Clinical Reasoning:

A case of acute onset bilateral ptosis in a young child

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SECTION 1

A 5-year-old boy presented with acute onset bilateral ptosis. An initial unilateral ptosis had evolved over the preceding 3 days, following a resolved pyrexial upper respiratory tract illness (URI) treated with oral penicillin. His mother reported that recently he was unable to walk half a mile to school, but had no difficulty with stairs. There was no history of ocular pain, vomiting, headaches, weight loss, dysphagia, constipation, or urinary disturbance. The ptosis was reported not to fluctuate, with no reported tearing, photophobia, or visual disturbance. His prior development was normal, and there was no family history of relevant neuromuscular or autoimmune disorders.

On examination he was alert and afebrile, without rash or lymphadenopathy. His systemic examination was unremarkable aside from enlarged noninflamed tonsils. He had bilateral ptosis obscuring the visual axis: marginal reflex distances were -3 mm and -2 mm on the left and right, respectively. There was no conjunctival injection or tearing. Pupil

sizes were 4 mm, equal, and reacted briskly to light and accommodation without relative afferent pupillary defect. Fundus examination was normal. There was full range and no fatigability of extraocular movements. Cover test findings were equivocal: a subtle left esophoria at near, and small (8 D) esotropia with horizontal diplopia at distance. Forced eye closure was normal without eyelid myotonia. Other cranial nerve examination was normal including facial sensation, bulbar strength, and gag reflex. He had normal muscle bulk, tone, and active muscle strength in all limbs. Gower sign was negative and limb girdle fatigability could not be elicited. His deep tendon reflexes (DTR) were normal, and symmetric with plantars downgoing. Gait was normal without cerebellar signs.

Questions for consideration:

1. What are the differential diagnoses for an acute onset ptosis?
2. Which diagnoses are most likely in light of the above clinical findings?

GO TO SECTION 2

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SECTION 2

The differential diagnosis for ptosis should include both acute onset and chronic conditions (table 1). Ptosis may present acutely irrespective of the underlying cause being acute or chronic. Parents may not have recognized a longstanding mild ptosis that does not fluctuate. Examining photographs from infancy can help to distinguish a recent onset from chronic ptosis.

The pertinent positive features were the acute onset following URI, bilateral involvement, and report of walking distance limitation pointing toward a form of myasthenia. Formal examination could not demonstrate limb-girdle fatigability which, as with manual muscle strength testing, is often difficult to demonstrate formally at this age. Fatigue is a nonspecific feature of many peripheral and CNS disorders.

Given the acute onset following URI, causes to consider include immune-related illnesses such as myasthenia gravis, postinfectious demyelination, diphtheria toxin-related neuropathy, and acute deterioration in mitochondrial and congenital myopathies. There was no persistent local pain, facial edema, rash, fever, or constitutional symp-

toms to suggest an ongoing systemic inflammatory pathology.

The bilateral involvement suggested a systemic or diffuse CNS pathology. The normal pupillary reflexes, visual acuity, and lack of involvement of parasellar cranial nerves did not support a focal pathology along the course of the third nerve.

The ptosis was painless, also against an anatomic third nerve lesion or migraine variant. Cavernous sinus thrombosis, orbital pathology, infection, and inflammatory disorders including the heterogeneous Tolosa-Hunt syndrome typically involve ocular pain, tearing, and conjunctival injection. A persistent mild, unilateral ptosis with other features of Horner syndrome may evolve over time in migraine.

The absence of ataxia and normal DTR were not in favor of Miller Fisher syndrome (MFS) (an ophthalmoplegia-predominant variant of Guillain-Barré syndrome [GBS]). The normal DTR were also against a widespread neuropathy, myopathy, or botulism. Botulism was unlikely since there was no cranial and peripheral muscle weakness, nor any autonomic disturbance, e.g., abnormal pupillary reflexes, constipation, and urine retention. Importantly, DTR are typi-

Table 1 Causes of ptosis

Causes	
Neurologic	
Muscle and neuromuscular junction causes	
Myasthenic syndromes	Myasthenia gravis, congenital myasthenic syndromes
Botulism	Including iatrogenic botulinum toxin
Congenital myopathies	Myotonic dystrophy, RYR1, and X-linked myotubular
Mitochondrial myopathies	POLG, Leigh syndrome
Acquired focal and generalized myopathies	Orbital myositis
3rd nerve lesions	
Compression	Raised intracranial pressure, tumors, aneurysm, hemorrhage, cavernous sinus thrombosis, skull base and orbital pathology
Demyelination	Guillain-Barré syndrome and variants (Miller Fisher syndrome)
Infection/inflammation	Basal meningitis, sarcoidosis, Tolosa-Hunt syndrome
Vascular	Basilar territory infarct, vasculitis, venous sinus thrombosis
Toxic	Diphtheria, drugs (highly active antiretroviral therapy)
Ophthalmologic/ocular	
Congenital	Myogenic dysgenesis, syndromes (e.g., Noonan, Smith-Lemli-Opitz)
Acquired	Aponeurotic disinsertion, lid tumors, and other lid lesions
Pseudo-ptosis	Microphthalmia, hypotropia, contralateral lid retraction
Others	
Psychogenic	"Functional pseudoptosis"
Endocrine/metabolic	Diabetes mellitus, thiamine deficiency, thyroid disorders
Migraine	Ophthalmoplegic migraine, trigeminal autonomic cephalalgias
Autonomic	Acquired Horner syndrome, genetic disorders including neurotransmitter synthesis

cally normal in myasthenia gravis. Ocular myasthenia was a possibility since limb girdle weakness and fatigability may be minimal.

