes simplex encephalitis can have similar clinical features of Wernicke's syndrome. Wernicke syndrome is a medical emergency with a 17% mortality if left untreated and, once suspected, requires the immediate administration of thiamine. Recovery of neurologic deficits can be dramatic, often with improvement of the ocular motor abnormalities within hours following the administration of thiamine. Although there is no evidence that this patient has a history of alcohol abuse or was on a fad or starvation diet, this diagnosis must be considered.

Tick paralysis following a bite from *Dermacentor andersoni* usually presents as ataxia, areflexia, and, occasionally, external ophthalmoplegia that precedes an ascending paralysis. In some cases, the clinical presentation is indistinguishable from that of the variant of GBS, the Miller Fisher syndrome (MFS, see below); however, the cerebrospinal fluid (CSF) in patients with tick paralysis generally remains normal throughout the course of the disease, whereas in patients with GBS or MFS, the CSF is normal only in 10% of the time and even then, only in the first days of the illness.

GBS is actually a group of disorders that share a common neurophysiology and pathophysiology. Acute inflammatory demyelinating polyneuropathy (AIDP) is one of the disorders that falls under the rubric of GBS. It is an acutely or subacutely evolving paralytic disease in which about 70% of patients experience an antecedent infection that can be viral, mycoplasmal or bacterial. Isolated cranial nerve involvement is the initial presentation in about 5% of patients with AIDP, most of whom subsequently develop limb weakness that is more typical.<sup>13,16,36</sup> Rarely is there exclusively cranial nerve involvement in AIDP, but frequently ophthalmoplegia occurs in association with motor paralysis.<sup>18,34</sup>

C. Miller Fisher first described a variant of GBS in detail in 1956. This condition, now called the Miller Fisher, or Fisher syndrome, consists of the triad of ophthalmoplegia, ataxia and areflexia.<sup>12</sup> A closely related condition is called Bickerstaff brainstem encephalitis (BBE). Although patients with this latter condition can have ophthalmoplegia and ataxia, such patients invariably also have disturbances in consciousness. In addition, hyporeflexia is more common than hyporeflexia or areflexia in BBE,<sup>3,50</sup> and the MRI is frequently abnormal in BBE, whereas it tends to be normal in MFS.<sup>35</sup>

In our opinion, the ophthalmoplegia, ataxia, and areflexia in this patient are most likely caused by MFS; however, a paraneoplastic syndrome must also be considered, as should a Wernicke syndrome (at least until a careful history is obtained relating to diet and alcohol intake). The issue, then, is to determine the best course of action in terms of confirming the diagnosis, providing supportive care, and initiating treatment. We believe that the first step in treating this gentleman should be administration of thiamine (which probably will not change his neurologic status) followed by admission to the hospital for close observation of his respiratory status in the event that he develops an ascending paralysis requiring ventilatory support.

We would then proceed with neuroimaging, including standard MRI with diffusion and perfusion images and MR angiography, with particular attention to the brainstem. Routine serum chemistries, especially the serum sodium should be obtained, because some patients with AIDP develop the syndrome of inappropriate antidiuretic hormone (SIADH). It also would be appropriate to obtain a complete blood count, thiamine and vitamin B12 levels, and an enzyme-linked immunosorbent assay (ELISA) for evidence of *C. botulinum* in the serum and stool. However, the most important test in this patient is assessment of the CSF. The classic finding 90% in of patients with MFS is albuminocytologic dissociation. The elevation of the protein typically rises a few days after the onset of symptoms and reaches a peak between the 4th and 6th week.<sup>38</sup> The presence of cells, particularly polymorphonuclear leukocytes, in the CSF is sufficient to cast doubt on the diagnosis of AIDP or MFS. Finally, and most importantly, we would include in the laboratory workup, assays for serum immunoglobulin G (IgG) antibodies to GQ1b, GD1a and GM1, the reason for which we will discuss below; however, the results of these assays can take several days to a few weeks to be reported.

Electromyography (EMG) evaluating the sensory and motor functioning of the peripheral nerves should be performed for two reasons. First, a progressive and ultimately total motor paralysis develops in 5–30%

of patients who present with MFS (*Guillain-Barré syndrome*). EMG studies would be useful in evaluating potential motor involvement in anticipation of supportive care. Second, sensory changes are typically present in both AIDP and MFS, and an EMG thus can be used to confirm the diagnosis. Indeed, the areflexia that occurs in patients with AIDP and MFS is thought to be secondary to a sensory neuropathy and not a motor neuropathy. Although unlikely in this patient, acute motor axonal neuropathy (AMAN) may occur after an episode of gastritis. However, this condition most often occurs in rural China and only rarely presents with ophthalmoplegia.<sup>17,23</sup>

Given the propensity of brief episodes of autonomic instability and parasympathetic over-activity in 65% of patients with AIDP, we would delay testing for myasthenia gravis with edrophonium chloride (Tensilon) or neostigmine bromide (Prostigmin), both of which can provoke or exacerbate such activity.<sup>10,43</sup> Only if the clinical course and laboratory results do not support a diagnosis of AIDP or MFS would we consider pharmacologic testing for myasthenia gravis.

