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Congenital Myasthenia Syndrome

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A 2-year-old girl with a history of celiac disease and eosinophilic esophagitis presented to the emergency department (ED) with 1 week of right-sided ptosis in the setting of isolated left-sided ptosis for 4 days during the prior week.

History. She had been seen initially by her primary care provider for evaluation of the symptoms, at which time significant dental caries had been noted, and the girl had been prescribed amoxicillin for a possible dental abscess. The left-sided ptosis then resolved; however, several days later, she developed similar symptoms on the right side with accompanying rhinorrhea. The ptosis appeared to worsen before sleep. A review of systems was negative for fever, eye drainage, lid swelling/erythema, abnormal gait, weakness, or generalized fatigue. Her medical history was significant for gross motor skill delay and expressive language delay.

Physical examination. In the ED, physical examination findings were notable for right-sided ptosis, with fatigability during prolonged upward gaze and abnormal left eye abduction causing dysconjugate gaze. Examination findings were otherwise unremarkable, with the exception of dental caries.

Diagnostic tests. A computed tomography scan of the head was obtained, the results of which revealed radiographic sinusitis without periorbital or orbital cellulitis. The results of cerebrospinal fluid studies were unremarkable. Given the persistence of symptoms, she was admitted to the hospital for further workup.

She was treated with intravenous ampicillin-sulbactam and intravenous amoxicillin-clavulanate for sinusitis without resolution of neurologic symptoms. Magnetic resonance imaging (MRI)/magnetic resonance venography with sedation was performed, the results of which demonstrated pansinusitis but most notably were negative for septic thromboembolism, mass lesion, optic neuritis, or demyelination (**Figures 1 and 2**). Specifically, the bilateral branches of the oculomotor nerve within the cavernous sinus appeared normal and did not explain the presence of ptosis. Furthermore, the optic chiasm and carotid arteries were without signs of compression to account for the fluctuating symptoms.

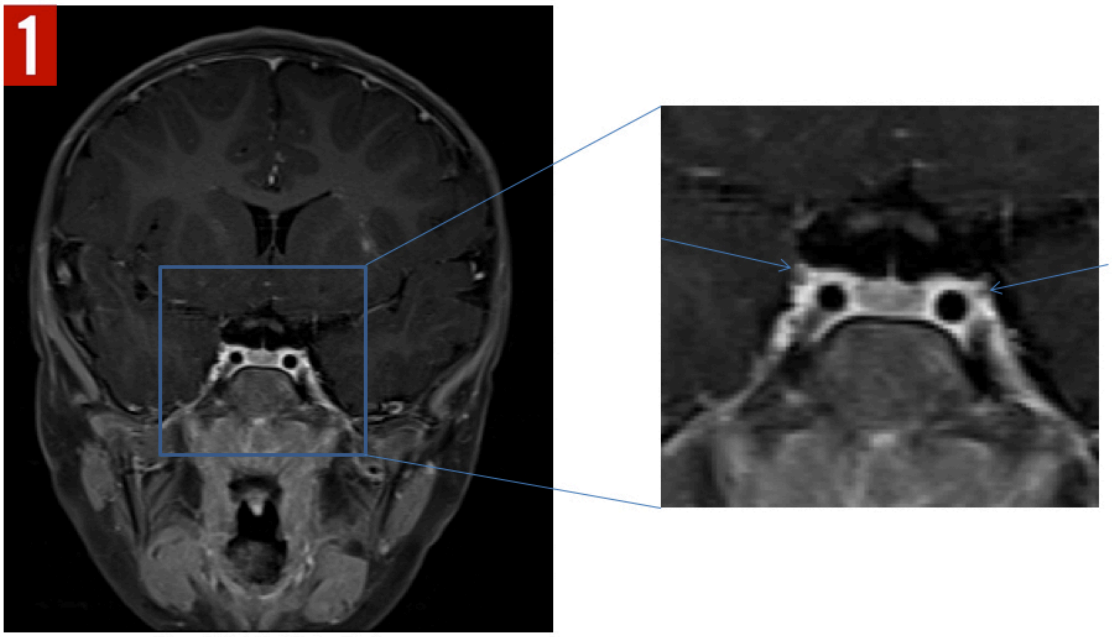

Figure 1. *T1-weighted fat-saturated post-gadolinium coronal MRI. Arrows indicate the bilateral branches of the oculomotor nerve within the cavernous sinus. Enhancement within the left internal capsule is related to an incidental developmental venous anomaly. Courtesy of Thomas Graham West, MD, Wake Forest Baptist Medical Center.*

