

DIPLOPIA LOCALIZATION: EXTRAOCULAR MUSCLES

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INTRODUCTION:

Double vision may be the first or only sign of orbital disease, leading to a myriad number of diagnoses including thyroid eye disease, localized and systemic inflammation, trauma, infection, neoplasm and congenital myopathies. Presentations may be difficult to differentiate from certain cranial neuropathies, but proptosis, peri-orbital edema and resistance to retropulsion are all suggestive of an orbital process. In many cases, limitation of movement actually reflects restriction of an antagonist muscle rather than weakness of an agonist, a phenomenon that may be confirmed with attempted forced ductions of the eye. Lack of pupil or lid involvement helps differentiate adduction defects localizing to the medial rectus from partial third nerve palsies.

As is evident in many of the cases presented in this lecture, traditional brain imaging with CT or MRI may miss disease of the extraocular muscles, leading to significant delays in diagnosis and treatment. A careful history and exam tailored at discovering myopathic causes of diplopia is therefore essential in determining which cases require dedicated orbital imaging. While most cases of myopathic diplopia are not emergencies, they may rarely be the first sign of life-threatening infection or neoplasm. This text will review the various causes of diplopia related to the extraocular muscles, with an emphasis on their diagnosis and basic management, through several examples from the author's clinical practice. When appropriate, exam techniques applicable to the diagnosis of diplopia of all types will be reviewed as well.

Case 1: A Young Woman with "Migraines"

A 19 year old girl was admitted by neurology with peri-orbital headache on the left for several weeks. She *also complained that vision was "unclear" at times*, especially when looking to the left. She had a history of headaches since age 10 with nausea and preference for a dark room. MRI of the brain had shown only an incidental frontal cavernous angioma. She had therefore been treated with migraine medications including nortriptyline and opiates but had found no relief. Left gaze also exacerbated her headache. Further questioning clarified that by "unclear," the patient meant that there was a second ghost image next to the first "real image." This resolved with covering either eye, and was exacerbated by distance fixation.

EXAMINATION: Testing of versions showed some subtle scleral show with abduction of the left eye, and cross-cover testing showed an esophoria that was worse in left gaze, together confirming either weakness of the left lateral rectus muscle or restriction of the left medial rectus muscle. Medial orbital pain with abduction suggested the latter, and an MRI of the orbits was obtained.

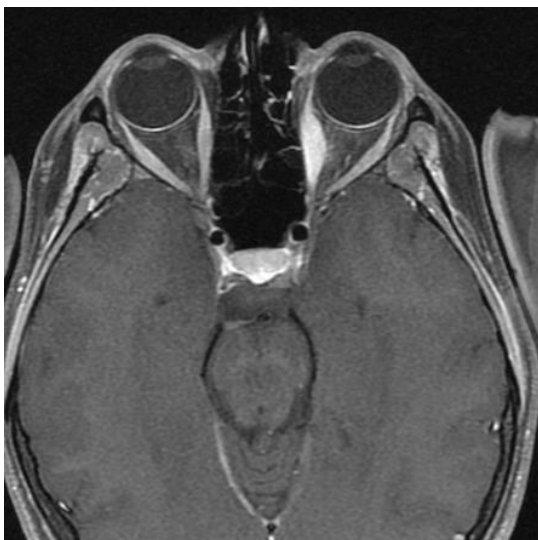


Figure 1. MRI orbits revealed enlargement and intense enhancement of the left medial rectus muscle, consistent with orbital myositis. The patient was treated with oral prednisone and all symptoms resolved within a week.

Diagnosis: Presumed orbital myositis

I. APPROACH TO DIPLOPIA

This presentation is a good example of how patients with a small degree of diplopia may express their complaint as “blurry” or “unclear” vision. With focused questioning, the patient described the lack of clarity as a “ghost image” that was side by side with the “real image” and a horizontal diplopia in left gaze was diagnosed. She confirmed that the ghost image resolved with closure of either eye, ruling out a monocular diplopia as might occur from retinal or corneal disease. When asked, the patient described the blurriness as worse in the distance, suggestive of a left lateral rectus palsy, since abduction must occur for fixation in the distance. Finally, it soon became evident that her “headache” was really a pain focused in her medial orbit, and was exacerbated by attempted lateral gaze. Pain with attempted eye movement in the direction of limited motility is suggestive of orbital disease, either of the muscle or at the orbital apex. Based on this history, the best localization is therefore a disease tethering the medial rectus and restricting abduction in the opposite direction. The exam was then used to confirm or modify this localization. In this case, examination of ductions (movement of each eye individually) and versions (movement of both eyes together) revealed that the left eye indeed did not abduct 100%, as evidenced by some scleral show lateral to the fully abducted eye.

