

THOSE OTHER CAUSES OF DIPLOPIA

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As neurologists, we commonly assume that the patient complaining of diplopia has an abnormality of one of the ocular motor cranial nerves. But binocular diplopia, the symptom of misalignment of the ocular axes, can result from lesions anywhere along the pathways of ocular motor control, from cortical and supranuclear pathways, to the cranial nerves, the neuromuscular junction, and the extraocular muscles within the orbit. Although "neurogenic" disorders have classically been the domain of the neurologist, and "orbital" and "strabismus" disorders the domain of the ophthalmologist, they all cause double vision. Hence, the patient's symptom will prompt neurologic consultation, regardless of the underlying etiology.

Neuromuscular Junction Disorders (Myasthenia Gravis)

For all intents and purposes, the only disorder of common clinical importance that affects the extraocular muscle neuromuscular junction and causes diplopia is myasthenia gravis. Ocular manifestations, in particular ptosis and extraocular muscle weakness, are frequent in patients with generalized myasthenia, there at presentation in about 84% of cases and subsequently developing in at least 90%. In about 53% of cases, isolated ocular manifestations are the presenting signs, so-called ocular myasthenia gravis, and in 15-50% of these cases, the ocular findings remain the only manifestations of the disease. Generalization of the disease, if it is going to occur, will typically do so within two years. If myasthenia remains purely ocular for three years, then clinical generalization is very unlikely. As opposed to generalized myasthenia in which women are affected more frequently than men (especially under the age of 40), in ocular myasthenia, men are more frequently affected (especially after the age of 40).

Extraocular muscles require small motor unit size, precise dependence of muscle force upon motor neuron discharge rate, high contractile speed but low tension development. There are several important differences in the anatomy and physiology of the extraocular muscles and generalized skeletal muscles. These differences likely contribute to the frequent involvement of the extraocular muscles in myasthenia gravis. Some potential reasons for preferential eye muscle involvement in ocular myasthenia include: 1) the distributed synapses in the tonic fibers of the eye muscle may be more sensitive to antibodies; 2) there is preservation of the fetal type gamma subunit receptor in the eye muscle fibers (antibodies directed toward the gamma subunit would affect only the eye); 3) there are fewer receptors at each synapse in the eye muscles; 4) there is less acetylcholine released at each synapse on eye muscle fibers (ie., a lower safety margin for neuromuscular transmission); 5) eye muscle metabolic requirements are higher are more susceptible to disruption; and 6) vision changes are noticeable even with subtle eye muscle weakness because of misalignment of the visual axes.

Clinical Features:

The clinical features of ocular myasthenia are protean and can mimic any disorder of ocular motility, including supranuclear, internuclear and cranial nerve abnormalities. Like other manifestations of myasthenia, these signs will typically be variable and worsen over the course of the day. Other important features of myasthenic diplopia that aid in the differential diagnosis are the absence of pain and the absence of pupillary involvement.

Ptosis may be unilateral or bilateral, and frequently asymmetric. It can occur without ophthalmoplegia and can be brought on by exposure to bright sunlight, repetitive blinking, or prolonged upgaze. Typically, worsening of the ptosis will occur with manual elevation of the contralateral lid (so-called enhanced ptosis). Cogan's lid twitch is a brief excess elevation of the lid when the patient rapidly looks from downgaze to primary gaze. It is best elicited after fatiguing the upper lid with sustained upgaze.

Ophthalmoparesis usually, but not always, occurs with some ptosis. It may mimic any disorder of eye movement, including a single muscle weakness, gaze palsy, internuclear ophthalmoplegia (complete with abducting nystagmus!), or complete external ophthalmoplegia. The neuromuscular junctions supplied by the third cranial nerve appear particularly susceptible to myasthenia gravis, but isolated lateral rectus and superior oblique weakness can certainly occur. The key to diagnosing ocular myasthenia gravis in the patient with an isolated muscle palsy is to have a high suspicion for the disease, especially in the younger patient in whom the deficit varies.

Eye movement recordings have shown hypometric large saccades and hypermetric small saccades, as well as abnormal saccadic velocity which fatigues with repetitive stimulation. All these features may also be seen clinically, and it has been noted that the rapid small saccades of ocular myasthenia make the patient's eye movements look "twitchy".

Weakness of the orbicularis oculi muscles is almost always found in patients with ocular myasthenia. Indeed, some have suggested that if weakness of forced eyelid closure is not found, the diagnosis of ocular myasthenia should be questioned. With mild sustained eyelid closure, one or both orbicularis oculi may fatigue, resulting in the so-called "peek-a-boo" sign as the patient appears to be peeking at the examiner during attempted eyelid closure.