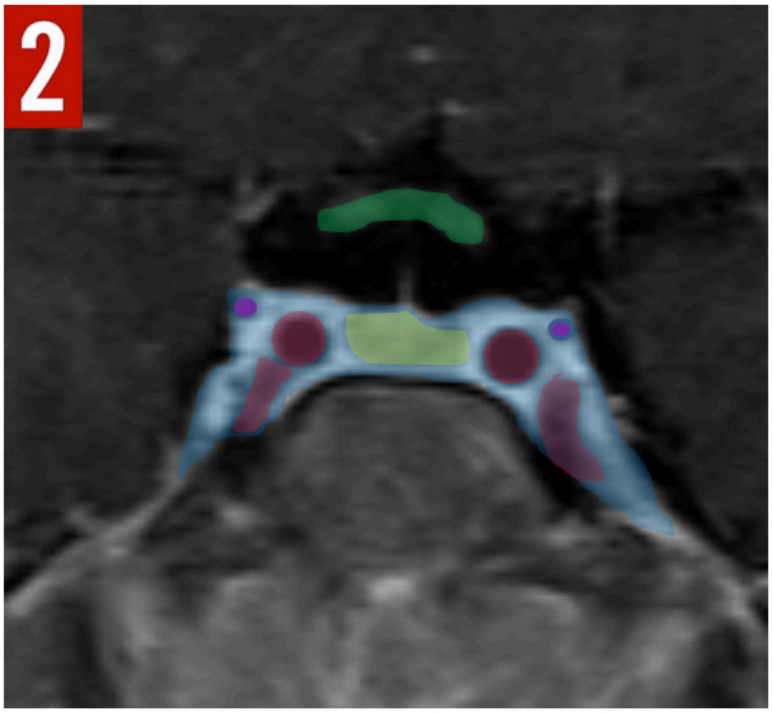

Figure 2. *Color-coded view showing the internal carotid arteries (red), the pituitary gland (yellow), and the oculomotor nerve branches (purple) within the cavernous sinus (blue), along with the optic chiasm (green). Courtesy of Thomas Graham West, MD, Wake Forest Baptist Medical Center.*

A pediatric neurologist was consulted in the setting of fatigable weakness, normal MRI findings, and diurnal variation of ptosis. Further testing included negative electromyography (EMG) results and negative test results for anti-acetylcholine receptor (AChR) and anti–muscle-specific tyrosine kinase (MuSK) antibodies.

Treatment and outcome. She remained well appearing without other signs of illness, and thus she was transitioned to oral amoxicillin-clavulanate for sinusitis and was discharged with plans to follow up with the pediatric neurology clinic. Given her history of motor skill developmental delays and the fatigable nature of her ptosis, she was started on pyridostigmine, an acetylcholinesterase inhibitor, for presumed congenital myasthenia syndrome (CMS). She experienced clinical improvement on this medication, which was felt to be likely diagnostic of CMS in the absence of positive antibody test results. Pyridostigmine was slowly titrated to symptom management at follow-up visits with subsequent improvement.

Discussion. Causes of acquired ptosis include foreign bodies, trauma, allergic reactions, conjunctivitis, cellulitis, Horner syndrome, and intracranial mass. Rapidly progressive ptosis suggests a serious underlying problem that requires immediate evaluation. Conversely, congenital ptosis results from localized myogenic dysgenesis or denervation of the levator palpebrae superioris muscle via neurologic or neuromuscular dysfunction.[1] Thus spinal muscular atrophy, muscular dystrophies, and brainstem anomalies should all be considered in the diagnosis.

CMS is one cause of congenital ptosis and is classified into 4 subtypes: presynaptic, postsynaptic (fast channel), postsynaptic (slow channel), and synaptic. It is inherited in an autosomal recessive fashion, apart from slow-channel CMS, which is autosomal dominant.[2-4] When CMS is suspected, a complete neurologic examination and ophthalmic evaluation should be performed, including visual acuity testing and refraction testing with dilation. Typically, patients with CMS will demonstrate fatigable weakness suggestive of neuromuscular junction disease.

Testing for anti-AChR and anti-MuSK antibodies should be performed, the results of which will be negative in this non–immune-mediated disorder. EMG studies generally show characteristics similar to disorders of synaptic transmission, although some phenotypes have unique features that can be seen on EMG.[5] Obtaining an MRI may be helpful for ruling out other etiologies and for evaluation of fatty infiltration caused by mutations of the proteins involved in the glycosylation pathway. Many gene mutations have been implicated, and whole-gene sequencing may be performed. At this time, at least 11 mutations have been confirmed, predominantly of the postsynaptic type, such as *RAPSN* and *CHRNE* mutations.[1,6,7]

Although CMS is a congenital syndrome, weakness can present variably from infancy to adulthood, with later presentations being classically milder. Response to treatments that are known to ameliorate neuromuscular transmission is a significant diagnostic and prognostic factor. Disease severity can range from early childhood death to minor morbidity.[1] It is important to recognize that, unlike myasthenia gravis, CMS is not an autoimmune disease and is unresponsive to immunosuppressive therapy. Furthermore, although juvenile myasthenia gravis (JMG) comprises the largest proportion of pediatric myasthenia cases, no cases of JMG have been documented in patients younger than 1 year of age; instead, this disease typically occurs in school-aged children.[8]

Early recognition and diagnosis is critical to optimize clinical management, anticipate complications, and provide appropriate genetic counseling. Genetic testing should be dictated by clinical features and presentation, since it requires DNA testing from both parents and can be costly for families.[9] Our patient's ocular findings, fatigable weakness, and age at presentation were fairly typical, as was her immediate response to pharmacologic intervention, despite normal EMG and MRI results, since findings may be intermittent in childhood.[10,11] Genetic testing in this patient's case was unavailable as a result of insurance coverage limitations.

Treatment is largely supportive.[5] However, expedited use of medication is crucial to preventing further morbidity, especially in patients with preexisting developmental delays. Most children benefit from acetylcholinesterase inhibitors (AChEIs) and/or a potassium-channel blocker (amifampridine).[12,13] Additionally, prophylactic AChEIs may be used to prevent sudden episodes of apnea or respiratory insufficiency provoked by fever or infections.[2] Many cases of pediatric myasthenia are unrecognized or misdiagnosed given the subtleties of clinical findings,

If familial genetic mutations are known, targeted testing can be used to identify asymptomatic newborns and infants to prevent acute respiratory failure and early death.[14]

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