Understanding tropias, phorias and the cross cover test

The limitation of movement described above may be termed ophthalmoparesis, and in this case was accompanied by an associated “tropia,” which refers to a misalignment of the two eyes even when both eyes are uncovered. Since the affected eye is aligned just a bit inward, this is termed an “esotropia.” Similarly, when an eye’s placement is a bit lateral compared to the other eye, it is called an exotropia. Hypertropia and hypotropia describe the situations where an eye is either higher or lower than the other eye when both eyes are open, respectively.

In some cases, a muscle may be strong enough that it can move the eye to where it needs to be when it is involved in stereoscopic fixation along with the fellow eye, but when the eye feels it is not needed (when it is covered or when it is made to view a different stimulus than the fellow eye), it slips back to its position of weakness. In other words, the misalignment of the two eyes is latent, only coming out of hiding when one eye is prevented from fixating. This type of weakness is referred to as a “phoria” so that one may describe an esophoria, exophoria, hyperphoria or hypophoria. The most expedient way to detect a phoria is to perform the Cover-Uncover Test, as was performed in this case. The patient was asked to fixate on a target of interest. When the weak eye was covered by the practitioner’s hand, it drifted inward, but as soon as it was uncovered, it moved back to midline in order to fixate on the target. At the same time, the strong eye was covered. Interestingly, while the strong eye was covered, it too deviated inward, and returned to the fixation target as well when uncovered. This occurs NOT because this eye is weak too, but rather because the same force that is applied to the weak eye to move it outward (to the left) must be applied to the strong eye as well (Herring’s Law). This is known as the “secondary deviation.” Since both eyes will move during a positive cross cover test, one needs to perform the test again with gaze aimed in either direction and observe which direction exacerbates the corrective eye movements. In the case of an esophoria like this, a worsening in left gaze implicates the left lateral rectus, while a worsening in right gaze implicates the right lateral rectus.

Maddox rod testing

As mentioned above, a second method of detecting a phoria is to make it so that each eye is seeing a different target so there is no impetus for ocular alignment. This can be done by placing a red prism lens called a Maddox rod over the right eye (it is always placed over the right eye by convention) which converts a white light held by the practitioner into a red line. This line can be made to be horizontal or vertical depending on how the Maddox rod is held. Since the right eye sees the red line and the left eye sees the white light, stereo vision is not possible and the eyes drift away based on the pattern of weakness. In the above case where there is an esophoria from left eye abduction weakness, the left eye drifts to the right of center, and the white light is therefore observed to the left of center. Assuming the right eye is stationary, the white light will be perceived to be to the left of a centered vertical red line as seen by the right eye through the Maddox rod. Further testing of this relationship can be done in all fields of gaze and the results can be charted in a tic-tac-toe configuration. Examination of the distance between the white light and red line in various directions can lead to a proper localization of the diplopia.

II. ORBITAL MYOSITIS AND IDIOPATHIC ORBITAL INFLAMMATION

Presentation

Orbital myositis is inflammation of an extraocular muscle, often in association with pain and diplopia. It is a subset of the broader entity idiopathic orbital inflammation (IOI, formerly known as “orbital pseudotumor”) which can affect the muscles, soft tissue and optic nerve, potentially resulting in blindness.

Differential Diagnosis

IOI is a diagnosis of exclusion, since orbital inflammation can occur in many systemic inflammatory diseases, and serologic testing should aim to uncover such entities. Other entities that need to be ruled out include neoplasm and infection, which are discussed below, and systemic inflammatory diseases such as thyroid eye disease, sarcoidosis and rheumatoid arthritis. Peri-orbital edema and proptosis have been reported with dermatomyositis, but true orbital myositis has not been clearly established.¹ Some vasculitides may lead to orbital ischemia, including Wegener’s granulomatosis² and giant cell arteritis. It may be challenging to differentiate orbital myositis from thyroid eye disease based on clinical examination, but orbital myositis tends to be more acute, painful and responsive to corticosteroids. Recently, some cases of idiopathic orbital inflammation, particularly with ocular adnexal inflammation, have been linked to immunoglobulin 4 (IgG4), a subclass of IgG that appears linked with multiple forms of systemic inflammatory disease.³

