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MAJOR REVIEW

Intraocular Pressure Change in Orbital Disease

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Abstract. Intraocular pressure change has been found concurrent with many orbital pathologies, particularly those involving proptosis. The objective of this review is to offer an inclusive classification of orbital disease–related intraocular pressure change, not only for oculoplastics and glaucoma specialists, but also for general ophthalmologists. Various orbital conditions associated with increased intraocular pressure and glaucoma are comprehensively summarized, and pathophysiology, clinical manifestations, and treatment options of these diseases are discussed. Graves disease, arterio-venous shunts, trauma, and orbital neoplasia, and other common conditions are discussed in detail; less frequent syndromes such as orbitocraniofacial deformities, phakomatoses, and mucopolysaccharidoses are included for the sake of comprehensiveness, but discussed less extensively. (**Surv Ophthalmol 54**:519–544, 2009. © 2009 Elsevier Inc. All rights reserved.)

Key words. Intraocular pressure • ocular hypertension • glaucoma • orbit • proptosis

I. Introduction

Changes in intraocular pressure (IOP) are related to many orbital disorders including hereditary, structural, inflammatory, traumatic, and neoplastic diseases.[69,131,269] These relationships can be described either as causal or associative. There are four primary pathophysiological mechanisms that lead to IOP change in orbital disease:

(i) structural abnormalities, including congenital and hereditary diseases and disruptions to the anatomical integrity of the globe and orbital tissues caused by trauma and surgical procedures
(ii) mass effect, which may develop secondary to neoplasm (rapidly-growing tumor) and/or infiltrative disease (e.g., leukemia, multiple myeloma) compressing ocular and orbital structure
(iii) vascular disease, including arterio-venous malformations and tumor interference in the proper venous drainage of the globe and orbit
(iv) infections and inflammations that change the anatomy of the orbit and the vascular function, including cellulitis and other forms of orbital inflammation such as Graves disease.

This review covers most of the conditions, disorders, and situations in which IOP is elevated due to the mechanisms listed herein. In addition, a large number of associated pathologies, such as collagen tissue diseases, inborn errors of metabolism, autoimmune disorders, and other pathologies in which the IOP change and proptosis appear to coexist, are discussed. This latter group of disorders is designated "associated" because there is no causal relationship in most of these cases, so the co-occurrence of orbital manifestations with IOP change is more of a simultaneous presentation.

In most individuals, there is no bona fide correlation between the size, location, and type of the compressive orbital lesions and the level of IOP.

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Conversely, the flow rate of arterial–venous malformations is directly correlated with IOP; the faster the blood flow from the arterial to venous system, the higher the IOP. Once the flow rate is stabilized, however, the IOP ceases to fluctuate.

The secondary ocular manifestations of orbital disease include loss of visual acuity, field and color vision, refractive errors, external eye exposure problems, lid malfunction, extraocular motility disturbances, conjunctival and retinal vascular changes, chorioretinal folds, and optic disc edema and/or atrophy. None of these clinical features, except the extraocular muscle problems in some instances of Graves disease, is quantitatively correlated with elevated IOP. Also, the individual clinical manifestations that develop as the result of the displacement of the eye are not always directly correlated to the degree and the type of proptosis. For example, there is no clear relationship between the size of a space-occupying lesion in the orbit and the extent and direction of the chorioretinal folds. Congestion and increased tortuosity of conjunctival and retinal veins generally occur with masses located in midorbit, causing stasis through the vortex veins. Contrary to what might be expected, the severity of these changes which is best judged clinically with flourescein angiography, does not correlate directly with the degree of proptosis and/or the level of IOP.

Disk edema and optociliary shunt vessels are other conditions that deserve particular attention in a proptotic eye.[132,265] Optociliary vessels are venous shunts that develop between the retinal vasculature and the juxtapapillary choroidal circulation when the retinal venous return in the central retina vein is blocked. However, the presence of retinochoroidal venous shunt vessels does not necessarily cause a rise in IOP, because they primarily involve the retinal vasculature.[121]

II. Anatomical Relationship between the Vasculature of the Globe and the Orbit

To understand the complex relationship between IOP and the globe's position in the orbit in different types of ocular and adnexal pathology, one must evaluate the anatomy as well as the embryology of the orbital vascular network and its impact on eye pressure (Figs. 1 and 2). The episcleral venous system mainly empties into the anterior ciliary and superior ophthalmic veins, eventually draining into the cavernous sinus.[167] Thus, any disease process that affects this drainage pathway as a result of structural, occlusive, compressive, or destructive physiopathology may alter the IOP.

A. EPISCLERAL VENOUS PRESSURE

According to the Goldmann equation, IOP [P_o] equals episcleral venous pressure [P_v] plus rate of aqueous formation [F] in microliters per minute (μL/mL) divided by facility of outflow [C] in microliters per minute per milliliter of mercury (μL/min/mm Hg). [$P_o = (F/C) + P_v$]. Episcleral venous pressure is usually constant but may be altered by head position or diseases of the orbit, head, or neck, which may hinder the venous return to the heart and/or shunt the arterial blood into the venous system. As a result of the lack of valves in orbital veins, venous blood flow is controlled by pressure gradients. Although acute fluctuations correlate well with changes in episcleral pressure, the correlation between IOP changes and chronic episcleral pressure alterations are more variable. Hence, direct or indirect increased episcleral venous pressure can cause changes in Schlemm's canal, thereby raising IOP. Examples of this physiopathological mechanism that lead to high IOP include nevus flammeus, thyroid ophthalmopathy, space-occupying orbital lesions, and carotid-cavernous or dural AV fistulas. In these situations, blood can sometimes be seen in Schlemm's canal, since the aqueous humor drains from Schlemm's canal into episcleral veins via endothelial-lined outlet aqueducts.

For example, a small comparative study[124] proposed that modified ophthalmodynamometry demonstrated an increase in central retinal vein colla pse-pressure in patients with dilated episcleral veins and, subsequently, an increase in IOP. The authors postulated that modified ophthalmodynamometry has a role in the diagnosis of secondary glaucoma and disease processes associated with dilated episcleral veins.

B. VENOUS VASCULATURE OF THE ORBIT

Most venous drainage from the orbit occurs through the superior and inferior ophthalmic veins, which ultimately feed into the cavernous sinus. In contrast to the arterial system, the venous system has a significant amount of variability in its classification, distribution, arrangement, amount, and trajectory. The tributaries of medial palpebral, superior vortex, lacrimal, muscular, central retinal, anterior ethmoidal, and inferior ophthalmic veins drain into the superior ophthalmic vein.

The angular, nasofrontal, supratrochlear, and supraorbital veins converge posteriorly to form the superior ophthalmic vein, which has three divisions. The first (anterior) segment, formed by the convergence of the angular and supraorbital veins, drains posterolaterally and lies next to the trochlea on the inferomedial side of the superior rectus muscle. The second section of the vein runs underneath the superior rectus muscle within the muscle cone and

