ISSN: 3033-3504

Journal of Clinical Medicine and Regenerative Medicine

SCIENTIFIC Research and Community

Review Article

Open Access

The Eyes have it: A Case of Ptosis and an Overview

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ABSTRACT

Ptosis, formerly blepharoptosis, has a very broad differential which can make correct and timely diagnosis difficult. This is a fairly common presenting conundrum in a busy clinical practice. A case of ptosis and fatigablity in a young female which evaded diagnosis for nearly two years is presented highlighting some of the diagnostic challenges as well as literature overview and current treatment strategies.

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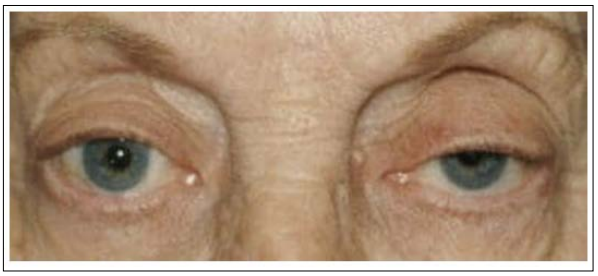
Received: February 15, 2024; **Accepted:** February 19, 2024, **Published:** February 29, 2024

Introduction

Ptosis can be classified as congenital or acquired. This differentiation is based on age. A more comprehensive classification is based on etiology and includes myogenic,neurogenic, mechanical, traumatic, aponeurotic and pseudoptotic. The most common cause of congenital ptosis is myogenic due to the improper development of the levator muscle. Common neurogenic causes include microvascular ischemic third nerve palsy, aneurysm (eg. PCOM aneurysm), neoplasm, trauma, inflammatory and infectious etiologies, Horner's syndrome (unilateral ptosis, pupillary miosis and facial anhidrosis secondary to interruption of eye sympathetic innervation,myasthenia gravis. Myogenic causes include: muscle dystrophy as well as its adult onset variant, myotonic dystrophy, oculopharyngeal dystrophy, myasthenia gravis, chronic progressive external ophthalmoplegia (CPEO), as well as steroid induced ptosis and HAART associated myogenic ptosis. Other acquired etiologies include aponeurotic ptosis, mechanical ptosis, traumatic ptosis, and pseudoptosis [1-9].

Treatment of ptosis is based on the etiologies. For traumatic or mechanical ptosis, with underlying conditions corrected or excluded, surgical intervention is the mainstay of management. For MG associated ptosis, pharmacologic therapy includes anticholinesterase medications and immunosuppressive agents such as corticosteroids, as well as non-steroid immunosuppressants like mycophenolate mofetil, azathopine, methotrexate, cyclosporine, tacrolimus, sirolimus, rituximab, IVIG, cyclophosphamide, and plasmapheresis. Plasmapheresis and thymectomy are also part of the treatment armamentarium for myasthenia gravis. While they are not traditional medical immunomodulating therapies, they function by modifying the immune system. Thymectomy is an important treatment option for myasthenia gravis especially when a thymoma is present. Even without a thymoma present, thymectomy has been shown to improve outcomes in myasthenic patients [10-12].



Left ptosis is noted in the image above. The lid crease is absent on the left. As patient is elevating her eye brows superior sulcus deformity is seen on the left and right.

Methods and Results

Description of Case

A 48 years old female with past medical history significant for bronchial asthma was referred to our center for symptoms of intermittent bilateral eyelid droppiness, worse on the right with intermittent diplopia at far lateral gaze to the right. No associated focal extremity muscle weakness but reports intermittent fatigue which sometimes impaired her work performance. She reports that others comment on how tired and sleep deprived she often looks. She denies any prior head injury as well as no exposure to agricultural or environmental toxins. No skin rash, fever, chills or rigors. Her symptoms have been ongoing for about a year. She had seen several specialists including general neurologists and ophthalmologists and had several MRIs of the brain and spine but were unrevealing. On exam, visual fields and visual acuity were normal. Pupils reactive bilaterally with no relative afferent pupillary defect. Fundus: no optic atrophy, nor hemorrhage nor papilledema. EOM; intact with no nystagmus. Noted was mild moderate bilateral ptosis, right> left. Rest of cranial nerves as well as motor and sensory exam were normal. Given the diurnal fluctuation and bilateral ptosis as well as fatigue myasthenia gravis