Table 1. Inflammatory Causes of Orbital Disease

Entity	Testing
Sarcoidosis	Chest CT, ACE level
Thyroid Eye Disease	Thyroid function tests, thyroid antibodies
Systemic Lupus Erythromatosis	Antinuclear antibody (ANA)
Rheumatoid Arthritis	Rheumatoid factor (RF)
Wegener’s granulomatosis	Central Antineutrophil Cytoplasmic Ab (c-ANCA)
Giant cell arteritis	ESR, CRP, Temporal artery biopsy
Sclerosing idiopathic orbital inflammation	IgG4

Risk factors for IOI may include a higher body mass index, lower socioeconomic status, and in women, a younger age at childbirth.⁴ Iatrogenic orbital inflammation is rare, but includes the use of bisphosphonates.⁵

Radiological Features

IOI and orbital pseudotumor are best detected with fat-saturated orbital MRI with and without contrast or with post-contrast CT. Unlike with thyroid eye disease, the enlargement and increased enhancement of extraocular muscles in IOI tends to include the tendons.

Management

Typically, biopsy is initially deferred in order to avoid damage to intra-orbital structures, but in refractory and recurrent cases, it may be necessary to rule out alternative diagnoses such as rare neoplasm. The mainstay of treatment for IOI and orbital myositis is corticosteroids which results in a clinical response in approximately 80% of patients but should be continued for several months to prevent quick recurrence. Second line therapies for refractory or recurrent cases include radiation therapy, which resulted in long term control in 81.2% of patients who failed steroids in one series,⁶ intra-orbital injections of triamcinolone,⁷ and alternative anti-inflammatory and chemotherapeutic agents including methotrexate, azathioprine, mycophenolate and low dose cyclosporine A.⁸

Case 2: A Woman with diplopia and “staring” of the left eye

A 62 year old woman with a 20 year history of smoking presented with diplopia and mild orbital discomfort. Examination of the left eye revealed eyelid erythema and edema, lid retraction, conjunctival injection, chemosis and proptosis. Intraocular pressure was normal but increased by 5 mm of Hg in upgaze. CT of the orbits revealed enlargement of the inferior rectus and medial rectus muscles. She was treated conservatively with ocular lubricants and prisms.

III. THYROID EYE DISEASE

Demographics

Approximately 40% of patients with Grave's disease will develop thyroid eye disease, but some patients with Hashimoto's thyroiditis may develop orbital involvement as well. Patients may be hyperthyroid or euthyroid at the time of orbital involvement. There is a 4:1 female predominance. Average age of onset is 20-50, but severity increases after age 50.⁹ Risk factors include a family history and smoking.

Pathophysiology

The immune mediated reaction typically consists of lymphocytes and plasma cells within orbital soft tissue and muscles with sparing of the tendons. It appears to be triggered by a type II reaction associated with antibodies targeting EOM antigens such as TSH receptor antibodies. T cells proliferate and release cytokines that trigger fibroblasts to produce glycosaminoglycans which are hydrophilic and lead to increased osmotic pressure and edema. Venous congestion and proptosis ensue. Fibrosis and atrophy are later findings.

Clinical Findings

Common findings include proptosis, conjunctival injection over points of EOM insertion, chemosis, lid edema and erythema and curuncular swelling. Other signs suggestive of thyroid eye disease include:

Lid Retraction – Resulting in the characteristic stare, lid retraction, which may be either unilateral or bilateral, initially occurs due to circulating thyroid hormone. Eventually, infiltration of the levator palpebrae and Muller's muscles results in scarring and permanent retraction. Lid retraction from dorsal midbrain disease (Collier's sign) can be differentiated by its association with near-light dissociation and bilateral paralysis of upgaze.

Lid Lag (Von Graefe's sign) - A delay in the lowering of the lid with downward rotation of the globe may be seen in up to 8% of patients with TED.¹⁰ It should be differentiated from pseudo-Von Graefe's sign where depression of the eye causes simultaneous lid elevation due to aberrant regeneration of the oculomotor nerve.