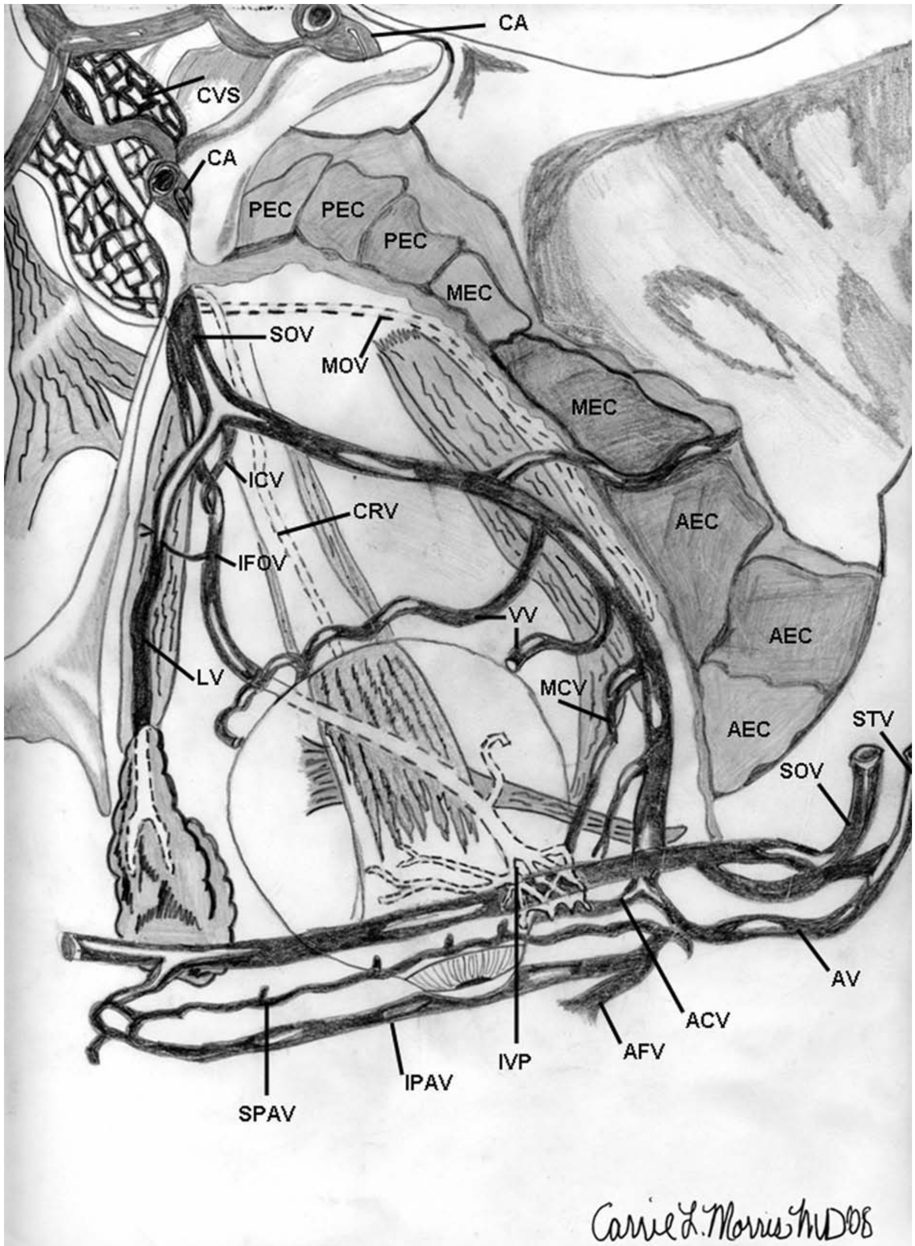

Fig. 1. Axial view of anatomical drawings of orbital vasculature. ACV = anterior collateral vein; AEC = anterior ethmoidal cells; AFV = anterior facial vein; AV = angular vein; CA = carotid artery; CRV = central retinal vein; CVS = cavernous sinus; ICV = intermediate collateral vein; IFOV = inferior ophthalmic vein; IPAV = inferior palpebral vein; IVP = infraorbital venous plexus; LV = lacrimal vein; MCV = medial collateral vein; MEC = middle ethmoidal cell; MOV = medial ophthalmic vein; PEC = posterior ethmoidal cell; PTP = pterygoid plexus; SOV = superior ophthalmic vein; VV = vortex vein.

annulus of Zinn. The vein assumes a lateral trajectory at the midorbit posterior to the globe, receiving outflow from the superior medial and lateral vortex veins and the superior rectus and anterior ethmoidal veins. Notably, the superior ophthalmic vein may reach 5–6 mm in diameter at this location, serving as a reservoir and affecting hemodynamics; however, it narrows toward the orbital apex. The third section of the vein passes through the superior orbital fissure to join the cavernous sinus. However, this pass takes place along the temporal border of the superior rectus muscle *outside* the annulus of Zinn. Some anatomy texts describe anterior, medial, lateral, and posterior collateral vein anastomoses with the superior and inferior ophthalmic vein.[106] Muscular branches of the medial rectus and superior oblique muscle join the superior ophthalmic vein.

A medial ophthalmic vein, emerging off the angular or supraorbital vein posterior to the trochlea,

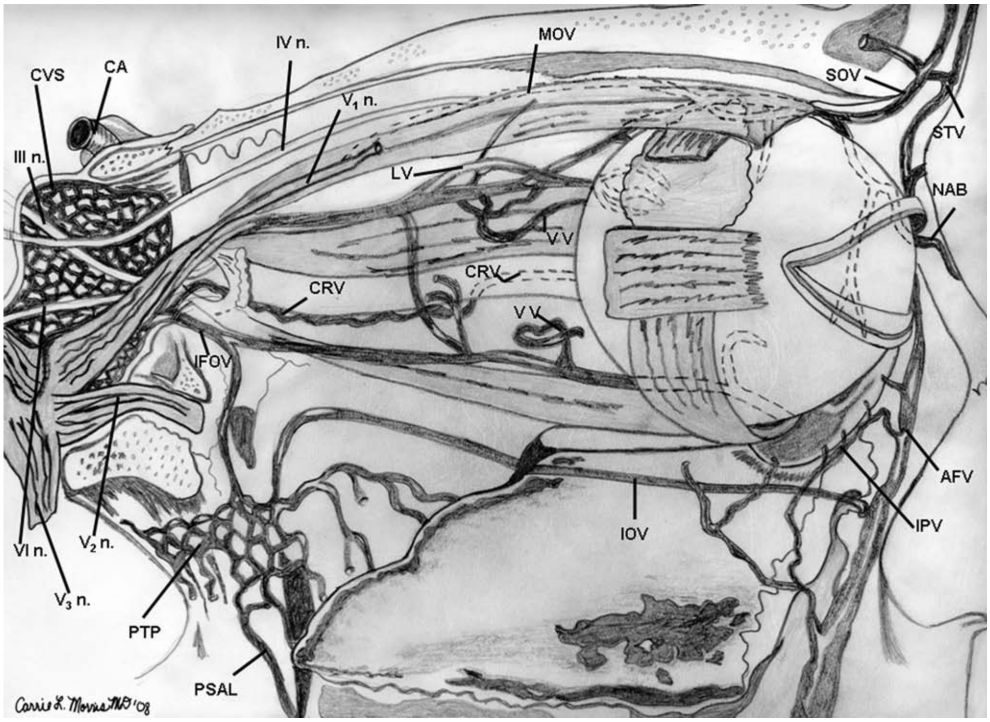

Fig. 2. Sagittal view of anatomical drawings of orbital vasculature. ACV = anterior collateral vein; AFV = anterior facial vein; AV = angular vein; CA = carotid artery; CRV = central retinal vein; CVS = cavernous sinus; IFOV = inferior ophthalmic vein; IOV = infraorbital vein; IPV = inferior palpebral vein; LV = lacrimal vein; MCV = medial collateral vein; MOV = medial ophthalmic vein; NAB = nasal artery branch; PSAL = posterior superior alveolar vein; PTP = pterygoid plexus; SOV = supraorbital vein; STV = superior trochlear vein; VV = vortex vein.

may also be present in some individuals. It passes between the superior oblique and superior rectus muscles, receiving drainage from the medial and superior rectus muscles. The medial ophthalmic vein may travel through the muscle cone to converge with the superior ophthalmic vein before exiting through the superior orbital fissure.[49] Brismar found a medial ophthalmic vein in 40% of the orbital phlebograms that he performed. According to Brismar, it travels along the roof and medial wall, emptying into the cavernous sinus independently.[34]

Occasionally, the *vein ophthalmique moyenne* or middle ophthalmic vein is present, originating from a muscular branch of the medial rectus muscle. It serves as another outlet for the inferior orbit, connecting the inferior ophthalmic vein to the collateral veins. It assumes an extraconal position at the orbital apex before draining into the cavernous sinus.[107] The central retinal vein emerges medially from the optic nerve (sometimes branching in the subdural space), pierces the dura, and converges with the superior ophthalmic vein at the apex.[70,223] However, in some individuals it joins the inferior ophthalmic vein or cavernous sinus directly.[70,223]

A fascial sling composed of septa of the medial, lateral, and superior recti support the superior ophthalmic vein along its posterior extension. The arrangement of the orbital veins in relation to the orbital fascial network has clinical implications. Because the superior ophthalmic vein lies between and superior rectus muscle and the fascial sling, enlargement of the muscle due to Graves disease or myositis may impede the outflow of the vein and lead to orbital congestion. In contrast to the arteries of the orbit, which pass through the orbital septa, the veins travel within the fibroconnective tissue of the septa. The large veins are suspended by fascia, preventing distention and collapse of these valveless vessels due to eye muscle movements or changes in intraorbital pressure.[26] However, this protective mechanism has its limits; enlarged extraocular muscles or intracranial and/or orbital masses may cause venous stasis.