was considered high on the differential. However other differential had to be rule out including endocrinopathy; inflammatory or infectious etiologies; intrinsic eye muscle pathologies, toxic agent exposures; demyelinating diseases and intracranial pathologies. Several MRIs brain and cervical spine recently performed prior to referral to our center were normal. CT scan chest and thorax to rule out mass were normal. Routine serologies including Lyme titer, TSH, Vitamin B12, Folate, ACE level and RPR and thyroglobulin antibody were negative. Acetylcholine Receptor (AChR) Binding Abs was negative, 0.06 nmol/l (range: 0-0.25); AChR Blocking Abs was negative, 18% (range 0-25%); AChR Modulating Abs was negative, 0.09 nmol/l. Serum MuSK Abs was then sent for further testing. Results was: Serum MuSK Abs was positive at 4184 U/ml (Range: 0-1). The clinical presentation and positive high serum MuSK Abs level confirmed the diagnosis of muscle specific tyrosine kinase myasthenia gravis, a rare, frequently more severe, subtype of myasthenia gravis with a different pathogenesis. She was started on gradual escalating dose of Mestinon which she tolerated but at higher dose hypersecretion of mucus required the addition of glycopyrrolate. Mucus hyper secretion as control and she did well for several weeks but then sudden she developed respiratory failure requiring prolonged ICU management. With steroids and IVIG acute and steroids chronically she was successfully extubated and sent to pulmonary rehabilitation and then ultimately discharged home on steroids. She is now on Imuran and will be considered for rituximab if her symptoms continue to deteroriate long term and will ultimately be referred to University of Pennyslvania Medical Center for enrollment in the newly FDA approved CAR T cell therapy protocol for MuSK MG patients [13].

Discussion

Myasthenia gravis (MG) is a relatively rare acquired, autoimmune disorder caused by an antibody-mediated blockade of neuromuscular transmission resulting in skeletal muscle weakness and rapid muscle fatigue. The autoimmune attack occurs when autoantibodies form against the nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction of skeletal muscles. Although the chief target of the autoimmune attack in most cases is the skeletal muscle nicotinic acetylcholine receptor (nAChR), other antigenic targets that are components of the neuromuscular junction (NMJ) including post synaptic transmembrane tyrosine kinase MuSK receptors and LRP4 LDL LDL associated lipoprotein receptor and agrin proteoglycan have also been implicated. According to the Myasthenia Gravis Foundation and based on the Osserman classification, there are 5 classes of patients with myasthenia gravis; I(ocular weakness) to V(requiring intubation). The classic presentation of MG is the diurnal fluctuation of muscle weakness that worsens with activity and improves with rest. 50% to 60% of MG patients who present initially with isolated involvement will progress to generalized myasthenia, often within 3 years of onset of symptoms. The disease remains exclusively ocular in only 15% to 25% of patients through the clinical course of the disease. Differential diagnosis of MG includes: brain stem gliomas, botulism, basilar artery thrombosis, ciguatera toxicity, tetrodotoxin toxicity, diphtheria, neurosarcoidosis, Miller Fisher syndrome; Guillian Barre syndrome variants, Lambert Eaton syndrome, multiple sclerosis, organophosphate poisoning,tick borne diseases, thyroid ophthalmopathy,Tolosa Hunt syndrome etc.

MuSK (muscle specific kinase) subtype of myasthenia gravis (MG) prevalence varies among countries and ethnic groups and this subtype of MG affects about 5 to 8 % of MG patients. MuSK MG is known to have an acute course involving the facial bulbar muscles but there are a subset of cases that present with a gradual course as in the case of our patient. Respiratory crises are frequent with MuSK MG and the disease may lead to generalized muscle weakness including muscle atrophy ultimately. MuSK MG is known for its mainly bulbar presentation, histologic absence of significant thymus gland alterations as well as association with HLA class II DR 14,DR16 and DQ5 alleles. It is usually associated with frequent acetylcholine esterase inhibitors failure as well as frequent negative results of electrophysiologic testing, If not performed involving the mainly involved muscle groups. The majority of MuSK patients are refractory to treatment but steroids are effective in several cases of these patients. Conventional immunosuppressants cannot easily replace steroids in maintaining long term satisfactory control of symptoms. The use of rituximab is showing promising results in symptoms control in these patients. Efforts are underway to use the recently FDA approved CAR (chimeric antigen receptor) T cells therapy to treat MuSK MG patients [2]. Enrollment is ongoing at U Penn Medical Center. Our patient was being prepared for recruitment before she had a sudden relapse requiring intubation and prolonged ICU management [14].

Conclusions

Ptosis, whether congenital or acquired, has a myriad of etiologies as well as a broad differential. Astute diagnostic acumen with appropriate neurologic and ophthalmologic diagnostic workup are important cornerstones in arriving at timely and correct etiologic diagnoses , which will then inform correct therapeutic and/ or surgical intervention in a timely manner. Neurologic and neuroopthalmologic referrals are important in the appropriate management of patients who present with ptosis to the usually busy clinical practice.

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