

Clinical Reasoning: Acute onset of diplopia in pregnancy

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Section 1

A 32-year-old woman presented at 27 weeks gestation with new-onset diplopia. She awoke with persistent binocular horizontal diplopia. She denied headache, ocular pain, or other associated neurologic symptoms. There were no previous episodes. A month prior to review, 4 of her family members had diarrheal illness; the patient experienced minor nausea for 1 day only and attributed this to morning sickness. She has no relevant medical history and is usually fit and well. Her pregnancy had been uncomplicated; she was reviewed by her midwife, who reported no fever, hypertension, hyperglycemia, or proteinuria. Initial examination demonstrated a right esotropia and bilateral restriction in abduction, right greater than left, indicating bilateral sixth nerve palsy. Further ophthalmic examination was normal, demonstrating an intact visual field with no evidence of afferent pupillary defect, nystagmus, or papilledema. The rest of the cranial nerve examination was unremarkable. There were no bulbar signs, eyelid ptosis, or muscle fatigability. Peripheral neurologic examination demonstrated absent reflexes in both upper limbs and blunted reflexes in both lower limbs. There were no motor deficits or gait ataxia.

Question for consideration:

What is the differential diagnosis of the patient's bilateral sixth nerve palsy?

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Section 2

The abducens nucleus and fascicles in the pons can be affected by tumor, microvascular infarct, hemorrhage from vascular malformation, demyelinating plaque, granulomatous disease (neurosarcoidosis, tuberculosis, or Wegener granulomatosis), or infection. Infection is unlikely as the patient is systemically well. Demyelination is less likely because relapses occur less often in pregnancy.¹ Hormonal changes in pregnancy may affect tumor growth. Preeclampsia has been reported to cause isolated sixth nerve palsy; the pathophysiology is unclear, although microvascular insult to abducens nucleus is postulated.²

Raised intracranial pressure (ICP) secondary to meningeal infiltration, space-occupying lesion, or idiopathic intracranial hypertension (IIH) can affect the sixth nerve as it traverses the prepontine cistern. If IIH is present, venous sinus thrombosis should be excluded given the hypercoagulable state in pregnancy.

Infective or inflammatory meningitis from a variety of causes including tuberculosis, syphilis, Lyme disease, HIV, cryptococcal, neurosarcoidosis, Wegener granulomatosis, and carcinomatous meningitis can cause sixth nerve entrapment within inflamed meninges in the skull base or result in secondary raised ICP.

Cavernous sinus thrombosis or infection can cause bilateral sixth nerve palsy. The mechanism is likely due to raised ICP

secondary to associated venous sinus thromboses or congestion. Isolated cavernous sinus infection or thrombosis more typically affects the ipsilateral third, fourth, fifth (ophthalmic and maxillary division), and sixth nerves due their proximity to each other within the cavernous sinus.

Bilateral Tolosa-Hunt syndrome was not considered as this patient did not have ocular pain or other craniopathies.

Thyroid eye disease is considered as this patient is young, female, and pregnant.

Isolated ophthalmoplegia without other neurologic abnormalities may be the first presenting symptom in myasthenia gravis (MG), which may be unmasked in pregnancy.

Wernicke syndrome can present with ophthalmoplegia in pregnancy and is usually due to thiamine deficiency from hyperemesis gravidarum. This patient did not have hyperemesis.

Miller Fisher syndrome (MFS), a variant of Guillain-Barré syndrome (GBS), is classically described as a triad of ophthalmoplegia, areflexia, and ataxia. Incomplete MFS with ophthalmoplegia and reduced reflexes has been reported and thus was considered in this patient.

Question for consideration:

1. What investigations will assist in narrowing the differential diagnosis?

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Section 3

Baseline blood pressure, blood sugar, and urinalysis were unremarkable, important in assessing an underlying microvascular cause and excluding preeclampsia. Complete blood count, urea and electrolytes, liver function test, C-reactive protein, calcium, HbA1c, thyroid function tests, antinuclear antibodies, anti-ds-DNA antibody, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, serum angiotensin-converting enzyme (ACE), serum immunoglobulin, and electrophoresis were unremarkable. Both anti-acetylcholine receptor antibody and anti-MUSK antibody assays for MG were negative. CSF analysis was undertaken to evaluate infective, malignant, and demyelinating causes. CSF cell microscopy, glucose, protein, gram stain, cultures and sensitivities, oligoclonal bands, immunoglobulin G index, *Cryptococcus* PCR, acid-fast bacillus stain, tuberculosis culture,

venereal disease research laboratory, ACE, cytology for malignant cells, and flow cytometry were all normal or negative. There was no albuminocytologic dissociation, a typical finding in GBS. MRI brain, orbits, and magnetic resonance venography brain were normal, thus excluding tumor, microvascular lesion, demyelinating disorders, venous sinus thrombosis, raised intracranial pressure, and orbital myopathy. Gadolinium was not given as the patient was pregnant.