The infraorbital vein is made up of a confluence of an inferiormedial venous plexus comprised of muscular, medial collateral, vortex, and lateral collateral vessels. It originates anteromedially between the globe and inferior rectus muscle, where it receives drainage from the medial and inferior rectus, inferior oblique, inferior vortex veins, lower eyelid, and lacrimal sac. At this point, it is adjoined to the superior ophthalmic vein by the medial collateral vein. It assumes a posterolateral trajectory, intersected by the medial and inferior lateral vortex veins and muscular branches from the inferior and lateral rectus muscles. The plexus of the infraorbital vein is located inferolaterally and travels posteriorly along the border of the inferior rectus muscle. Prior to traversing the inferior orbital fissure, a branch of the inferior ophthalmic vein anastomoses with the superior ophthalmic vein via the lateral collateral vein.[223] A small branch of the inferior orbital vein passes through Muller's orbital muscle via the inferior orbital fissure, connecting to the pterygoid venous plexus. The major portion of the inferior orbital vein runs through the annulus of Zinn and forms a network of blood vessels, where it is suspended by Muller's muscle before emptying into the cavernous sinus. Anteriorly, the inferior ophthalmic vein connects with the angular portion of the facial vein, a tributary of the external jugular vein.

The cavernous sinus is a plexus of venous channels enclosed by dura along the body of the sphenoid bone. It encases the internal carotid artery, the abducens nerve, and the sympathetics destined for the globe and orbit. The other ocular motor nerves (III, IV), and the first and second divisions of the trigeminal nerve lie within an incomplete sheath in the lateral wall of the cavernous sinus. It is interconnected with the ophthalmic veins, sphenopalatine sinus, cerebral veins, middle meningeal veins, and superior and inferior petrosal sinuses. Blood normally passes from the cavernous sinus to the transverse sinus and internal jugular vein via the superior and inferior petrosal sinuses, respectively. Retrograde flow may occur via the ophthalmic veins into the angular vein. The circular sinus, formed by the anterior and poster intercavernous sinuses and the basal plexus, serve as a conduit between the right and left cavernous sinuses. Thus, certain types of diseases may spread from one orbit to the other side. Whereas most drainage occurs posteriorly to the cavernous sinus, the remainder of the venous outflow exits to the pterygoid plexus and facial veins.

Venous outflow occurs medially in the eyelid by the supratrochlear and angular veins. Laterally, the eyelid is drained by a plexus of the inferior orbital vein, which empties into the facial vein. These inferior orbital veins form a plexus, connecting to the angular and facial veins with its tributaries connecting to the inferior palpebral veins. An additional distinctive quality of orbital arteries and veins is that veins do not trail the course of arteries as in other parts of the body; the exceptions are the lacrimal and ethmoidal veins.

C. ARTERIAL VASCULATURE OF THE ORBIT

The internal carotid artery serves as the main arterial source for the orbit. It enters the skull and courses through the petrous portion of the temporal bone in the carotid canal to enter the cavernous sinus and middle cranial fossa above the foramen lacerum. In the great majority of individuals, as the internal carotid artery penetrates the dura at the medial portion of the anterior clinoid process below the optic nerve, the ophthalmic artery arises from the carotid before it becomes intradural at the distal ring around the anterior clinoid. After paralleling the optic nerve through the optic canal, the ophthalmic artery emerges from the optic foramen into the orbit. The external and internal carotid arteries form an interconnecting vascular network including: (i) the superficial temporal artery and frontal artery; (ii) the infraorbital artery and ophthalmic inferior muscular artery; (iii) the angular artery and dorsal nasal artery; (iv) the middle meningeal artery and ophthalmic artery; (v) the anterior deep temporal and lacrimal via the zygomaticotemporal artery; and (vi) the anterior and posterior ethmoidal arteries.

The orbital portion of the ophthalmic artery yields small branches to supply neurovascular structures, including the ciliary ganglion and oculomotor nerves. These small branches are only 40–60 μm in diameter and include branches that originate from the posterior ciliary, muscular, and central retinal arteries, in addition to those originating from the ophthalmic artery.

Likewise, the muscular arteries vary in configuration and size. The lateral muscular artery nourishes the lateral rectus and occasionally supplies the superior rectus, levator superioris, and inferior oblique muscles as well. The medial muscular trunk provides blood flow to the medial and inferior rectus and occasionally to the inferior oblique muscles. A separate trunk directly provides blood to the superior oblique muscle, and another branch nourishes the levator superioris. Some of the muscular branches proceed anteriorly to form the anterior ciliary arteries, penetrating the sclera at the muscle insertion to join the uveal circulation. These branches also furnish blood to the bulbar conjunctiva and superior fornix.

In the majority of individuals, the lacrimal artery emerges near the origin of the central retinal artery. It passes superiorly and posteriorly along the lateral orbital wall, meeting with the accessory ophthalmic artery. Multiple branches supply the lacrimal gland with a terminal branch continuing to divide into superior and inferior palpebral arteries.

The supraorbital artery is extraconal and medial to the superior rectus and levator muscles, exiting at the foramen or notch. This vessel provides blood to the eyebrows and forehead and to the superior oblique, superior rectus, and levator muscles.

Small vessels originating from the cavernous portion of the carotid artery travel through the superior and inferior orbital fissures as well as the sphenoid bone, forming connections with the ophthalmic artery. They feed the periorbita, annulus of Zinn, posterior portions of the extraocular muscles, and fibroadipose tissues of the posterior orbit.[3]

D. LYMPHATIC VASCULATURE OF THE ORBIT AND PERIORBITAL TISSUES

The lymph channels of the eyelid are dispersed according to the anterior and posterior lamella, forming superficial and deep divisions, respectively. Additional divisions occur via drainage of the lateral two-thirds of the upper eyelid, lateral one-third of the lower eyelid, and lateral half of the conjunctiva into the preauricular nodes. The remaining medial portion of the upper and lower eyelids and conjunctiva drain into the submandibular nodes and then into the deep cervical nodes.

Much controversy exists regarding existence of orbital lymphatic channels. No lymph nodes have been identified in human and monkey orbit. The overload of extravasated serum and protein exit via the incomplete intermuscular septum between the intraconal and extraconal space in the posterior orbit. The intraconal excess fluid may flow along connective tissue septal planes to the conjunctiva that then pass into the anterior and deep cervical nodes via adjacent lymphatics.[65] Additional passageways for orbital lymph are via the vascular and neural structures to the cavernous sinus and the cerebrospinal fluid pathway. Gausas's research using human specimens somewhat clarified the proposed mechanism of lymph flow and presence of lymphatics within the orbit. Using immunohistochemistry, lymphatics were recognized in both portions of the lacrimal gland along with middle and outer layers of the dura of the optic nerve.[90] Lymphangiomas are occasionally seen in the orbit, and some consider this as additional evidence for the subsistence of lymphatics; others, however, claim that these tumors originate from primitive mesenchymal cells.[65]

III. Elevation of Intraocular Pressure in Orbital Disease

Intraocular pressure fluctuates in many orbital diseases, but in most instances (with the exception of some trauma cases with injured globes) it increases as the orbital pathology progresses. This elevation of IOP develops by various mechanisms in different disease categories.

The orbit is limited by bony walls and, anteriorly, by the orbital septum and eyelids. Thus, increased orbital volume may lead to increased hydrostatic pressure in the orbit. This is readily apparent during retrobulbar injection of anesthetic; the injection is followed by a palpably increased intraocular pressure. Extreme elevation of intraocular pressure can occur with retrobulbar injection of relatively small volumes of fluid.[199] Increased orbital pressure may have a direct effect on intraocular pressure by increasing hydrostatic pressure around the eye or may have an indirect effect by compression of episcleral and orbital veins, thereby raising venous pressure. Focal mass effects due to tumors or swollen extraocular muscles may directly compress the eye, causing increased IOP. Vascular changes affecting venous pressure, which can occur due to compression of episcleral veins or abnormal arterio-venous flow, may also increase IOP.

A. CONGENITAL ANOMALIES

1. Orbitocraniofacial Deformities

a. Syndromic Craniosynostosis

Crouzon disease is a syndromic craniofacial synostosis that is characterized by midface retrusion, proptosis, maxillary hypoplasia, and cleft palate. Ophthalmic manifestations include corneal exposure and eyelid malfunction secondary to proptosis (in this setting, sometimes called *exorbitism*); optic atrophy; lacrimal drainage system dysfunction; extraocular muscle, iris, and corneal malformations; ectopia lentis; and glaucoma. Unilateral or bilateral edema and/or unusual atrophy patterns of the discs are usually secondary to increased intracranial pressure or due to optic canal malformations rather than increased IOP.[58,61] Elevated IOP may also be secondary to increased intraorbital pressure because of bony deformity and/or abnormal position and insertion of the extraocular muscles.[95,101] Apert and Pfeiffer syndromes are additional syndromic craniosynososes with associated small orbits.

b. Awan Syndrome

Awan syndrome, characterized by low body weight, orbital hypertelorism, and angle-closure glaucoma, is a rare but distinct entity that often becomes symptomatic in elderly women. Orbital hypertelorism in thin women should alert the clinician of the need to measure IOP and conduct a gonioscopic examination even in the absence of optic disc changes.[116]

c. Pierre Robin Syndrome

This entity is characterized by cleft palate, micrognathia, glossoptosis, and respiratory distress due to airway obstruction at the level of the tongue.

