CASE REPORT

Simultaneous, Bilateral Ophthalmoplegia as the Presenting Sign of Paediatric Multiple Sclerosis: Case Report and Discussion of the Differential Diagnosis

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ABSTRACT

An 11-year-old female developed bilateral oculomotor nerve palsies without pupillary involvement and bilateral optic neuropathy as the presenting signs of paediatric multiple sclerosis (MS). Although ocular mono-neuropathies have been reported, this is the first bilateral mono-neuropathy reported in a paediatric patient due to MS. The differential diagnosis and evaluation for bilateral ophthalmoplegia are discussed in detail.

Keywords: Acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), ophthalmoplegia, optic neuritis, third nerve palsy

INTRODUCTION

Isolated ocular motor nerve dysfunction as a presenting sign of multiple sclerosis (MS) is rare,^{1,2} compared with nystagmus or internuclear ophthalmoplegia (INO).³ Simultaneous bilateral mono-neuropathies, regardless of the aetiology, are even more uncommon.

In 1984, Sergott and colleagues reported the first two cases of diabetic or vasculopathic simultaneous, bilateral ophthalmoplegia (BLO) in the literature.⁴ More recently, the first case of bilateral, pupil-sparing third nerve palsies as the presenting sign of adult-onset MS was reported.¹ We present a case of a young girl presenting with bilateral, pupil-sparing, third nerve palsies as the presenting manifestation of paediatric MS. To our knowledge, this is the first paediatric case of its kind in the literature. The differential diagnosis and diagnostic workup for BLO⁴ is updated to include advances in neuroimaging during the past two decades.

CASE REPORT

An 11-year-old Hispanic female previously in excellent systemic and ophthalmic health presented with 2 weeks of “seeing two of everything” and “blurry vision” in both eyes. Visual symptoms were noted upon awakening and were associated with intermittent hypogeusia and emotional lability in the 2 weeks prior to presentation. She had no prior viral illness and had received scheduled immunisations 1 month prior to presentation (tetanus/diphtheria/pertussis, meningococcal, and human papilloma virus).

Neuro-ophthalmic Examination

Near visual acuity at a distance of 12–14 inches was 20/400 OD and 20/200 OS. Both pupils were 4 mm in light and 6.5 mm in dark and moderately reacted to light stimulation without an afferent pupillary defect. Colour vision was decreased in both eyes, with 2 of 8 Ishihara plates OD and 4 of 8 OS.

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Bilateral ptosis and large angle exotropia were present in primary gaze, with an approximately 15-degree chin up position (Figure 1). Adduction was only 10% of normal in each eye and vertical

FIGURE 1 Lid and eye movement abnormalities with simultaneous, bilateral oculomotor palsies. Note the intact abduction in each eye.

movements were absent bilaterally. Lateral rectus function was normal in both eyes. Superior oblique function was intact, with bilateral intorsion on attempted downgaze. Dilated fundus examination disclosed normal discs, vessels, maculae, and peripheral retinae. Neurologic examination was normal.

Clinical Course

Magnetic resonance imaging (MRI) of the brain with contrast revealed multiple T2/FLAIR hyperintensities scattered throughout the white matter, with involvement of the basal ganglia, frontal periventricular area, and midbrain (Figure 2). Complete blood count (CBC), basic metabolic panel (BMP), erythrocyte sedimentation rate (ESR), Lyme immunoglobulin G/M (IgG/IgM) were normal. Lumbar puncture (LP) revealed normal opening pressure, protein, glucose, and 4 white blood cells. Myelin basic protein and oligoclonal bands were not performed due to inadequate cerebrospinal fluid (CSF) sample volume. A working diagnosis of acute disseminated encephalomyelitis (ADEM) was made while paediatric multiple sclerosis was considered.

Treatment was initiated with daily 1 mg/kg dosing of intravenous (IV) methylprednisolone and a loading dose of IV levetiracetam due to epileptiform activity and focal slowing over both frontal lobes, noted on electroencephalogram (EEG). There was no evidence of clinical seizure. The ptosis, ocular motility (Figure 3), visual acuity, and colour vision improved daily. Following 6 days of IV steroid treatment, the diplopia resolved in primary gaze and near visual acuity improved to 20/100 OD and remained 20/200 OS. At discharge, the patient read 8 of 8 colour plates in each eye.

Six months following this first admission, the patient was readmitted for confusion, ataxia, and

FIGURE 2 T2 axial (A) and T2/FLAIR sagittal (B) MRI disclosing multiple hyperintense foci throughout the white matter, with involvement of the midbrain at the level of the third nerve. There was no evidence of optic nerve enhancement.