Increased IOP in upgaze - A greater than 4mm of Hg increase in intraocular pressure in upgaze is suggestive of a greater infiltration in TED and is believed to occur because of compression of the globe by a hypertrophied inferior rectus. However, such an increase occurs in controls as well as may be of limited use in diagnosis of TED.¹¹ Extraocular muscle recession has resulted in a decrease in upgaze-related IOP increase.¹²

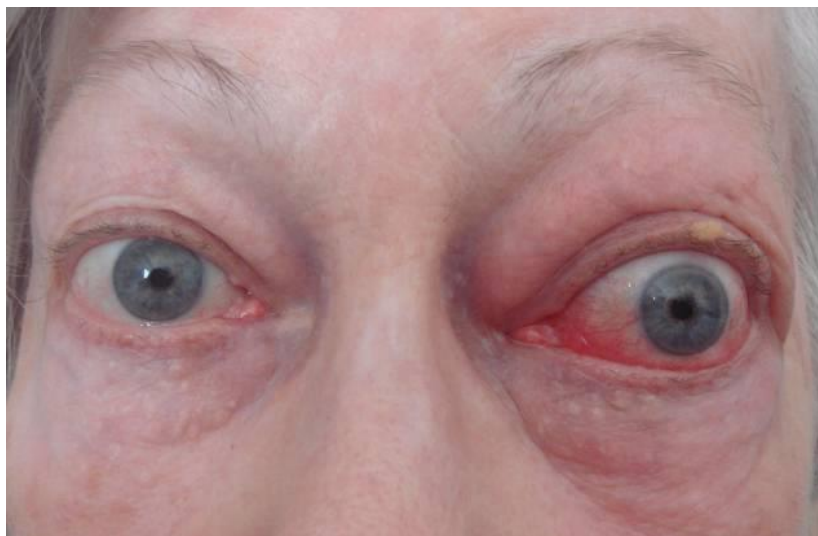


Figure 2. 65 year old woman presented with eyelid erythema, eyelid edema, conjunctival injection, chemosis and proptosis in her left eye.

Management

Treatment of TED must be tailored to disease severity, the risk of visual loss and the specific needs of the patient. Conservative measures include ocular lubricants, smoking cessation and prismatic therapy for diplopia. Steroids

do not show the strong response that is observed in idiopathic orbital inflammation, but can result in improvement in patients with acute congestive orbitopathy. This may be followed by orbital radiation to reduce chronic steroid use. Lid surgeries may be helpful in patients with severe lid retraction and secondary keratopathy. Recent evidence suggests reduced ocular involvement in patients with mild Grave's orbitopathy treated with selenium.¹³ Finally, orbital decompression may be necessary in patients with orbital apex disease resulting in optic neuropathy.

Case 3: An artist with acute diplopia

A 32 year-old female painter complained of a red, painful right eye and horizontal, binocular diplopia for 2 weeks. Examination with a Hertel's exophthalmometer revealed measurements of 24 mm OD and 20 mm OS. There was resistance to retropulsion of the right eye. Tensions were 23 mm Hg OD and 14 mm Hg OS. There was a conjunctival hemorrhage in the right eye. There was an exotropia in primary gaze as evidenced by the medial displacement of the light reflex in the right eye. Motility examination revealed limitation of the right eye in all directions. There was mild optic disc swelling in the left eye. MRI of the orbits revealed a large enhancing mass in the superotemporal orbit with compression of the superior rectus and medial rectus muscles. (see figure 3)

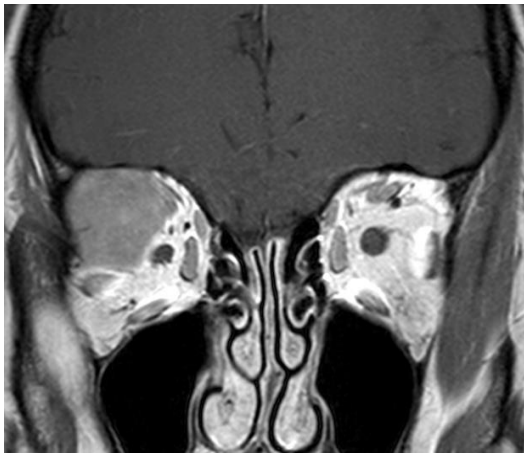


Figure 3. MRI orbits revealed a large intraorbital mass with decreased enhancement as compared to the surrounding soft tissue, encompassing the superior rectus and pushing the lateral rectus downward. CBC revealed acute myeloid leukemia (AML) and biopsy of the mass was consistent with a granulocytic sarcoma (chloroma), a leukemic mass that rarely presents in the orbit. The patient improved with chemotherapy.