Associated ocular findings may include microphthalmia, congenital glaucoma, and high myopia with or without retinal detachments.[114] Newborns with Pierre Robin malformation complex should be screened for other anomalies that might suggest Stickler syndrome, in which about 5% of patients develop glaucoma.

d. Kniest Dysplasia

This disorder is an autosomal dominant spondyloepiphyseal dysplasia that occurs due to abnormal synthesis of collagen type II.[187] Ophthalmic features include retroposition of infraorbital rim due to the flat midface with depressed nasal bridge.[85] Patients with this condition also develop high myopia, oblique astigmatism, retinal detachment, and congenital glaucoma.[178,183]

e. Rubinstein-Taybi Syndrome

Rubinstein-Taybi syndrome is characterized by mental retardation and typical congenital skeletal deformities with characteristically large, broad thumbs and first toes. Associated ocular findings include hypertelorism, bushy brows, epicanthus, and antimongoloid slant of eyelids; hyperopia and juvenile glaucoma have also been described in individuals with this syndrome.[278] The exact mechanism of IOP elevation is unknown, but it has been proposed that it may be due to angle anomalies such as flat-iris insertion into the trabecular meshwork.[217] Corneal and optic nerve changes including megalocornea, colobomatous or cystic optic disc, excavation of papilla, and large cup-to-disc ratios, which can be confused with glaucoma with which it is commonly comorbid.[33] Large, physiologic optic-disc cupping without glaucoma can also be seen in these patients. In patients with comorbid glaucoma, however, goniotomy or trabeculotomy can be successful in controlling the glaucoma.

f. Marshall Syndrome

Marshall syndrome is an autosomal dominant disease characterized by facial dysplasia, high myopia, fluid vitreous, and congenital cataracts.[179] It may be associated with hypertelorism, saddle nose, and subluxated lens. Elevation of IOP may develop secondary to rupture of the lens capsule.[72,113,224] Many patients with Marshall syndrome present with features also common in Stickler syndrome.[234]

g. Weissenbacher-Zweymüller Syndrome

This is an autosomal recessive disorder characterized by dwarfism, metaphyseal widening of the long bones, and vertebral coronal clefts. Its ocular manifestations include hypertelorism, proptosis, refractive errors, and occasionally strabismus.[218] Congenital glaucoma has also been reported with this disorder.[28,236]

h. Waardenburg Syndrome

This autosomal dominant disorder is characterized by hypertelorism, hyperplasia of the medial brows, a prominent, broad root of the nose, sectorial or complete iris heterochromia, congenital deafness, and a white forelock.[73,188,267] Elevation of IOP in this syndrome may be attributed to abnormal uveal pigment distribution; in some cases, it has been reported to coexist with branch retinal vein occlusion.[127,200]

2. Clefting Syndromes

Encephalocele has been reported jointly with micro-ophthalmia and glaucoma.[274]

3. Anophthalmia/microphthalmia

Although microphthalmia is not a primary orbital pathology, it may lead to resultant maldevelopment of the socket. In cases of microphthalmia and anophthalmia, the orbit may initially be normal in size but does not ultimately reach its full adult volume. The mechanisms by which the globe maturation affect the expansion of the orbit are not well understood. Syndromes associated with anophthalmia and increased IOP are summarized in Table 1.

B. ORBIT AND HEAD TRAUMA

1. Orbital Fracture

Temporary elevation of IOP has been reported after orbital bone grafting in orbitozygomatic fractures,[79] but no change in IOP was detected following reduction of orbitozygomatic fractures.[189,211] The reason for the IOP variations in patients who undergo different types of orbital surgical procedures is not clear. Orbital exploration for trauma with or without foreign bodies has also been reported to cause increased IOP, which usually resolves postoperatively.[195]

2. Carotid-cavernous Fistula

Changes in IOP associated with direct carotid-cavernous fistula are regarded to be a complication of orbitocranial trauma (see section III.B.4).

3. Orbital Compartment Syndrome

Orbital compartment syndrome may be due to generalized swelling and congestion of the orbit or

TABLE 1

Anophthalmia Syndromes Associated with High Intraocular Pressure

Syndrome	Description
Hallermann-Streiff-Francois syndrome	A dyscephalic syndrome characterized by mandibulofacial malformations, dental anomalies, microphthalmia, and congenital cataract.[83] Glaucoma is attributed to the angle anomalies and secondary intraocular inflammation. Miotics and acetazolamide have been found to successfully decrease IOP; filtering surgery is discouraged.[110]
Oculo-dento-digital dysplasia syndrome	An autosomal dominant condition characterized by micropthalmia, enamel hypoplasia, hypotrichosis, long narrow nose, syndactyly, and neurological manifestations.[168] Both chronic angle-closure glaucoma due to congenital attachment of the iris to the trabecular meshwork[252] and open-angle glaucoma have been reported in this syndrome.[32]
Oculo-dento-osseous dysplasia syndrome	The autosomal recessive form of the oculo-dento-digital syndrome, characterized by the same skeletal and dental features but with more far-reaching ocular involvement,[260] particularly with juvenile glaucoma.[261]
Osteoporosis-pseudogliom syndrome	The "ocular form" of osteogenesis imperfecta, characterized by myopia, retinal detachment, secondary IOP elevation, optic atrophy, subhyaloid hemorrhage, vitreous hyperplasia, micro- or megalocorneas, and keratoconus.[77] Proptosis and orbital craniosynostosis[59] with secondary IOP elevation have been reported in this syndrome.[18]
Trisomy-13 (Patau syndrome)	Consists of mental retardation, cleft lip and palate, hypotonia, and cardiac and skeletal abnormalities.[210] Ocular features include cataracts, iris and retinal colobomas, persistent hyperplastic primary vitreous, persistent tunica vasculosa lentis, retinal dysplasia, microphthalmia,[169] and congenital glaucoma.[37,141,152,165]
Trisomy-18 (Edward syndrome)	Characterized by mental and developmental retardation, clenched hands, hernias, and craniofacial and cardiac anomalies.[27] Ocular manifestations include microphthalmia, hypoplastic supraorbital ridges, epicanthal folds, hypertelorism, colobomas, cataract, retinal dysplasia, and congenital glaucoma due to anterior rotation of the iris.[92,140,184,259]

focal mass effect. It may be associated with ecchymosis, subconjunctival hemorrhage, proptosis, external ophthalmoplegia, and acute elevation IOP due to increased intraorbital pressure, and some surgical procedures are known to cause orbital compartment syndrome. Retrobulbar hemorrhage may occur after injection of retrobulbar anesthetic, due to inadvertent laceration of orbital vessels. Orbital hemorrhage may also occur following surgery around the orbit particularly with interruption of the anterior or posterior ethmoid arteries which may retract into the orbit. Intraorbital pressure may be relieved immediately by performing a lateral canthotomy,[293] although if bleeding is active this may not solve the problem. In case of orbital emphysema, IOP should be monitored as an indirect guide of intraorbital pressure.[43] In some cases, IOP may normalize after needle aspiration of air.[66] Endoscopic sinus surgery, which can cause orbital hemorrhage and/or emphysema, is the most common cause of OCS.[67] The risk of these ophthalmic complications is even higher when powered dissection is used during endoscopic sinus surgery.[97] Intraocular pressure can normalize after evacuation of orbital hematoma, even if it is performed in the late stages of hematoma.[126]

If the mechanical insult during endoscopic sinus surgery is apical to involve the ophthalmic artery, the IOP may be lowered because of the ciliary body hypoperfusion. Hypotony would be exceptional due to collateral circulation.

Other causes of IOP elevation related to orbital compartment syndrome are listed in Table 2.