### Case Report (Continued)

Complete blood count, thyroid function testing, electrolytes, and acetylcholine receptor and striated muscle antibodies were normal. A gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain was normal. An edrophonium test was negative. A nerve conduction study showed normal repetitive nerve stimulation, mildly abnormal bilateral ulnar sensory nerve action potentials, and mild reduction in the sural sensory nerve action potential amplitude.

A lumbar puncture showed no cells with a protein of 90 mg/dL (15–45) and glucose of 68 mg/dL (45–80), cryptococcal negative and a non-reactive Venereal Disease Research Laboratory (VDRL) test. A serum GQ1b auto-antibody was 400 (<100).

*What is the most likely diagnosis?*

### Comments (Continued)

*Comments by Dr. Monsul and Dr. Miller*

Miller Fisher Syndrome, monophasic polyneuropathy characterized by ataxia, areflexia, ophthalmoplegia, and sometimes other craniobulbar deficits, without limb weakness, is the most likely diagnosis. The initial symptom is usually diplopia followed by gait ataxia, then, a few days later, by areflexia. Paresthesias are noted in about 50% of patients, and proximal weakness is present in 30% of patients. About 30% of MFS patients go on to develop profound weakness, and thus are considered an overlap of MFS and GBS.

Patients with MFS often give a history of an antecedent infection, usually a gastritis. This infection is

most frequently caused by a particular strain of *Campylobacter jejuni*. Indeed, the risk of developing GBS following an infection with *C. jejuni* is 30 per 100,000 (0.03%), a 100-fold increased risk compared with the general population.<sup>22</sup> MFS also may follow infection by mycoplasma (usually *M. pneumoniae*), human immunodeficiency virus type 1, cytomegalovirus, or Epstein-Barr virus, and it has been reported in patients with lymphoma, after measles-mumps-rubella vaccination, and following surgery.<sup>30</sup>

The clinical features, neurophysiology, and pathophysiology of the group of disorders that are known together as GBS have in common IgG auto-antibodies to neuronal gangliosides, including GM1, GM2, GD1a, GD1b, GT1b and GQ1b. In particular, auto-antibodies against GQ1b gangliosides are found in about 90% of patients with MFS.<sup>49,51,52</sup> Interestingly, the GQ1b has a higher relative concentration in cranial nerves II, III, IV, and VI.<sup>8</sup> The accumulation of the GQ1b epitope is predominately within the paranodal region of the third, fourth, and sixth cranial nerves. The GQ1b epitope in the second nerve, however, is found diffusely within the tissue and may explain the relative infrequent occurrence of optic neuritis in patients with MFS.<sup>8</sup> Although the exact pathophysiologic mechanism by which the GQ1b auto-antibody produces MFS remains speculative, recent work indicates that the circulating antibodies produce both a pre- and postsynaptic blockade.<sup>5</sup> In addition, several studies have found that many of the anti-ganglioside antibodies, including anti-GQ1b, block the release of acetylcholine at the neuromuscular junction.<sup>6,32</sup>

In a series of 194 patients, Odaka et al. found that the clinical similarities between MFS, GBS, and BBE were often related to the subtypes of antibodies. In

some instances, they also were able to correlate specific clinical findings to the different antibody subtypes.<sup>29</sup> For example, patients with anti-GQ1b IgG had a statistically significant correlation with ophthalmoplegia and ataxia, but not with areflexia.<sup>29</sup> Thus, patients with GQ1b auto-antibodies are more likely to have acute ophthalmoplegia and hyporeflexia without ataxia, or ophthalmoplegia alone.<sup>48,49</sup> In some cases, the ophthalmoplegia is incomplete and suggests specific ocular motor nerve dysfunction. For example, Kruijk et al reported a patient who developed bilateral sixth nerve palsies following a *C. jejuni* enteritis and was found to have GQ1b auto-antibodies.<sup>44</sup> Conversely, Mori et al described a patient with anti-GQ1b antibodies who presented with acute ataxia and areflexia without ophthalmoplegia.<sup>26</sup> Thus, it is important to emphasize that the diagnosis of MFS should be considered in any patient who develops an acute ophthalmoparesis with or without either ataxia or hyporeflexia, or even acute onset of either ataxia or areflexia without ophthalmoplegia. In such patients, an assay for the GQ1b antibodies should always be part of the evaluation.