Other factors may affect the signs and symptoms of ocular myasthenia. Symptoms typically worsen with heat and improve with cold. Bright light can worsen the ocular symptoms, as can fever, emotional stress, thyroid dysfunction, a recent surgical procedure, and a variety of drugs.

Diagnosis:

Confirmatory diagnostic tests in the clinical setting of ocular myasthenia gravis include the ice test, the sleep test, the Tensilon test, the Neostigmine test, tests for acetylcholine receptor antibodies, and electrophysiologic testing, including repetitive supramaximal nerve stimulation and single fiber EMG. If the clinical setting is highly suggestive of myasthenia, a positive Tensilon test or a dramatically positive sleep or ice test is probably all that is necessary to confirm the diagnosis. I usually do antibody testing because it is so specific to the disease. If positive, I stop there, even in the patient with a negative or equivocal Tensilon test. However, acetylcholine receptor antibodies may be positive in as few as 34% of patients with ocular myasthenia. It is in these patients that I will move on to electrophysiologic testing.

If there is anything "atypical" about a case of ocular myasthenia gravis, I perform an MRI of the brain and orbits with gadolinium and special attention to the orbits, superior orbital fissures and cavernous sinuses. In patients with a confirmed diagnosis of ocular myasthenia, I obtain a chest CT looking for thymoma. I also have a low threshold for obtaining thyroid function tests since thyroid disease occurs with a higher frequency among these patients.

Treatment:

Treatment of myasthenia can be divided into those agents which reduce the symptoms of the disease (Mestinon, Neostigmine), and those which alter the immunologic aspects of the disease (prednisone, cyclosporin, azathioprine, mycophenylate, plasmapheresis, IVIg, thymectomy). In general, it is the latter group, especially prednisone, that appears to be most effective in controlling the symptoms of ocular myasthenia. There is some retrospective evidence that treating ocular myasthenia with immunotherapy (especially steroids) may delay or prevent systemic generalization of the disease. Other symptomatic treatments pertinent to ocular myasthenia include lid crutches, monocular patching, prisms, and even lid and strabismus surgery.

Ocular Myopathies and Orbital Disorders

Various disorders within the bony orbits can result in binocular diplopia by causing weakness of one or more of the extraocular muscles or, more commonly, by restricting movement of the globe. In most cases of orbital disease, accurate localization can be accomplished by the history and neuro-ophthalmological examination, and confirmed by neuroimaging.

Historical features which suggest orbital disease include periorbital swelling, redness of the eye, protrusion of the eye, chemosis and eye pain. Signs of orbital disorders include proptosis, lid retraction, diffuse or localized conjunctival injection, chemosis, arterialized conjunctival veins, restricted ocular motility with normal saccadic velocity, resistance to retropulsion of the globe through a closed lid, associated optic nerve involvement, and retinal or choroidal folds.

Forced duction testing is the classic maneuver to reveal a restrictive cause of ocular misalignment. In the cooperative patient, topical anesthetic is applied to the eye, especially in the region of the corneal limbus. The eye is then moved by the examiner in the direction of the motility deficit using either tweezers or two cotton applicators. The patient is asked to try to move the eye in the same direction. Resistance to full movement is an indication of restrictive disease, either intrinsic to the muscles or a result of orbital abnormalities. The ocular misalignment must be substantial for forced duction testing to be definitely abnormal. Subtle restrictive disorders can not be assessed with forced ductions.

Orbital disorders which can cause diplopia include thyroid ophthalmopathy, orbital myositis, ocular myopathies and dystrophies, orbital tumors, carotid-cavernous fistulae, the silent sinus syndrome, and orbital trauma.

Thyroid Ophthalmopathy:

Patients with thyroid eye disease typically already carry the diagnosis of Graves' disease (hyperthyroidism), with eye symptoms and signs usually presenting within 18 months of the systemic manifestations of the disease. However, in approximately 20% of cases, the patients are euthyroid or have a history of hypothyroidism. Presumably, loss of suppressor T-cell activity allows for B-cell proliferation producing antibodies to orbital tissues, especially the extraocular muscles, and to the thyroid gland. Middle aged women are most often affected and some individuals are genetically susceptible. Cigarette smoking is a definite risk factor for the development of eye findings in patients with Graves' disease.