4. Traumatic Intramuscular Orbital Hemorrhage

Incidence of proptosis and acute elevation of IOP secondary to bleeding into extraocular muscles or within the muscle cone have been reported in cases of penetrating injuries and following peribulbar and retrobulbar injections. Evacuation of the hematoma that relieves the proptosis brings the IOP back to normal.[93] Posteriorly located large heme cysts and cholesteatomas may also increase the IOP (Fig. 3).

5. Post-traumatic Subgaleal Hematoma

Subgaleal hematoma may extend to the orbit and cause IOP elevation (Fig. 4). Intraocular pressure drops after draining the blood through superotemporal subperiosteal approach.[215]

TABLE 2

Miscellaneous Causes of Intraocular Pressure Elevation in Orbital Compartment Syndrome

Endoscopic sinus surgery[67]
Blunt trauma to the orbit[42,166]
Ischemic compartment syndrome[160]
Intraorbital use of bacitracin[45]
Fluid resuscitation in burn patients[76,253]
Traumatic asphyxia[216]
Maxillofacial surgery[163]
Rhinoplasty[117]
Thrombolytic therapy[52]
Hemorrhage due to retrobulbar injection

C. ORBITAL INFLAMMATION

1. Idiopathic Orbital Inflammation (Orbital Pseudotumor)

Secondary rise in IOP encountered in idiopathic orbital inflammation is explained on the basis of increased episcleral venous pressure. This is a similar process to that seen in other types of orbital inflammatory diseases. As such, the glaucoma encountered in orbital pseudotumor patients is usually the open-angle type.[288] However, acute angle-closure glaucoma has also been reported as the presenting clinical feature in the orbital pseudotumor patients with scleritis subgroup; these patients usually show acute decline of IOP when the inflammation is resolved with oral corticosteroids.[156,294] Evidence obtained with magnetic resonance imaging (MRI) and ultrasound biomicroscopy indicates that the pathophysiology of angle-closure glaucoma in idiopathic orbital inflammation cases is the anterior rotation of the lens–iris diaphragm and the ciliary body secondary to choroidal effusion, resulting from the venous stasis.[21]

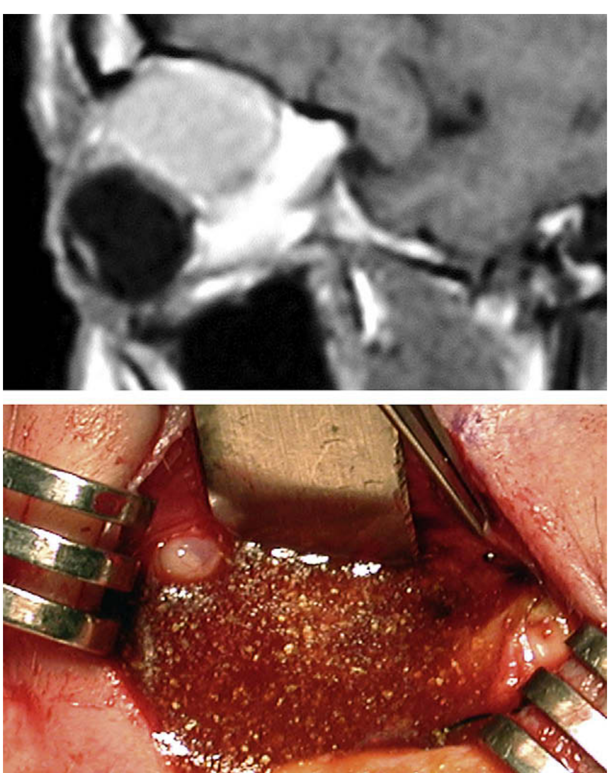

Fig. 3. A large choleostoma of the orbit compressing onto the globe. The lower frame is the intraoperative photograph of the opened choleostoma containing numerous sparkling yellowish cholesterol particles.

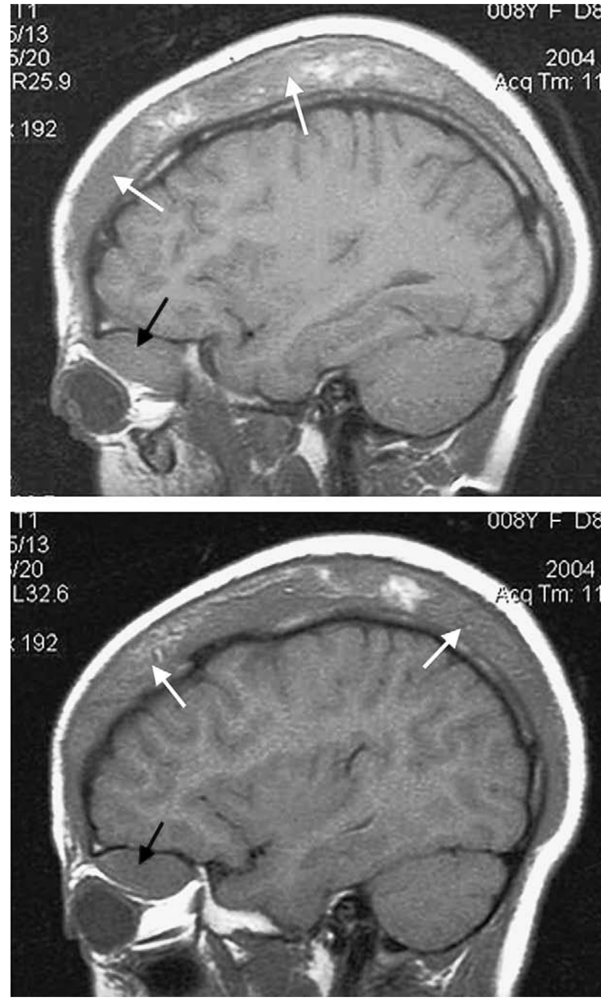

Fig. 4. Right and left T-1 weighted sagittal MRIs depicting extensive subgaleal hemorrhage (*white arrows*) with orbital extension bilaterally (*black arrows*); the intraocular pressure was elevated in the right eye but not in the left.

A case of acute angle-closure glaucoma associated with orbital pseudotumor has also been reported in the context of myelodysplastic syndrome.[243] Ocular myositis with proptosis may also be associated with elevated IOP, as well as retinal detachment and papillitis.[22] There has also been a reported case of superior oblique myositis coupled with elevated IOP in upgaze such cases of myositis in some instances may remain as isolated muscle problems.[249]

2. Thyroid Eye Disease (Graves Disease)

Graves disease is an autoimmune disorder with an incidence of 16 per 100,000 women per year; the incidence for men is far less, around 3 per 100,000.[16] The pathogenesis of this disease is the excess collection of mucopolysaccharides and lymphocytic infiltration in the orbit, primarily in the extraocular muscle tissues, and deposition of glycosaminoglycans and collagen within the ocular and orbital tissues.[57]

Elevated IOP is found more commonly in patients with thyroid eye disease compared with the general population. However, definite clinical glaucomatous manifestations of the optic nerve and visual fields are probably no more common in patients with thyroid eye disease than in the general population. The earliest recognition of glaucoma associated with thyroid disease found in the review of literature was in the *Guy's Hospital Reports* of London in 1897.[30] In 1918, the German ophthalmologist Karl Wessely initially described the connection between the Graves orbitopathy and IOP elevation.[279] Later, Braley contributed further by reporting that many thyroid orbitopathy patients presented with increased IOP in upgaze rather than in primary gaze.[31]

In patients with Graves disease, increased IOP in up-gaze is due to the loss of normal tissue structure of the inferior rectus muscle (the most commonly affected muscle in this pathology) secondary to inflammation and fibrosis.[213,279] The most commonly accepted mechanism of this condition is that, as the antagonist muscles attempt to pull the eye upward, the limited flexibility of the inferior rectus muscle causes compression onto the globe.

