Exophthalmos

Synonyms: proptosis, exorbitism

Introduction
The term exophthalmos is derived from Greek, literally meaning with prominent eyes. It refers to the protrusion of one or both eyes. It is often used interchangeably with the term proptosis although some reserve the term exophthalmos for endocrine-related eyeball protrusion and use the term proptosis for other causes. It has been described in history and depicted in art, and the common causal link with underlying (thyroid) disease has been known since antiquity.[1,2]

In adults, thyroid orbitopathy is the most common cause of unilateral and bilateral exophthalmos. In children, unilateral exophthalmos is commonly caused by orbital cellulitis, whereas neuroblastoma and leukaemia are likely if the condition is bilateral.

Anatomy[3,4]
The orbit is a pear-shaped cavity, the 'stalk' being formed by the optic canal. Its rigid walls provide a protective space for the globe and its surrounding soft tissues. However, there is a relatively small amount of redundant space and so any swelling within these tissues rapidly results in forward displacement of the globe ± bulging out of the tissues themselves.

The globe's movements are controlled by the extraocular muscles, four of which project forward from a single attachment at the apex of the orbit, forming a cone around the globe. Orbital lesions are said to be intraconal (eg, a tumour of the optic nerve) or extraconal (eg, a tumour of the lacrimal gland).

Exophthalmos can therefore result from:
- Foreign matter being forced into the orbit.
- Interference with venous return from the orbit.
- Extension of inflammation into the orbit.
- Invasion of the orbit by new growth.

Exophthalmos may be accompanied by other signs. The orbital disease may be isolated (eg, orbital varices) or may be a manifestation of a more proximal problem (eg, carotid-cavernous fistula) or of systemic disease (eg, Graves' disease). Pseudo-proptosis refers to the false impression of proptosis caused by:
- Facial asymmetry.
- Severe unilateral enlargement of the globe (eg, high myopia, buphthalmos - enlarged globe associated with congenital glaucoma).
- Lid retraction.
- Enophthalmos of the fellow eye.

Dystopia refers to an abnormal positioning of the globe without it actually projecting forward, as might occur with a lacrimal gland adenoma (the increased gland mass pushes the globe down rather than out).

Exophthalmos in children
- In children proptosis occurs far more readily than in adults because the eyeball is more distensible and the size of the orbit in relation to that of the eyeball is smaller than in adults.
- Aetiology is also different in children, in whom Graves' disease is almost never seen, whilst early tumours of types almost entirely confined to children must be considered.

Presentation[4]
This varies with the underlying cause although there are some features common to all cases. The direction of protrusion, its severity, the speed of onset and associated symptoms often give an indication as to the underlying cause but this usually has to be confirmed with further investigation.

There may also be signs and symptoms associated with the underlying cause - eg, signs of endocrine disturbance in thyroid disease, or headache and other neurological features in the case of tumour.

Symptoms
- Bulging eyes - this may not be the primary complaint if the progression has been slow and particularly if the problem is bilateral.
• Eyelid swelling - this may be associated with chemosis of the conjunctiva (the conjunctiva is seen as red and bulging, often beneath the globe).
• Double vision - this is caused by restriction of the extraocular muscles. They may be the source of inflammation (myositis) or they may be compressed by a growing tumour.
• Red eye - conjunctival injection increases with the exophthalmos. In severe cases, there may be a secondary exposure keratopathy as a result of incomplete lid closure over the cornea.
• Pain - tends to occur in the presence of inflammation, infection or a rapidly progressing tumour. Compromise of the cornea is also painful.
• Decreased vision - visual acuity may be impaired by:
  • Direct optic nerve involvement due to the pathophysiology.
  • Distortion of the macula by a lesion pushing in behind the globe.
  • Exposure keratopathy (see above) can also affect the visual acuity.
  • Vision can also be affected by the optic nerve being stretched forward - this would be quite a severe case, as the optic nerve has some 'slack' - ie it is longer than it needs to be.