IV. ORBITAL NEOPLASM

Diplopia may be the first sign of orbital tumors or infiltrative neoplasm. Findings include proptosis and resistance to retropulsion. Tumors in the superior orbital region may also cause hypoglobus and metastatic breast cancer may cause enophthalmos.¹⁴ Table 2 shows examples of orbital tumors and their relative incidence in one study.¹⁵ Diffusion weighted MRI can be helpful in differentiating benign from malignant disease with a 75% concordance rate of diffusion positivity with malignancy in one study.¹⁶ Biopsy provides the definitive diagnosis. Current teaching recommends complete excision of lacrimal gland tumors that may be pleomorphic adenomas, without preoperative biopsy, as the latter may result in a greater incidence of recurrence and malignant transformation, but this point is controversial.¹⁷

Table 2. Orbital Tumors	
Tumor	% of all orbital tumors
Lymphoma	19%
Orbital extension of sinus tumor	9%
Adenoid cystic carcinoma (lacrimal gland)	7%
Cavernous hemangioma	6%
Orbital extension of brain tumor (i.e. meningioma)	5%
Plasmacytoma	3%
Metastatic breast cancer	3%
Ocular adnexal basal cell carcinoma	3%
Optic nerve and sheath tumors	3%
Reactive lymphoid hyperplasia	3%
Ocular adnexal melanoma	2%
Rhabdomyosarcoma	2%
Metastatic gastrointestinal cancer	2%

Case 4. *A teenager with diplopia and sleepy eyes*

A 17 year old girl presented with progressive ptosis in both eyes and also complained of mild chronic intermittent diplopia. Her mother also had similar complaints. Examination revealed 4 mm of ptosis OD and 5 mm OS. Extraocular motility examination showed 30% elevation, 10% abduction and depression and no adduction OU. Fundus examination revealed a pigmentary retinopathy. MRI revealed bilateral subcortical white matter hyperintensities on T2-weighted imaging. Lumbar puncture showed a protein of 120 mg/dL. Muscle biopsy showed ragged red fibers. Kearns-Sayre disease was diagnosed.

V. CONGENITAL MYOPATHIES AFFECTING THE ORBIT

Congenital orbital myopathies are typically progressive and accompanied by severe progressive ptosis. Patients may complain of diplopia, but its incidence is relatively low, owing to both the symmetric limitations in eye movement in each eye and the compensation that occurs in congenital strabismus. Table 3 presents a selection of myopathies affecting the extraocular muscles and includes symptoms that can help differentiate one from another. Chronic progressive external ophthalmoplegia (CPEO) is a mitochondria, maternally inherited disease, with progressive symmetric limitations of ocular motility and bilateral ptosis. Kearns Sayre syndrome is similar to chronic progressive external ophthalmoplegia with the addition of a pigmentary retinopathy and a predilection for heart block. EKG should therefore be performed in all patients with suspected disease.

TABLE 3. Selected myopathies that may affect extraocular muscles				
Myopathy	Progressive External Ophthalmoplegia	Kearns Sayre Syndrome	Myotonic Dystrophy	Oculopharyngeal Muscular Dystrophy
Pathophysiology	Mitochondrial mutations such as transfer RNA	Large mitochondrial mutations	CTG repeat in a muscle protein kinase gene.	GCG repeat in polyadenylate-binding protein gene
Associated Symptoms	Ptosis. The EOM limitation is equal in both eyes so typically there is no diplopia.	Like CPEO plus pigmentary degeneration of retina and heart block	Ptosis with rare strabismus, myotonia, diabetes, cardiac defects, frontal balding, cataracts	Ptosis, dysphagia presenting after age 40, more common in French-Canadians.

Pathophysiology

In cases of mitochondrial myopathy, a subsarcolemmal accumulation of mitochondria may appear as ragged red fibers within the myocytes, but up to 75% of biopsies of patients will miss this finding,¹⁸ in which case a search for one of the many mitochondrial mutations can be helpful in cementing the diagnosis.