Elevated episcleral venous pressure has also been identified in patients with thyroid eye disease.[125] In the chronic phases of Graves orbitopathy, there may be marked orbital congestion of the muscle and adipose tissues within the orbit, which raise the intraorbital pressure to levels that can compress more compliant structures, such as the ophthalmic veins, and lead to elevated episcleral venous pressure and, hence, elevated IOP (Fig. 5). Furthermore, mucopolysaccharide deposits in the aqueous outflow network, which can reduce the outflow facility, may also contribute to IOP increase.[108] Corneal exposure can cause a severe anterior chamber inflammation and peripheral anterior synechiae formation, which can lead to secondary glaucoma.[108]

Although many individuals without thyroid disease also show increased IOP on upgaze, this association is most commonly seen in thyroid orbitopathy patients (Fig. 6).[247] The rates reported for increased IOP on upgaze vary extensively varying, ranging from about 25% to 75%.[8,88,89]

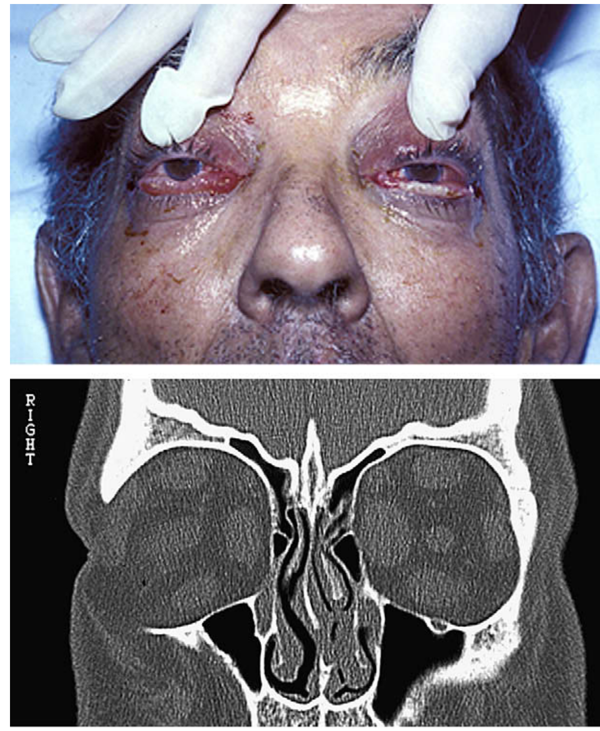

Fig. 5. A patient with hyperthyroidism in "thyroid storm" with marked elevation of intraocular pressure in both eyes due to bilateral "frozen" orbits with markedly enlarged extraocular muscles as seen in the coronal computed tomography (CT). The patient underwent bilateral lateral canthotomies, which lowered the intraocular pressure in the right eye but not in the left.

The association between Graves disease and elevated IOP is well documented.[6,10,55,102,112,177,268] In a prospective study of 104 patients with Graves disease, 22% (23 patients) had ocular hypertension, a rate much higher than the 1.37% prevalence of ocular hypertension in the general Japanese population.[204] The prevalence of clinically symptomatic open-angle glaucoma in patients with Graves disease, on the other hand, is similar to that in the general population.[48,198]

Management of elevated IOP in patients with Graves disease and glaucoma may be influenced by the treatment of the thyroid eye disease. Corticosteroid therapy may control orbital inflammation, which may have a lowering effect on IOP initially. Treatment is not indicated for infiltrative ophthalmopathy with gaze-dependent elevation of IOP. Patients with sutained elevation of IOP in primary gaze, however, may require treatment. First-line treatment for these patients should be topical antiglaucoma medications, particularly aqueous suppressants. In patients with elevated episcleral venous pressure, cholinergic drugs may have minimal effects; aqueous-humor suppression with beta-adrenergic blockers, alpha-adrenergic blockers, and carbonic anhydrase in hibitors may yield better results.

Fig. 6. Attempted upgaze in a patient with thyroid eye disease. This patient had a history of Graves disease with lid retraction, proptosis, and strabismus. She also had preexisting, primary open-angle glaucoma. Her intraocular pressure was elevated on attempted upgaze in the right eye but remained in the normal range on medical therapy in primary gaze. She refused surgery and was, therefore, treated medically; her visual fields and optic nerve appearance remained stable during monitoring of medical therapy for glaucoma.

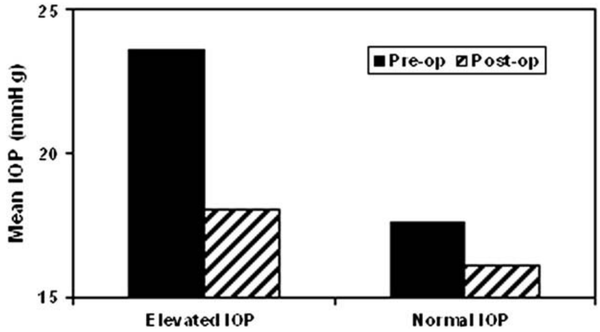

Fig. 7. Mean intraocular pressure for patients with thyroid eye disease and elevated (n = 8) or normal (n = 14) intraocular pressure, before and after orbital decompression surgery. Patients with elevated intraocular pressure (21 mm Hg or higher) pre-operatively showed a significant reduction of intraocular pressure after orbital decompression surgery (mean decrease of 5.6 mm Hg, p = 0.0014). IOP = intraocular pressure. (Data from Dev et al.)[64]

A number of studies have demonstrated a significant reduction in IOP after orbital decompression surgery.[64,129] Not surprisingly, if restriction is playing a role in pressure elevation, relieving the restriction should result in a lowered IOP. Kalmann documented two cases in which surgical recession of the inferior rectus muscle led to reduction in IOP.[129]

A retrospective evaluation of 12 consecutive patients (22 eyes) with thyroid orbitopathy who underwent surgical decompression found significantly lower postoperative IOP compared with preoperative IOP (Fig. 7).[64] When considering surgical treatment, orbital decompression surgery should generally be performed before considering glaucoma operations. After filtration surgery, patients with Graves ophthalmopathy associated with elevated episcleral venous pressure may have an increased risk for choroidal effusion and suprachoroidal hemorrhage.[20]

3. Orbital Infections and Sinusitis Complications (Fig. 8)

Elevation of IOP in childhood orbital cellulitis with sub-periosteal abscess is experienced significantly more often in medically treated patients with antibiotics rather than surgically drained cases.[206] Based on their excellent study, Oxford and McClay proposed a set of criteria for medical management of orbital cellulitis with sub-periosteal abscess including: 1) IOP < 20 mm Hg; 2) normal vision, pupil, funduscopic appereance, and extraocular motility; and 3) proptosis of 5 mm or less with an abscess of 4 mm in width on imaging.[206]

A case of acute angle-closure glaucoma secondary to sneezing in allergic sinusitis has also been reported.[239] Unilateral IOP rise secondary to harsh serial seneezing has also been experienced by the authors (ZAK).

Although a case of bilateral frontoethomoidal mucocele with elevation of IOP in both eyes has been reported, it is uncommon to find IOP variations with sinus mucoceles. In this one case, the IOP was rapidly reduced to normal after surgical treatment.[47]

Necrotizing naso-orbital sinusitis secondary to intranasal cocaine abuse has been found to be associated with proptosis and acute angle-closure glaucoma, most likely secondary to the mydriatic effect of cocaine when it is inhaled.[3,186]

4. Tolosa-Hunt Syndrome

A case of Tolosa-Hunt syndrome with elevation of IOP has been reported that showed a dramatic response to systemic steroids, with improvement of orbital symptoms and ocular hypertension.[120] This occurrence, however, does not appear to be specific to Tolosa-Hunt syndrome; any pathology in the apex causing venous stasis is apt to lead to increased IOP.

5. Allergic Orbital Inflammation

A case of acute orbital inflammation associated with increased IOP has been reported following sub-Tenon's injection of hyaluronidase in anesthetic mixture. It was attributed to a type I hypersensitivity reaction to hyaluronidase.[190]

6. Foreign Body Granuloma

Increased IOP following an oily orbital foreign body has been reported in one patient, with the IOP elevation attributed to the pressure effect on the

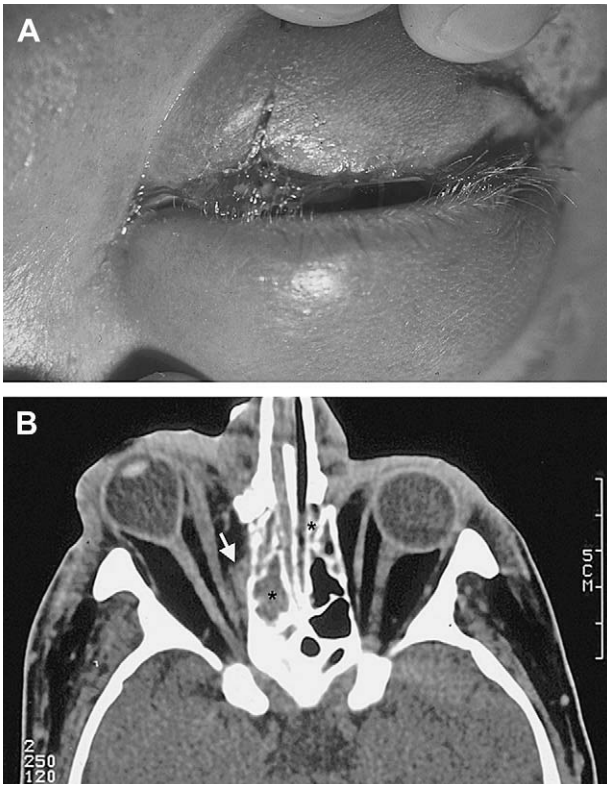

Fig. 8. A: Traumatic orbital cellulitis with severe edema of the eyelids and very tense orbit causing acutely increased intraocular pressure. *B:* Massive anterior displacement and distortion of the globe in orbital cellulitis secondary sinus disease (*asterisks*) and subperiosteal abscess (*arrow*).

globe by the enlarging granuloma.[75] One of the authors (ZAK) of this review has also encountered a similar patient with orbital injury due to the impact of a pneumatic grease-gun who developed a diffuse foreign body reaction and orbital inflammation with increased IOP (Fig. 9).