The neuro-ophthalmic findings in the MFS calls into question the nosologic classification of MFS as a disease that is strictly confined to the cranial nerves. Fisher thought that not all of the neuro-ophthalmic findings could be interpreted as manifestations of peripheral nerve disease.<sup>12</sup> Ropper, on the other hand, thought that some supranuclear input could overcome the oculomotor nerve palsy. In support of CNS involvement, Al-Din et al noted that the gaze palsies are remarkably stereotyped. He noted that a paralysis of upward gaze typically occurs first, followed by paralysis of horizontal gaze, and lastly, failure of downward gaze. Recovery usually follows in reverse order,

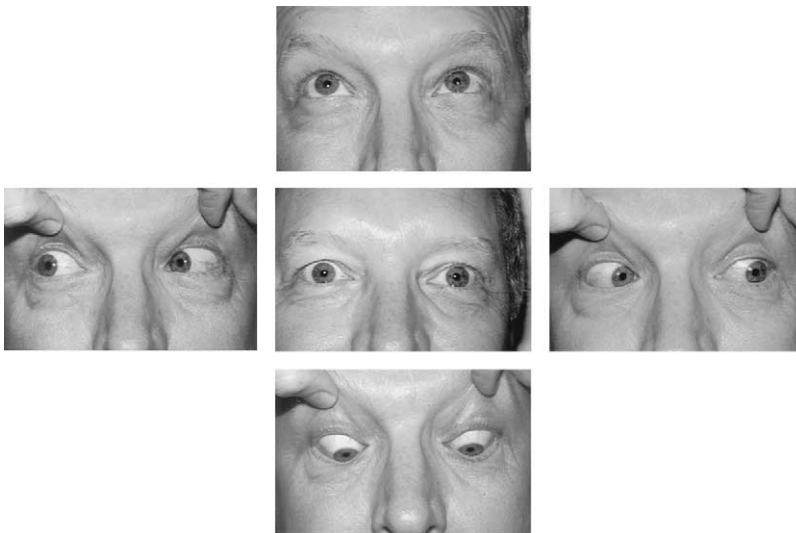


Fig. 2. Extraocular movements after treatment showing improved ocular motility OU.

with downward gaze being regained first. This progression is analogous to a rostral-dorsal-mesencephalic process moving ventrally, then caudally to include the oculomotor nucleus.<sup>1</sup> In an extensive review, Al-Din et al also noted that an internal ophthalmoplegia was present in 123 of the 243 cases (51%) then published in the literature. Since then, several cases have been reported that suggest that some cases of MFS affect the brainstem. These cases have included patients with Parinaud syndrome, internuclear ophthalmoplegia, selective sparing of down gaze, preservation of the Bell phenomenon despite paralysis of upgaze, nystagmus, and optic neuritis.<sup>1,25,52</sup> Although MR imaging in MFS is often normal, cases with enhancement within the brainstem or cerebellum has been noted in some patients with apparently clear-cut MFS.<sup>1,28,42</sup>

Although there has been no controlled clinical trial to determine the optimum treatment of MFS, the fact that its pathophysiologic mechanisms are similar to those of AIDP has provided the rationale for the use of plasma exchange (PE) or intravenous administration of IgG (IVIg).<sup>24</sup> In patients with AIDP, PE hastens recovery time and results in less time spent in the hospital. There may be, however, an increased incidence of relapses following the completion of PE when compared with non-treated patients.<sup>31</sup> In a subgroup of patients with AIDP who were positive for anti-GM1 antibodies in their serum, treatment with IVIg resulted in recovery that was significantly faster compared with a control group that received PE alone.<sup>19</sup>

Therapies other than PE or IVIg for AIDP are generally ineffective. Two large, retrospective clinical trials failed to show any difference between patients with AIDP treated with systemic corticosteroids and patients not treated with steroids.<sup>20,37</sup> Other retrospective trials using other immunosuppressive therapies have likewise been disappointing.

In summary, the importance of recognizing the significance of the triad of acute ophthalmoparesis, ataxia, and hyporeflexia, especially following either a gastroenteritis or upper respiratory infection, greatly limits the differential diagnosis. Other, less likely conditions discussed earlier can present with features of MFS, and these need to be evaluated appropriately. As discussed above, ophthalmoparesis without ataxia or areflexia does not eliminate a diagnosis of MFS, and therefore the diagnosis needs to be established with the combination of serologic studies, CSF, and electrophysiology. Anticipating autonomic instability and the possible need for ventilatory supportive care should be monitored as in a hospital setting while therapy initiated.

### Case Report (Concluded)

The patient received five treatments with plasma exchange (PE) and his examination on 16 October

2000 showed improved ocular motility (Fig. 2), and normal gait and tendon reflexes. For his continued horizontal diplopia a 25-diopter base out Fresnel prism was placed over his left lens with good results.

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**Abstract.** A 50-year-old man experienced the acute onset of ophthalmoplegia, ataxia, and hyporeflexia. Evaluation led to the diagnosis of Miller Fisher syndrome (MFS). Appropriate evaluation and management of MFS is discussed. (*Surv Ophthalmol* 48:85-91, 2003. © 2003 by Elsevier Science Inc. All rights reserved.)

**Key words.** anti-GQ1b antibody • ataxia • *Campylobacter jejuni* • hyporeflexia • ophthalmoplegia