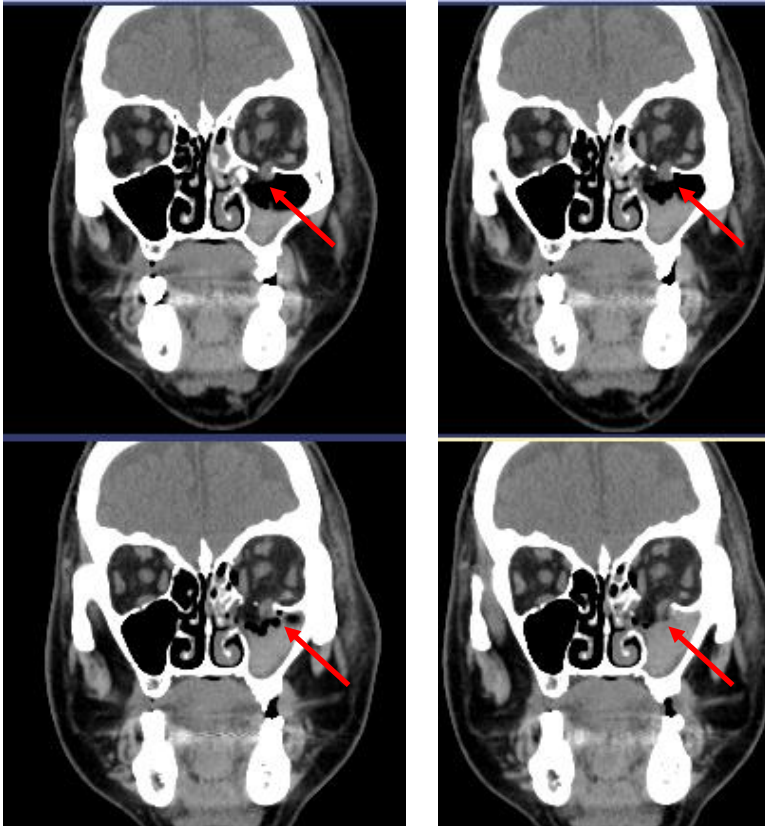
Management

When blepharoplasty is performed, a subsequent loss of the Bell's reaction during lid closure may lead to keratopathy from associated lagophthalmos. Lid crutches can treat ptosis and avoid this complication. Prisms can be quite effective for associated diplopia since there is a limited field of gaze and little opportunity for varied prismatic needs.

Case 4: Diplopia at the bottom of the Stairs

A previously healthy 53 year old woman complained of vertical diplopia after falling down the stairs. Exam showed limitation of elevation, depression and adduction of the left eye, suggestive of a partial third nerve palsy but there was no ptosis and no mydriasis. CT head showed a small subarachnoid hemorrhage but no cause for diplopia. MRI/A brain was unremarkable. Neurosurgery determined that the patient had a post-traumatic third nerve palsy and had decided to send the patient home because the "ophthalmoplegia is subtle and the imaging is fine."

Figure 4. Review of the CT of the orbits revealed a blowout fracture of the inferior orbit and protrusion of the inferior rectus through the defect with associated entrapment. (red arrows)



DIPLOPIA ASSOCIATED WITH TRAUMA

Presentation

Direct mechanical trauma to the orbit can result in a wide array of eye movement disorders, often through restriction and entrapment of orbital muscles. Muscle disinsertion from the globe may also occur. There may be associated hypoglobus or enophthalmos. Iatrogenic trauma to extraocular muscles may occur after cataract, retina, orbital, and sinus surgery. Peribulbar anesthesia may cause trauma to the muscle cone and occurs more frequently incidence in the left eye due to a greater difficulty of injections OS in right handed surgeons.

Imaging

While MRI is preferable in most other cases of orbital disease, CT of the orbit is preferred in cases of trauma because of its ability to show bony fractures and defects.

Management

Early surgical repair of the orbital wall with relaxation of involved muscles can help prevent scarring. Prismatic therapy may also be used.

VI. SUMMARY

Orbital disease is a common cause of diplopia, even in patients who present to the neurologist. A thorough knowledge of the various entities that can cause injury to the extraocular muscles leads to earlier diagnosis and treatment of these conditions and may decrease systemic morbidity from inflammatory and neoplastic entities. Orbital CT and MRI are essential tools in diagnosis of orbital disease even when cranial imaging appears to be normal.

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