7. Posterior Scleritis

Patients with severe episcleritis and scleritis may present with proptosis and elevation of IOP.[227] A case of scleritis secondary to graft-versus-host disease presented with sterile orbital abscess and elevation of IOP, which improved after drainage of the abscess.[143]

D. VASCULAR MALFORMATIONS

1. Orbital Varix

Orbital varix is a congenital vascular malformation that may present with intermittent proptosis; in some patients, the proptosis can be brought about with the Valsalva maneuver. Within the distended varix, the blood flow becomes stagnant, and this predisposes the varix to thrombus formation. Elevation of IOP secondary to orbital varix has

Fig. 9. Severe congestion of the episclera with tortuous blood vessels (*arrows*) and proptosis secondary to a grease-gun injury, associated with acute elevation of intraocular pressure. The histology reveals the presence of diffuse inflammatory reaction due to diffuse dissemination of grease foreign bodies (*asterisks*).

been well documented. These patients may develop intermittent or persistent increase in IOP, which may lead to significant optic nerve damage and visual field loss. The mechanism of this secondary IOP elevation is most likely the increased episcleral venous pressure, evidenced by dilated, tortuous episcleral veins and blood in Schlemm's canal on gonioscopy.[171] Medical control of coexisting IOP elevation should be attempted prior to consideration of surgical intervention in any patient with ipsilateral orbital varix.[149] These lesions are known to rupture due to retrobulbar injection, thereby causing orbital hematoma that produces sudden proptosis and an acute rise of IOP.[292]

2. Carotid-cavernous Fistula

a. Direct Carotid-cavernous Fistula

Direct carotid-cavernous fistula develops as a result of an abnormal arterio-venous communication between the internal carotid artery and the cavernous sinus and is associated with a high shunt volume.[203] It is idiopathic in the majority of cases and results from head trauma in fewer patients. In these fistulas, the primary abnormality is the rise of the orbital venous pressure (Fig. 10). Among the ocular manifestations, dilation and tortuosity of the conjunctival and episcleral vessels and chemosis are common, followed by proptosis, rise in IOP, retinal venous dilatation with or without hemorrhages, vascular bruits, and ocular motility problems.[123,142] Ocular motility problems can be twofold. Generalized ophthalmoplegia in this condition is probably due to congested swollen extraocular muscles, which also causes increased IOP at certain gaze positions.[161] Isolated abduction weakness as well as third or fourth cranial nerve palsies may also develop in patients with carotid-cavernous fistula. The abduction weakness is due to fourth nerve palsy occurring either in the cavernous sinus or more posteriorly near the inferior petrosal sinus.

Secondary acute angle-closure glaucoma has also been reported to occur with arteriovenous fistulas.[82] Elevation of IOP in carotid-cavernous fistulas is attributed to a variety of mechanisms including open-angle glaucoma due to elevation of episcleral venous pressure, acute angle-closure glaucoma due to increased intraorbital pressure, and neovascular glaucoma.[38,87,251] Evidence of thrombosis with stabilization of proptosis and IOP indicates spontaneous resolution of cavernous-dural shunts. Most cases are treated with embolization of the fistula. In some patients, however, the proptosis and IOP cannot be controlled with embolization, and a more invasive approach, such as orbital decompression, may be required.[181] If secondary choroidal effusion leads to angle-closure glaucoma, prompt surgical drainage should be considered to prevent permanent peripheral anterior synechiae formation.[256]

Fig. 10. A patient with a direct carotid-cavernous fistula affecting the right orbit with increased intraocular pressure of the right eye unresponsive to medical treatment. The proptotic and congested appearance of the right eye before (*upper frame*) and after (*lower frame*) balloon catheterization of the fistula. The middle frame depicts the MRI appearance of the markedly distended right superior ophthalmic vein.

b. Indirect Carotid-cavernous Fistula

An indirect carotid-cavernous fistula is an abnormal connection between small dural branches of the external and/or internal carotid system and the cavernous sinus. Commonly, this kind of pathology occurs spontaneously and is characterized by a low shunt volume. It may also be associated with elevated IOP but less commonly than its direct counterpart because of the low flow rate.[39,139]

About 1/4 to 1/2 of indirect carotid-cavernous fistulas close spontaneously. Therefore, the patients should be followed conservatively without angiographic studies. If the patient becomes severely symptomatic, then angiography with embolization should be undertaken. Among the resultant conditions for which patients present for treatment are visual loss, diplopia, severe headaches, proptosis leading to corneal exposure, and angle-closure glaucoma. In contrast to direct carotid cavernous fistulas, indirect carotid-cavernous fistulas less commonly require treatment. However, the most widely used method in the treatment of carotid-cavernous fistula is cerebral angiography and coil embolization. Balloon occlusion sparing the carotid may be possible if there is a large enough rent to provide transarterial access (Fig. 11). The success of this treatment depends on interventional neuroradiological access via arterial or transfemoral venous routes; if this fails, transvenous coil occlusion of the superior and inferior ophthalmic veins can be attempted.[13,145]

Some authors propose that intralesional sclerosing therapy be utilized in the low-flow orbital vascular lesions. The resolution of proptosis without further elevation of the IOP has been reported in some cases.[235]

3. Cavernous Sinus Thrombosis

Proptosis and IOP elevation have also been reported in cavernous sinus thrombosis.[118,119] Acute angle-closure glaucoma may also be a rare but hazardous presenting manifestation of cavernous sinus thrombosis.[162] Ophthalmic vein thrombosis with painful proptosis and angle-closure glaucoma has been documented as a consequence of tamoxifen use. Signs and symptoms of cavernous sinus thrombosis may resolve after the discontinuation of this drug.[237]

4. Superior Vena Cava Syndrome

Obstruction of the superior vena cava can cause face and neck swelling, distended neck and upper limb veins, and elevated IOP. Radical neck dissection, especially if bilateral, may also alter normal cranial venous outflow. The clinical course is dependent on the rapidity of the obstruction and on effective collateral development.[225] Superior vena cava syndrome can develop spontaneously, or it may be iatrogenic, most commonly due to superior vena cava ligation.[4,5] Elevation of IOP has been described in conjunction with superior vena cava compression and/or infiltration by mediastinal space occupying lesions such as, lymphoma, and sarcoidosis.[287]

5. Arterio-venous Malformation

An arterio-venous malformation is another vascular lesion that may elevate the IOP either due to its mass effect compressing the globe or due to increased pressure in the episcleral veins.[11,285] A case of severe, asymmetric IOP elevation in a patient with Weill-Marchesani syndrome with an arterio-venous malformation in the area of the straight sinus and vein of Galen has been reported.[63] The patient had conventional clinical signs and symtoms of Weill-Marchesani syndrome including short stature, microspherophakia, lens subluxation, and secondary elevation of IOP. In addition, he had unilateral proptosis and asymmetric elevation of IOP. This case documented an unusual occurrence of IOP elevation secondary to an arterio-venous malformation not located in the cavernous sinus. Another case of an intraocular arterio-venous malformation joining temporal branches of the central retinal artery and vein was documented with normal IOP but visual field loss.[281] Arterio-venous malformation may also affect the ophthalmic artery, causing proptosis and elevated IOP; it should be noted that these malformations may spontaneously rupture and cause sudden loss of vision.[146]