FIGURE 3 Ocular motility following initial IV steroid treatment. Ptosis and adduction deficits are significantly improved.

dysarthria. Repeat MRI disclosed new T2/FLAIR hyperintensities localised to bilateral internal capsules, bilateral cerebral peduncles, and left pons. An interval increase in size and intensity of bilateral periventricular white matter lesions was also noted. Anti-neuromyelitis optica (NMO) antibodies were not sent; however, cervical and thoracic spine MRI were normal. Repeat CSF studies were within normal limits with respect to opening pressure, protein, glucose, white count, IgG index, and myelin basic protein. However, CSF oligoclonal bands disclosed >5 gamma restriction bands not present in the patient's serum. Visual acuities were 20/20 OU, with normal colour vision and ocular motility. The only abnormal finding on neuro-ophthalmic examination at this time was a mild left beating, horizontal nystagmus worse in right gaze. Based on the finding of CSF-restricted oligoclonal bands,⁵ the overall pattern and duration of MRI findings, and fulfilment of both Poser and McDonald criteria, a diagnosis of relapsing-relapsing MS was made. After a 5-day course of pulsed intravenous methylprednisolone 800 mg daily, the patient was placed on a slow taper of oral prednisone and was

scheduled for outpatient follow-up with paediatric neurology and neuro-ophthalmology services. She has since been lost to follow-up with the neuro-ophthalmology service.

DISCUSSION

To our knowledge, this case represents the first report of paediatric MS presenting as bilateral, simultaneous pupil-sparing third nerve palsies and bilateral optic neuritis. Although optic nerve enhancement was not found on MRI of the brain, the patient was deemed to have bilateral optic neuritis given the steroid-responsive decreased acuity and colour vision in each eye. It is conceivable that an MRI of the orbits may have been able to detect more subtle enhancement, but this was not obtained. A similar constellation of symptoms (without optic neuritis) was reported in a 30-year-old man.¹

The crux to narrowing the wide differential diagnosis of bilateral ophthalmoplegia is anatomic localisation (Table 1). A focused history and ophthalmologic examination guides the diagnostic evaluation. In patients with ptosis and acquired single- or multiple-eye muscle deficits, myasthenia gravis should always be considered.⁶ Anti-acetylcholine receptor antibody serology, ice testing in cases with ptosis, intravenous edrophonium testing, and single-fibre electromyography (EMG) of the orbicularis oculi and repetitive stimulation nerve conduction studies (NCS) are useful in confirming suspected cases of myasthenia gravis. Ophthalmoplegia with pupillary involvement or pain excludes myasthenia gravis as a potential diagnosis.

Graves disease, like myasthenia gravis, can mimic intracranial disease with binocular diplopia and impaired ductions without pupillary involvement.⁶ Myasthenia gravis and Graves disease may share similar pathogenic mechanisms, as approximately 5% of patients with myasthenia gravis also have autoimmune-related thyroid dysfunction.⁷ Recognition of lid retraction, proptosis, lagophthalmos, and positive forced-duction testing are useful in confirming restrictive thyroid-related myopathy.^{8,9} Orbital computed tomography (CT) or MRI frequently demonstrates extraocular muscle enlargement. If ptosis is present with thyroid eye disease, the coexistence of myasthenia gravis and Graves' disease should be considered.

Presentations with chronic, symmetric ophthalmoplegia (usually without diplopia) and ptosis can be confused with myasthenia but is more likely due to chronic progressive external ophthalmoplegia (CPEO). Most patients with CPEO confirmed on muscle biopsy have an exo-deviation with impaired ductions that can relatively spare downgaze.¹⁰ Additionally, diplopia is uncommon in CPEO.

TABLE 1 Bilateral ophthalmoplegia differential diagnosis.