Signs
These depend somewhat on the underlying pathology but critical signs of orbital disease are the presence of proptosis and a restriction of ocular motility. Other associated signs are outlined in the list of differential diagnoses below.

Assessment of exophthalmos

History
• Establish whether the condition is monocular or binocular.
• Ask about the above symptoms.
• Rate and duration of onset should be noted.
• Transient visual loss may signify optic nerve compromise and warrants a rapid referral.
• Explore other systems - consider whether this could be a manifestation of systemic disease.

Examination
Periorbital changes can be assessed in a well-lit room:

The proptosis
• Note the direction of the proptosis. Look down at the patient from above and behind, so that you are looking at their eyebrows and the nose below. Observe the proptosed eye and whether it is displaced forward or to the side. Intraconal lesions tend to push the globe directly forwards, whereas extraconal lesions push it to one side.
• Establish how severe it is. This can be assessed formally using a Hertel exophthalmometer which uses a system of small mirrors to visualise the corneal apices against a scale. Although less accurate, one can also measure these, using a clear plastic ruler, by placing it at the lateral canthus (where the upper and lower lids meet) and holding it parallel to the patient's nose. A difference of 2 mm between the two eyes is significant.
• Note whether it is reducible.
• Ascertain whether it is pulsatile.
• Establish what degree of chemosis is present.
•Ascertain how immobile the eye is.

The orbit
Look for lid swelling, engorged conjunctival and episcleral vessels and lagophthalmos/incomplete lid closure. Palpate the orbit for any tenderness or masses and examine the regional lymph nodes. If you suspect a high-flow lesion, listen to the globe over the closed eyelid with a stethoscope.

The optic nerve
Check for optic nerve function (visual acuity, relevant afferent pupil defect (RAPD), and dyschromatopsia; assess brightness sensitivity and do a confrontational visual field test).

You may find the separate article Examination of the Eye helpful.

Differential diagnosis
A range of conditions can result in exophthalmos. Below is an outline of some of these conditions. Of key importance is to identify the exophthalmos and its related features and to initiate investigations where possible (eg, blood tests).

Urgency of referral relates to severity of condition and speed of onset.

Thyroid eye disease
Thyroid eye disease, particularly Grave's disease, is the most common cause of exophthalmos. It may be unilateral or bilateral, and is covered in a separate article.

Infection
Orbital and preseptal cellulitis are important and potentially sight-threatening causes of exophthalmos due to preseptal infection and swelling. It is most commonly due to spread of infection from the sinuses or through the blood. It is covered in detail in a separate article.

Inflammatory disease

- **Description**: idiopathic orbital inflammatory disease (IOID) - previously called an orbital pseudotumour - is an uncommon disease characterised by non-neoplastic and non-infectious space-occupying orbital lesions. It is usually unilateral (more so in adults) but can be bilateral (more so in children). It may be acute, chronic or recurrent. Lacrimal gland involvement occurs in about 25% of cases when the condition is then known as dacryoadenitis (this can also occur spontaneously in a self-limiting fashion). Another subtype of IOID involves the extraocular muscles - orbital myositis. Proptosis can also occur in the Tolosa-Hunt syndrome and in Wegener's granulomatosis.

- **Symptoms**: pain is a common feature of all types of IOID, associated with acute discomfort in the lacrimal gland in dacryoadenitis and diplopia in orbital myositis and in Tolosa-Hunt syndrome. Children with IOID may have systemic complaints such as fever.

- **Signs**: in addition to proptosis (which may be mild), ophthalmoplegia occurs in IOID along with tenderness over the lacrimal gland or worsening of diplopia on attempted gaze in the field of action of affected muscles where the lacrimal gland or muscles are involved respectively. Ocular motor nerve palsies also occur in Tolosa-Hunt syndrome and Wegener's granulomatosis patients may additionally have scleritis or keratitis.