It would be extremely unusual to consider psychogenic causes at this age. Psychogenic causes should be considered in an adolescent with an appar-

ent acute onset ptosis in the absence of other cranial or peripheral neurologic signs.

Question for consideration:

1. Which investigations would you consider to distinguish among the differential diagnoses?

GO TO SECTION 3

SECTION 3

The investigations were targeted toward identifying myasthenia gravis (table e-1 on the *Neurology*[®] Web site at www.neurology.org). Normal investigations included complete blood count, urea and electrolytes, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, and thyroid function tests. Anti-streptolysin O titer was raised at 300 IU/mL. The ice-pack test was attempted but the child could not cooperate. The ice-pack test is a safe and sensitive alternative to the Tensilon test.¹ The Tensilon test was deferred because of its side effect profile and the ready availability of single fiber EMG (SFEMG) in the department.

An MRI of the brain without contrast enhancement showed a type 1 Chiari malformation with

18 mm tonsillar herniation, without other abnormalities. A lumbar puncture was deferred on neurosurgical advice due to concern of inducing decompensation of the Chiari malformation.

The child had stimulated SFEMG (SSFEMG) of orbicularis oculi, repetitive nerve stimulation test (RNS) of abductor pollicis brevis, and nerve conduction studies (NCS) under propofol sedation. The RNS and SSFEMG were normal. NCS revealed absent F waves but was otherwise normal. Propofol can transiently abolish F waves, but is not typical in children having NCS performed with sedation in our department.

Question for consideration:

1. What diagnoses would you consider at this stage?

GO TO SECTION 4

SECTION 4

A neuromuscular junction disorder was unlikely in light of the neurophysiologic studies. Neurophysiologic studies including RNS and SSFEMG can be used to diagnose myasthenic syndromes in young children. These investigations are highly operator dependent, relying on expertise of the neurophysiologist with children, compliance of the child, and specific muscles chosen for study. The sensitivity of RNS for ocular myasthenia is low, whether facial, axial, or limb nerve-muscle pairs are tested.² SSFEMG involves stimulation of the nerve to the muscle undergoing single fiber recording. SSFEMG can be performed under general anesthesia and is not limited by the child's compliance, unlike unstimulated SFEMG, which requires volitional activity. SSFEMG of the orbicularis oculi muscle in ocular myasthenia is highly specific (97%) and the sensitivity approaches 80%.³

There were no systemic signs or encephalopathy to suggest an infection or inflammatory disorder requiring specific treatments.

A diagnosis of postinfectious partial third nerve demyelinating neuropathy was made on clinical grounds. The child was discharged home with conservative treatment.

FURTHER EVOLUTION OF CASE HISTORY Ten days later, the child was readmitted with a new left squint. On examination, he remained well. His bilateral ptosis remained unchanged. The left eye was adducted with a large angle (40 D) esotropia, unchanged visual acuity, and diplopia on left gaze. Left eye hypometric abduction saccades suggested a partial abducens nerve palsy although eye movements remained full range. The DTR in upper limbs and knees were absent; ankle reflexes were weakly present. The rest of his neurologic and system examination was unremarkable. Repeat MRI of the brain was unchanged.

The overall findings were consistent with MFS. He was treated with infusion of 2.1 g/kg IV immunoglobulin (IVIg) over 3 days. His ptosis and esotropia improved considerably soon afterwards. He was prescribed alternating occlusion and subsequently corrective lenses for mild hyperopia. At 3 months after onset, DTR were weakly present, the ptosis had completely resolved, and eye movements remained full range. A variable angle left esotropia was present with improvement of diplopia, continuing treatment with corrective lenses.

Serology and antibodies to viruses, Borrelia, AChR, MuSK, and membrane glycolipids were normal.

DISCUSSION The clinical diagnosis was MFS. Clarifying the diagnosis took 3 weeks, requiring the evolution of neurologic deficits from the initial isolated ptosis, and exclusion of alternative diagnoses. The absent F waves and the response to the IVIg supported the diagnosis.

MFS is a GBS variant characterized by partial or complete ophthalmoplegia, ataxia, and areflexia. These deficits may evolve after initial presentation.⁴ MFS is an immune-related disorder, associated with a specific antibody to a peripheral nerve antigen, the glycolipid GQ1b.⁵ The antibody appears to be directly involved in pathogenesis. Treatment with IVIg may be beneficial but its efficacy remains unclear.⁶ Serology in our child was negative for GQ1b and other antiglycolipid antibodies associated with GBS variants.

Abnormalities of F-waves on NCS may be seen early in the course of the disease in GBS variants, before more unequivocal signs and NCS abnormalities appear.^{7,8} F-waves can be abnormal in up to 92% cases of GBS; the most frequent abnormalities are complete absence or prolongation of minimum and mean latency.⁹ Elevated CSF protein, with other normal biochemical findings and microscopy (<10 white cells per high power field), are expected in MFS; however, abnormalities may not be present until the second week of the illness.⁶ Raised CSF protein may also be found in mitochondrial myopathies, thus raised CSF protein is neither sensitive nor specific for diagnosis of MFS. CSF tests including microscopy and serology are typically indicated to exclude infectious and neoplastic causes.

The investigation of acute ptosis in children can be challenging, relying on consultation with colleagues across specialties (neurology, ophthalmology, radiology, and neurophysiology), meticulous serial examination, and appropriate interpretation of investigation results.

AUTHOR CONTRIBUTIONS

Dr. Das qualifies as an author because he was involved in the initial concept, gathered the data, and wrote the draft manuscript and manuscript revisions. Dr. Spinty qualifies as an author because he analyzed and interpreted the data and revised the manuscript content. Dr. Kumar qualifies as an author because he supervised the initial concept, analysis and interpretation of data, and was involved in writing revisions of the manuscript.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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