Thyroid eye disease is the most common cause of proptosis. Onset of eye findings is typically subacute and painless, although some patients may have some discomfort, usually associated with dryness of the eyes from exposure and an inadequate tear film. Diplopia is the most common presenting manifestation to the neurologist. Infiltration of the extraocular muscles by an inflammatory process causes subsequent scarring and loss of elasticity, with resultant restriction of the globe. The frequency of involvement from the most to the least commonly involved muscles is the inferior rectus, medial rectus, superior rectus and lateral rectus. Hence, the most common patterns of restriction are loss of upgaze and decreased abduction with esotropia (the latter simulating a sixth nerve palsy). Findings may be unilateral or bilateral. Marked periorbital swelling, conjunctival injection especially over the extraocular muscle insertions, and lid retraction during the acute phase may, in some patients, allow for early and easy diagnosis. However, in other cases, other signs and symptoms are minimal, often leading to the mistaken diagnosis of a cranial nerve palsy. Subtle lid retraction or lid lag may provide clues to the correct diagnosis. Optic nerve compression occurs in about 5-10% of patients with thyroid orbitopathy.

When a motility disorder is present, imaging will usually show at least one enlarged extraocular muscle. There is typically fusiform enlargement of the muscles with relative sparing of the tendon insertions where the muscles attach to the globe. Imaging commonly reveals bilateral involvement even in cases that clinically seem to affect only one muscle. Other imaging features include proptosis, increased orbital fat, and straightening of the optic nerve. Good MRI of the orbits with special fat suppression techniques will show thyroid ophthalmopathy, as will CT scanning of the orbits with direct axial and coronal views. Ultrasound of the orbits and the extraocular muscles can also be used.

In the patient diagnosed with thyroid ophthalmopathy but no known history of Graves' disease, endocrinologic work-up and referral should be performed periodically. Screening should consist of a free T4, a TSH, and TSH receptor antibodies (thyroid stimulating antibodies). Treatment of the hyperthyroidism will not necessarily change the progress of the orbitopathy, although normalization of thyroid status may improve some of the orbital signs in some patients. Most patients will require direct treatment of the orbitopathy, depending on the severity and type of involvement. Steroids are appropriate for the acute phase of the disease, especially if there are signs of optic neuropathy or acute congestion. Other treatment modalities include lubrication for the external signs, radiation (although this has become controversial), orbital decompression, lid surgery, prisms and strabismus surgery. Surgical correction of diplopia-causing ocular misalignment should be withheld until the misalignment has been stable for at least 6 months.

Orbital Myositis:

Orbital inflammation can be caused by specific pathogens, including bacterial and fungal disease, or be part of a systemic inflammatory disease, such as sarcoidosis or Wegener's granulomatosis. Idiopathic orbital inflammation, so-called "orbital pseudotumor", can occur diffusely within the orbit, or involve specific orbital structures such as the extraocular muscles (orbital myositis), the sheath of the optic nerve (optic perineuritis), the sclera of the globe (posterior scleritis), or the lacrimal apparatus (dacryoadenitis). When an extraocular muscle is affected in isolation it is called orbital myositis, and the only sign may be ocular misalignment. IgG4 disease has been recognized as a cause of orbital as well as intracranial inflammation.

Orbital myositis may occur at any age. The onset is typically acute and painful, with pain exacerbated by eye movement. There may be associated proptosis, orbital congestion and periorbital swelling, but not necessarily. The medial and superior rectus muscles are most typically affected, although any extraocular muscle may be involved, either in isolation or in any combination. Eye movement may be limited in the direction of the involved muscle (parietic), in the opposite direction (restrictive), or both. Thus, a swollen lateral rectus may resemble a sixth nerve

palsy or an internuclear ophthalmoplegia. A brisk saccade in the direction of "paresis" will usually distinguish orbital myositis from a neurogenic disorder. Careful inspection of the insertion of the involved muscle will usually reveal overlying conjunctival injection.

Good MRI with fat suppression will reveal orbital inflammatory disease, as will CT scanning, both excellent for demonstrating the shaggy scleral thickening and enhancement in posterior scleritis, lacrimal gland enlargement in dacryoadenitis, and the diffuse swelling of orbital structures with shaggy borders and so-called "dirty fat" in the generalized forms. Muscle enlargement in orbital myositis shows prominent involvement of the anterior portion of the muscle, especially the tendinous insertion on the globe, and shaggy borders rather than the sharp margins typically seen in thyroid disease. Findings are usually unilateral. The ESR may be elevated in some patients, but laboratory testing is typically negative.

Orbital pseudotumor, including orbital myositis, is classically dramatically responsive to steroids. Failure of pain to remit within 24 hours of starting treatment with prednisone (typically at doses of 60-100 mg per day) should prompt consideration of other diagnoses. Patients can usually be weaned off steroids over 1-2 months, although recurrences are not uncommon. An incomplete response or immediate relapse are the usual indications for diagnostic biopsy. Other modes of treatment include radiation therapy (usually up to 2000 g) or other immunosuppressive agents (such as azathioprine or methotrexate).