Anatomic site	Aetiology	Pupil	Pain	Diagnostic aids	Comments
Neuromuscular junction	Myasthenia gravis	–	–	Endrophonium test, AChR Ab assay (binding, blocking, modulating), MuSK Ab assay, ice test	Orbicularis oculi weakness, transient signs
	Botulism	+	–	Toxin in serum or gastric contents is confirmatory	Nausea and vomiting, dietary history
Extraocular muscle vasculature	Arteritis	±	±	Erythrocyte sedimentation rate, C-reactive protein, platelets, orbital Doppler	Headache, jaw claudication, polymyalgia rheumatica, ischaemic neuropathy, amaurosis
Extraocular muscles	Graves' ophthalmopathy, orbital inflammatory syndrome/orbital pseudotumor	–	+	Forced ductions, CT, MRI, thyroid function tests	Foreign body sensation, headache, lid retraction, lid lag, proptosis, congestion
	Chronic progressive external ophthalmoplegia	–	–	MRI (may show atrophic muscles)	Family history, slowly progressive, history of cardiac arrhythmia, clinical examination suggests myasthenia but no diplopia
Cranial nerve	Mucormycosis	±	+	Culture, CT, biopsy of infected tissue	Life-threatening, poorly controlled diabetics, transplant patients, immunosuppressed patients (HIV, chemotherapy)
	Diabetic—vascular	Usually –	±	Glucose tolerance test	Pain limited, 10 days
	Multiple sclerosis	±	–	CSF electrophoresis, MRI	Cranial neuropathies uncommon, diplopia generally from midbrain syndrome and pontine syndromes
Cavernous sinus	Polyradiculitis (Fisher-variant Guillain-Barré)	±	–	CSF protein, anti-GQ1b antibody	Postinfectious, subacute, ataxia, areflexia
	Neurosyphilis	+	–	CSF and serum VDRL	History of syphilis
	Diphtheria	±	–	Culture	
Interpeduncular cistern	Lyme disease	±	–	Lyme Ab (IgG and IgM), MRI	History of tick exposure, can be associated with multiple cranial neuropathies
	Pituitary apoplexy	+	++	CT, MRI/MRV	Field defects variable; mimics optic neuritis
Interpeduncular cistern	Metastasis	±	+	CSF protein, cells, CT, MRI/MRV	Severe persistent pain
	Basilar artery Aneurysm Occlusion	+	±	CT/CTA, arteriogram	May mimic posterior fossa tumour
		+	–	Clinical signs	Coma

(continued)

TABLE 1 Continued

Anatomic site	Aetiology	Pupil	Pain	Diagnostic aids	Comments
Skull base/clivus	Tumour, primary	±	±	MRI, CT	Slow evolution, chordomas and chondrosarcomas
	Chronic inflammation	—	—	MRI, CT	Slow evolution
Brainstem	Meningeal carcinomatosis	±	—	MRI, CSF	Consecutive palsies
	Wernicke's encephalopathy	—	—	Alcoholism	Thiamine administration, ataxia, mental status change, nystagmus, encephalopathy not diagnostic requirement
	Dorsal midbrain syndromes	+	—	MRI, CT	Lid retraction, convergence-retraction nystagmus
	Multiple sclerosis	±	—	CSF electrophoresis, MRI	Bilateral internuclear ophthalmoplegia, one and a half syndrome
	Whipple's disease	±	—	PAS + tissue biopsy, PCR for <i>T. whipplei</i> , CSF, protein, cells	Uveitis, peripheral neuropathy, gastrointestinal symptoms, arthralgia/arthritis
	Progressive supranuclear palsy	—	—	MRI, PET scan	Dementia, dystonic rigidity, gradually progressive
	Olivopontine cerebellar degeneration	—	—	MRI, PET scan, anti-Purkinje cell Ab	Ataxia, intention tremor, loss of deep tendon reflexes, nystagmus
	Spinocerebellar ataxia	—	—	MRI, SCA genetic testing	Ataxia, dysarthria, family history
	Trauma	±	±	CT, MRI	Can present with incomplete Parinaud's syndrome

Simultaneous vasculopathic or diabetic ophthalmoplegia is rare. Approximately 0.5–1.0% of diabetics will develop a cranial neuropathy over a 25-year period,¹¹ but very few develop simultaneous BLO. In a series of 1400 patients with oculomotor palsies, approximately 2.5% of bilateral cases (4 of 150) were due to diabetic vasculopathy.¹² Another series of patients from the Mayo Clinic with multiple ocular motor cranial neuropathies showed that 4.1% of cases were attributed to vascular causes, but the distinction between diabetes and inflammatory vasculitis was not made.¹³ A recent Italian series revealed that 11% of diabetic ophthalmoplegia involved multiple ocular cranial nerves.¹⁴ Reflecting the fact that ophthalmoplegia involving multiple cranial nerves due to diabetes is a diagnosis of exclusion, the clinical axiom developed 30 years ago is still valid: "...a diabetic is permitted one cranial neuropathy at a time. Exceptions to this rule, either more than one motor nerve per eye, or simultaneous bilateral cranial palsies, make investigation mandatory."⁴

Ophthalmoplegic migraine (OM) has been reported to present with bilateral involvement, presumably via peripheral microvascular ischaemia;¹⁵ however, more recent evidence suggests that the underlying aetiology is inflammatory, as patients with OM demonstrate transient cranial nerve enhancement on MRI.¹⁶