- **Management issues**: refer if you suspect any of these conditions, as treatment is secondary care. Management involves confirmation of the diagnosis (biopsy or imaging) and treatment modalities variously include observation only, steroids and cytotoxic drugs, radiotherapy and occasionally, surgery.

Vascular malformations

- **Description**: varices can occur within the orbit and are of variable length and complexity. Most are unilateral and situated in the upper nasal quadrant. About 20% are associated with phleboliths. Lymphangiomas can also occur in the orbit and may result in blood-filled 'chocolate' cysts. Lymphangiomas are usually seen in the first decade of life and progress slowly unless the tumour bleeds.

- **Presentation**: these variably present from early childhood (especially lymphangiomas) to adulthood. Varices present with intermittent proptosis (evident in the Valsalva manoeuvre) ± visible lesions in the eyelid. Lymphangiomas may be anterior, seen as bluish masses, usually with a cystic conjunctival component or posterior when they cause a slowly progressive proptosis which may suddenly become painful if there is a spontaneous haemorrhage. The proptosis may be intermittent and exacerbated by upper respiratory tract infections.

- **Management issues**: surgical excision of these conditions is tricky but may be indicated in certain situations - eg, pain or optic nerve compression.

Carotid-cavernous fistula

- **Description**: this is an arteriovenous fistula between the carotid artery and the cavernous sinus. The net effect (as the blood flows anteriorly into the ophthalmic veins) is blood stasis around the eye and orbit:
  - A carotid-cavernous fistula may be spontaneous or traumatic.
  - 70-90% of cases are direct high-flow shunts in which the carotid artery blood passes directly into the cavernous sinus.
  - Of these, 75% occur as a result of trauma.
  - Postmenopausal hypertensive women are most at risk of a spontaneous event.
  - Indirect fistulae (dural shunt) can also occur from congenital malformations or spontaneous rupture: there is a connection formed between meningeal branches of the internal or external carotid arteries and the cavernous sinus.

- **Presentation**: Direct fistulae can occur days or weeks after a head injury and signs are not necessarily ipsilateral to the fistula. 60-70% of cases experience ophthalmoplegia: ophthalmoscopy will show disc swelling, venous dilatation and intraretinal haemorrhages.
  - Indirect fistulae present with a more gradual picture of redness of one or both eyes and variable signs of dilated conjunctival/episcleral vessels, exaggerated ocular pulsation and raised intraocular pressure.

- **Look for the triad of**: Pulsatile proptosis. Conjunctival chemosis. Flushing noise in the head.

- **Management issues**: most fistulae are sight-threatening rather than life-threatening. A spontaneous fistula may close on its own but others will require interventional radiology for the placement of a detachable balloon which will occlude the fistula.

Cystic lesions

- **Description**: various cystic lesions can occur around the globe. Most do not cause proptosis. An exception is the formation of a mucocele which develops when the drainage of the paranasal sinus secretions becomes obstructed (eg, infection, allergy or trauma). Frontal or ethmoidal mucoceles are most likely to cause a problem.

- **Presentation**: proptosis, dystopia, diplopia and epiphora (excess tears). There may be tenderness over the affected sinus.

- **Management issues**: once the mucocele is confirmed by CT, these patients need surgery for removal of the mucocele and re-establishment of normal sinus drainage.

Tumours
Capillary haemangioma
This is the most common tumour of the orbit and the periorbital areas in childhood. The superior anterior orbit is most commonly involved and diagnosis is made on inspection. However, occasionally, a deep orbital tumour gives rise to proptosis (exacerbated by crying) in the absence of discoloration. CT may be required to diagnose these lesions. Growth tends to occur until about 1 year of age with spontaneous resolution thereafter. 70% of tumours have completely resolved by the age of 7 years. Certain situations do warrant treatment, including amblyopia, optic nerve compression, exposure keratopathy and necrosis or infection. It involves injected or systemic steroids or local resection. Low-dose radiotherapy may also occasionally be used.