Ocular Myopathies:

Some congenital myopathies, muscular dystrophies and myopathies may involve the extraocular muscles in addition to their other systemic and neurologic manifestations. Indeed, in some of these disorders, the ophthalmoplegia secondary to extraocular muscle involvement is the primary manifestation of the disease. Even though the eye muscle involvement is typically bilateral and symmetric, some of these patients do complain of diplopia, especially with attempted convergence.

Chronic progressive external ophthalmoplegia (CPEO) is a syndrome of slowly progressive weakness of the extraocular muscles, usually associated with bilateral ptosis and orbicularis oculi weakness. It may be a manifestation of a number of neurodegenerative disorders, but it is most commonly seen among the mitochondrial myopathies. In that setting, other ocular, neurologic, and systemic abnormalities may be associated, including pigmentary retinopathy, sensorineural hearing loss, generalized myopathy, ataxia, basal gangliar lesions, elevated CSF protein, cardiac conduction defects, short stature, diabetes mellitus and other endocrine abnormalities. The classic pathology is that of "ragged red fibers" on modified trichrome staining of muscle biopsies. Most cases of CPEO are related to abnormalities in mitochondrial DNA, 50% of them mitochondrial DNA deletions. Mitochondrial deletions are found in 90% of patients with the full-blown Kearns-Sayre syndrome, the most severe on the spectrum of CPEO cases. Most cases of CPEO are sporadic, but some pedigrees show maternal or autosomal dominant or recessive inheritance.

Other ocular myopathic disorders include myotonic dystrophy and oculopharyngeal dystrophy.

Carotid-Cavernous Fistula:

Carotid-cavernous fistulas can be grouped into two general categories: the high-flow, usually traumatic, direct fistulas from a tear in the intracavernous carotid artery; and the low-flow, usually spontaneous, indirect fistulas secondary to communication between small dural arterial vessels and the cavernous sinus. The former present acutely with severe proptosis, chemosis and ophthalmoplegia from congestion of the extraocular muscles. Dural cavernous fistulas usually have a more insidious onset with less marked orbital signs. Signs and symptoms include diplopia, variable pain or headache, proptosis, conjunctival injection with arterialization of the conjunctival veins. An audible, pulsatile bruit may be present. Additional findings include chemosis, elevated intraocular pressure and dilated retinal veins, occasionally with a full-blown central retinal vein occlusion. Diplopia may be secondary to cranial nerve involvement within the cavernous sinus or petrosal sinus, or may reflect extraocular muscle congestion.

Definitive diagnosis usually requires angiography of the internal and external carotid systems. Suggestive signs on neuroimaging include enlargement of the superior ophthalmic vein and enlarged extraocular muscles. Some dural fistulas close spontaneously or following angiography. Indications for treatment include intractable pain, medically uncontrollable glaucoma, marked proptosis or progressive visual loss. Treatment usually entails interventional angiography with balloon occlusion.

Orbital Tumors:

Orbital tumors, such as optic nerve sheath meningiomas and optic gliomas, are more likely to affect optic nerve function and disrupt vision unilaterally rather than cause ocular misalignment and binocular diplopia. However, a variety of other benign and malignant tumors can occur in the orbit and cause double vision. These include orbital

hamartomas and choristomas, dermoids and teratomas, capillary and cavernous hemangiomas, lymphangiomas, orbital varices, schwannomas, rhabdomyosarcomas, lymphomas and plasma cell tumors, lacrimal gland tumors, and metastatic disease to the orbit and to the extraocular muscles themselves. The mechanism of diplopia is usually restrictive. CT or MRI specifically of the orbits (with the techniques required for good orbital viewing) will adequately delineate most of these lesions.

Other Orbital Syndromes:

Orbital trauma, either acute or remote, can cause injury or entrapment of the extraocular muscles with resultant restriction of movement of the globe and diplopia. The diplopia may be present in all fields of gaze or only on particular eccentric gazes. The most common orbital traumatic injuries that cause diplopia are the orbital floor and medial orbital wall fractures, so-called blow-out fractures. In floor fractures, upgaze is typically limited, and in medial wall fractures, abduction of the affected eye is usually restricted. Clues to the diagnosis include a past history of trauma, enophthalmos on the affected side, and hypoesthesia in the distribution of the ipsilateral infraorbital nerve. Orbital surgery may be required, but usually strabismus surgery with extraocular muscle realignment proves sufficient.

In the "silent sinus syndrome" slow, insidious enophthalmos and settling of the orbital contents occurs on the side of a hypoplastic maxillary sinus. Some of these patients may experience vertical ocular misalignment with diplopia.

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