The finding of absent reflexes on examination was important. When coupled with ophthalmoplegia, this finding was suggestive of incomplete MFS, given the lack of ataxia. Therefore, serum was tested for anti-GQ1b antibodies, yielding a positive result.

Question for consideration:

1. Given the likely diagnosis of incomplete MFS, what is the treatment?

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Section 4

The patient was incapacitated by her diplopia; a Fresnel prism and eye patch offered little relief. She underwent treatment with IV gamma globulin 0.5 g/kg/d for 4 days, commencing on day 7 post initial presentation, within the 2-week timeframe of evidence-based treatment in GBS.³ Initially an improvement on left gaze, with reduced deviation, was noted on orthoptic review. Within 2 weeks, she reported complete resolution of her diplopia. Final orthoptic review revealed full range of eye movements. She delivered a healthy baby at 39 weeks gestation.

Discussion

MFS is a variant of GBS. It is a rare disease with an annual incidence of 1 per 1,000,000. Classic MFS manifests as a triad of ophthalmoplegia, areflexia, and ataxia. An antecedent infection was reported in 82% in one study, with respiratory infection being the most common, followed by gastroenteritis. Median time between antecedent infection and onset of neurologic symptom is reported to be 8 days in this study, although the interval ranges between 1 and 30 days.⁴

Research into antigangliosides and GQ1b has led to substantial advancements in the diagnosis of MFS. There is evidence to suggest molecular mimicry between *Campylobacter jejuni* and anti-GQ1b. The GQ1b ganglioside is strongly associated with MFS. Testing for anti-GQ1b antibodies in the classical triad of MFS has a high sensitivity at 92%, coupled with a high specificity of 97%.⁵ It is an easily accessible investigation given that serum results are equivalent to CSF levels.

Incomplete MFS has been reported. In a study of 100 cases of isolated sixth nerve palsy, of which 29 patients reported bilateral sixth nerve palsy, anti-GQ1b was positive in only 25%. GQ1b serology was more likely to be positive if patients reported both antecedent infection and hyporeflexia or limb paresthesia. In comparison, 81% of patients with classic MFS had positive anti-GQ1b during the first week of neurologic illness.⁶

Other investigations typically used in the diagnosis of GBS are less useful in MFS. There is often evidence of albuminocytologic dissociation in CSF sampling. However, this finding occurs later, often rising by 3 weeks, whereas the anti GQ1b antibodies rise within the first week, thus increasing its utility in the acute setting.⁷ Neurophysiology testing in MFS can demonstrate axonal neuropathy, neuronopathy, or demyelinating neuropathy. Access to neurophysiology testing was limited in our provincial hospital setting in which this case was investigated. Nerve conduction studies were undertaken 11 weeks after presentation and were therefore unsurprisingly normal. Given the largely unremarkable investigation of other differentials, the anti-GQ1b result was useful in this case, yielding the most likely diagnosis of MFS.

It is well-recognized that GBS is associated with pregnancy. Incidence rates in pregnancy are significantly higher than nonpregnant rates at 1.2–1.9 per 100,000 per year. GBS in pregnancy is associated with poor fetal and maternal outcomes. Plasmapheresis and IV immunoglobulin (IVIg) have been used in pregnancy, although the evidence available on safety is limited.⁸ There are adverse effects associated with IVIg that would be compounded in the pregnancy, notably venous thromboembolism (VTE). In nonpregnant populations, the risk of VTE has been cited as high as 1.1%–4.5%. Therefore, when considering treatment benefit against possible risk, conservative management is frequent in pregnancy.⁸

There is limited literature regarding MFS in pregnancy. One case report presents a case of MFS masquerading as Wernicke syndrome, where once the diagnosis of MFS was established, the patient was treated conservatively.⁹

MFS is often a self-limiting condition with a good outcome. The condition begins to subside from 1 to 3 months following onset, with almost complete resolution of symptoms within 6 months. However, there have been several cases identified that have progressed to severe bulbar dysfunction and respiratory failure. A Cochrane review reported that IVIg can hasten the recovery of ophthalmoplegia and ataxia, but does not affect the final outcome in MFS, presumably because of favorable natural recovery of this condition. Data on incomplete MFS were limited, although it was reported in small case series that prognosis was good in both IVIg treated and untreated patients.¹⁰

As there is a lack of prospective controlled trials in MFS, the treatment in patients with severe clinical symptoms is often extrapolated from treatment given for GBS. IVIg should therefore be considered in patients with disabling clinical symptoms, as this may hasten symptom improvement.

Awareness of MFS is essential in assessing patients with isolated bilateral sixth nerve palsy, as recognition of this condition enables utility of serum anti-GQ1b assay as an investigation tool and consideration of IVIg especially when diplopia is disabling despite conservative management.

Author contributions

Zea Munro was involved in drafting and revising the manuscript for content. Desiree Fernandez was involved in drafting, revising, and reviewing the manuscript for content.

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Disclosure

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