Rarely, giant cell arteritis (GCA; temporal arteritis) presents with bilateral ophthalmoplegia and is typically associated with systemic symptoms, including headache, mild fever, jaw claudication, weight loss, and proximal muscle weakness.^{17,18} In patients over the age of 55 with ophthalmoplegia, erythrocyte sedimentation rate, C-reactive protein, and platelet count should be obtained. Steroids should be administered if temporal arteritis is suspected, until a definitive diagnosis is made.¹⁹ The exact mechanism of GCA-related ophthalmoplegia is under debate. The lone histopathologic correlation of GCA and ophthalmoplegia suggested inflammation of the orbital vasculature with secondary extraocular muscle necrosis;²⁰ however, there are case reports suggest that inflammation of vessels supplying nerve fascicles may play a role.¹⁸

Patients with acute, painful bilateral ophthalmoplegia with pupillary involvement raise the clinician's suspicion for pituitary apoplexy.²¹ Carotid cavernous sinus fistula^{22,23} and Tolosa-Hunt syndrome^{24,25} can present in a similar fashion. The incidence of ocular palsy related to pituitary tumours has been reported to be between 14% and 32%.²⁶ Multiple cranial nerves can be affected and bitemporal hemianopia can occur due to parasellar compression of the optic tracts.^{21,27} Interestingly, there are two recent case reports of pituitary apoplexy that resulted in bilateral oculomotor nerve palsies without involvement of other cranial nerves.^{21,28} Initial imaging with CT established

a rapid diagnosis and confirmatory MRI was then obtained for pre-surgical planning in both cases.

Presentations without pain typically indicate an insidious, slow-growing neoplastic pituitary or skull base process. Again, multiple cranial nerves are typically involved. Primary and metastatic neoplasms can produce bilateral ophthalmoplegia via infiltration of the cerebral peduncles,^{29,30} cavernous sinus,³¹ or meninges.^{32,33} Neuroimaging focusing on the orbits, cavernous sinus, and skull base is essential to arrive to the diagnosis, followed at times by LP for CSF glucose and protein analysis and cytology to search for malignant cells.

Bilateral ophthalmoplegia secondary to infiltrative inflammatory or infectious processes of the skull base, orbits, and cavernous sinus can mimic neoplasms both clinically and radiographically.²⁹ Enhancing brainstem masses with a history of or concomitant presence of ocular inflammation can be indicative of sarcoidosis.^{34,35} Infectious entities such as mucormycosis,^{36–38} tuberculosis,^{39,40} syphilis,^{41,42} and herpes zoster⁴³ can manifest with progressive, often painless bilateral ophthalmoplegia for which neurologic evaluation and biopsy or CSF examination can be instructive of the diagnosis.

The acute polyneuropathies Guillan-Barré and its Fisher syndrome variant are associated with a bilateral, symmetric ophthalmoplegia.⁴⁴ Keane's retrospective review of 1400 patients with oculomotor palsies found that these entities were responsible for the majority (52 out of 150) of bilateral cases.¹² Guillan-Barré is characterised by ascending paralysis and respiratory distress, whereas Fisher syndrome is associated with the classic triad of acute ophthalmoplegia, ataxia, and areflexia and the anti-GQ1b antibody.⁴⁴

Occlusion of the basilar artery system has been reported to produce bilateral ophthalmoplegia secondary to third nerve palsy^{45,46} and internuclear ophthalmoplegia.⁴⁷ Basilar artery syndrome involving the midbrain is an acute, progressive brainstem process that includes alterations in consciousness, ataxia, vertigo, dysarthria, and unilateral or bilateral third and fourth nerve palsies as well as supranuclear disorders of ocular motility.

A number of other various brainstem syndromes can cause bilateral ocular motility defects. Wernicke's encephalopathy, characterised by ataxia, ophthalmoplegia with nystagmus, is typically improved with administration of intravenous thiamine.⁴⁸ Classically associated with pineal tumours, dorsal midbrain syndromes (Parinaud's, André-Thomas) are characterised by impairment of upward gaze, lid retraction, convergence-retraction nystagmus, and light-near dissociation.^{49,50}

Progressive supranuclear palsy (PSP), associated with intracellular accumulation of tau neurofibrillary tangles, initially manifests with disturbance of gait,

generalised slowing, and visual disturbances.^{51,52} Downward gaze limitation is typically affected greater than up and horizontal gaze, whereas saccades are greater diminished than pursuit movements, with relative vestibular ocular reflex sparing. Neuro-Whipple disease (confirmed by duodenal biopsy) presents with a supranuclear palsy, sometimes associated with a pathognomonic pendular nystagmus known as oculomasticatory myorhythmia.^{53,54}

When faced with a patient demonstrating new-onset bilateral ophthalmoplegia, a thorough ophthalmologic and neurologic examination, and prompt laboratory and imaging workup, is essential to rule out underlying primary diagnoses with high potential for significant morbidity and mortality.

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