Pleomorphic lacrimal gland adenoma
This painless slowly growing tumour presents in the fifth decade of life. Proptosis only occurs if there is a posterior extension. Treatment is via surgical excision.

Lacrimal gland carcinoma
This is a rare tumour presenting in the fourth to sixth decades of life with a long-standing proptosis (± swollen upper lid) which suddenly starts to increase, or as a rapidly growing (over months) lacrimal gland mass. It is the posterior growth which gives rise to proptosis. After CT, biopsy and a neurological assessment (it spreads perineurally), treatment is with radical surgery and radiotherapy. The morbidity and mortality are high.

Optic nerve glioma
Optic nerve glioma is a slow-growing astrocytoma typically affecting young girls, towards the end of their first decade. It is commonly associated with neurofibromatosis-1. The classic feature is optic nerve dysfunction and visual impairment out of proportion with the degree of proptosis. Some patients are observed (some tumours have an indolent course) but most require surgical excision ± radiotherapy. Some tumours are life-threatening.

Optic nerve sheath meningioma
Visual loss, optic nerve atrophy and shunt vessel formation between the two circulatory systems of the eye are virtually diagnostic of this rare condition in which proptosis occurs at a late stage when there has been intraconal tumour spread. These tumours tend to be aggressive in younger people who are treated with surgical excision ± radiotherapy. Older patients often have more slow-growing tumours; a watch and wait approach is sometimes appropriate then.

Neurofibroma
In about 10% of neurofibromatosis-1 cases, an isolated neurofibroma can form behind the globe, causing a slightly painful proptosis and associated visual impairment or restriction of ocular motility. Surgical excision is the norm.

Lymphomas
Orbital lymphoma accounts for about 8% of extranodal lymphomas. Any part of the orbit may be affected and it may be bilateral. Proptosis occurs if the lesions lie behind the globe. Treatment involves radiotherapy (localised disease) or chemotherapy (disseminated disease).

Rhabdomyosarcoma
The most common primary orbital tumour in childhood is the rhabdomyosarcoma and is managed by paediatric oncologists once the diagnosis has been made by the ophthalmology team.

Childhood metastatic tumours
Neuroblastoma is one of the most common childhood malignancies. Orbital metastases present with an abrupt onset of proptosis but by then, most of the patients will have been diagnosed with abdominal cancer. Another tumour affecting the orbit and so resulting in proptosis is granulocytic sarcoma (chloroma) which may present with rapid onset of (occasionally bilateral) proptosis at about 7 years of age.

Adult metastatic tumours
The most common primary sites of orbital metastases are breast, bronchus, prostate, skin melanoma, and tumours of the gastrointestinal tract and kidney. However, orbital metastases remain infrequent causes of adult proptosis. Other features may include indurated periorbital skin, chronic orbital inflammation and some degree of cranial nerve involvement.

Other causes
- The craniosyntoses are a group of rare, hereditary disorders characterised by abnormal fusion of the cranial sutures. Severe orbital abnormalities are associated with these. The most common ones include Crouzon’s syndrome and Apert’s syndrome.
- Trauma may result in orbital or facial fractures or in retrobulbar haemorrhages which, if large enough, can push the globe forward.

Investigations
- All patients should have TFTs, even if they are euthyroid on presentation (about 80% of patients with Graves’ disease develop thyroid eye disease within 18 months of onset).
- Imaging studies such as CT scan, MRI or ultrasound of the orbit may be necessary if neoplasm is suspected.
- If orbital cellulitis is suspected, FBC, nasal and blood cultures and imaging may be required.

Treatment
This depends on the underlying cause, although there are generic management approaches to eye care whilst the proptosis is present. Artificial teardrops (eg, Celluvisc®) may be used to provide symptomatic relief in the interim and protect the exposed cornea. Patching at night may also be indicated if severe.

Complications of exophthalmos

These tend to be related to the underlying disease but care has to be taken to protect the globe and the exposed cornea.

Further reading & references


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