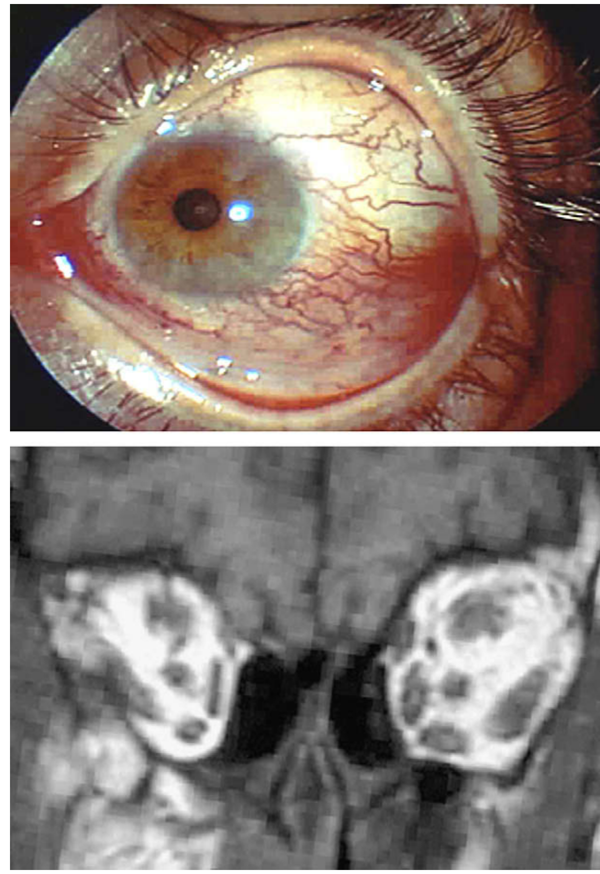

Fig. 11. Congestion of episcleral blood vessels and proptosis secondary to dural cavernous fistula. T1-weighted coronal MRI shows enlargement of extraocular muscles on the left side.

6. Cerebrovascular Accidents

Incidence of IOP elevation following subarachnoidal hemorrhages has been reported in the literature. The mechanism of this occurrence is not clear.[51]

7. Antiphospholipid Syndrome

Antiphospholipid syndrome may masquerade as an orbital ischemic syndrome, presenting with painful bilateral ophthalmoparesis, severe proptosis, increased IOP, and loss of vision.[271]

E. ORBITAL TUMORS AND CYSTS

1. Cavernous Hemangioma

In one study of 66 patients with cavernous hemangioma, the affected eye had an average of 5.5 mm proptosis, and the IOP of the involved eyes was 6 mm Hg higher than the fellow eye.[105] A hemangioma may also present as an orbital apex syndrome.[136]

Other vascular mass lesions may also affect the IOP. A case of hemangioblastoma arising from the medial rectus muscle was reported to be associated with proptosis and elevated IOP on attempted abduction.[56]

Two patients with orbital vascular malformations, ipsilateral facial nevus flammeus, and associated elevated IOP have been documented.[109] In cases like these, localized intraconal vascular lesions may raise the IOP by direct compression or due to secondary hemorrhage, which would cause sudden rise of intraorbital pressure.[268] A cavernous hemangioma developing inside a paranasal sinus with secondary orbital involvement, has also been documented to cause increased IOP and proptosis.[264]

2. Lymphangioma

Orbital lymphangioma is known to cause increased intraorbital pressure particularly when complicated with orbital hemorrhage (Fig. 12). A case of lymphangioma in an 11-year-old boy, associated with elevated IOP secondary to venous obstruction, has been reported in the literature.[25,196] The elevation of IOP dramatically responded to pilocarpine eye drops.

3. Idiopathic Angiolymphoid Proliferations

Kimura disease, which is primarily encountered in Asians, differs from angiolymphoid hyperplasia with eosinophilia by its more common extension to deeper tissues, abundant lymphoid tissue, and fibrosis.[17,36] A case of Kimura disease was reported with reactive proptosis and itching, which became more apparent after drinking alcohol and eating seafood. Increased IOP in this case was shown to be directly related to proptosis; IOP became normal after surgical removal of the tumor.[36]

4. Orbital Osteoma

Bone tumors of the orbit, even rapidly growing bone sarcomas, do not usually influence the IOP. An exceptional case of osteoma of the medial orbital wall, however, has been reported to present with transient loss of vision in abduction, proptosis, as well as markedly elevated IOP, up to 50 mm Hg.[241]

5. Lymphoproliferative Disorders

High IOP has been reported in the course of reactive lymphoid hyperplasia and primary orbital lymphomas of the anterior orbit and lacrimal gland.[202,205] The proposed mechanisms include ocular compression and decreased uveoscleral outflow due to orbital congestion.[170] Elevation of IOP is also well known to occur in primary intraocular lymphoma, mostly due to lymphocytic infiltration of the angle structures and exudative retinal detachment.[15,50,74]

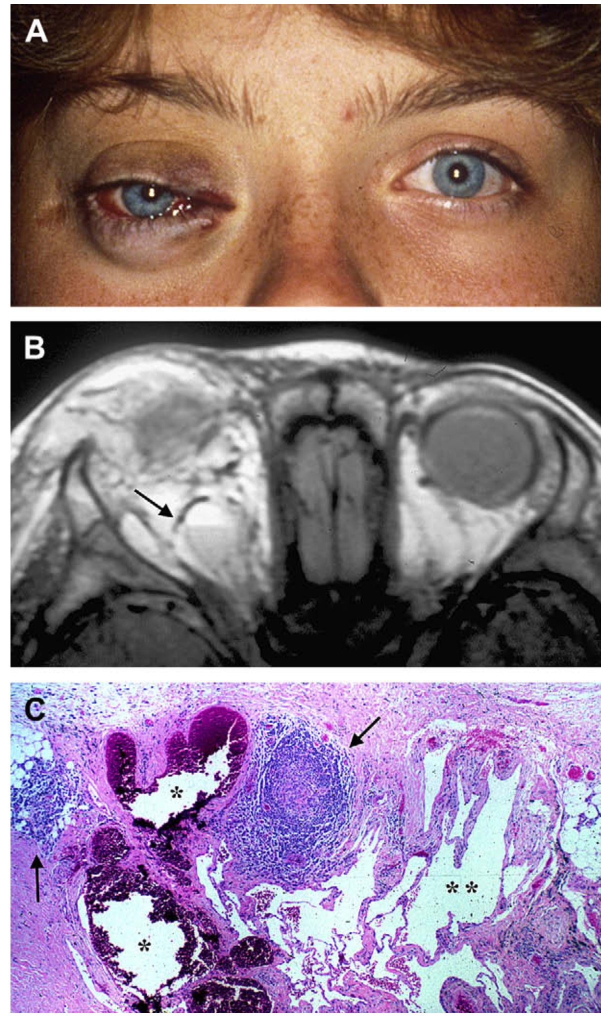

Fig. 12. *A:* A lymphangioma in the right orbit with recent bleeding of the tumor. *B:* T-1 weighted axial MRI depicts the multicystic lesion in the orbit with a horizontal demarcation line of intracystic blood (*arrow*) in a so-called "chocolate cyst." *C:* The light-microscopy reveals intracystic blood (*) on the left side and bloodless cystic spaces (**) of the lesion on the right; the tumor also contains a very active lymphoproliferative component studded with germinal centers (*arrows*).

6. Leukemia

Acute myeloid leukemia may present with bilateral proptosis and acute-angle closure glaucoma or with B-scan ultrasonography showing uveoscleral thickening, particularly of the ciliary body. Orbital imaging revealed bilateral streaking of intraconal fat indicating infiltration of leukemic cells. Temporary lowering of IOP was accomplished with lateral canthotomy and inferior cantholysis. Definitive treatment included systemic chemotherapy and steroids, which improved the vision, proptosis, and the IOP.[262]

7. Plasma Cell Tumors

Plasma cell dyscrasias may present with ocular and orbital involvement.[130] Multiple myeloma has been found with subconjunctival and intraorbital mass lesions, which can cause ophthalmoplegia and increased IOP secondary to progressive infiltration of orbital soft tissues.[230] In multiple myeloma, the IOP may also elevate secondary to increased protein content of the aqueous humor and intraocular inflammation.[174] Intraocular pressure and visual acuity usually improve following regional external beam radiation treatment and systemic chemotherapy. Orbital involvement in multiple myeloma may be the only sign of recurrent systemic disease.[153] Extramedullary plasmacytoma associated with elevated IOP has been reported within the soft tissues of the superior orbit, without bone destruction. In this case, the tumor completely regressed after external beam radiation treatment. The IOP returned to normal, and the patient was disease-free for 4 years.[266]

8. Lacrimal Gland Tumors

A pleomorphic adenoma (benign mixed tumor) arising from the palpebral lobe of the lacrimal gland and compressing onto the globe, without proptosis, was found to be associated with elevated IOP.[290] The conventional presentation of the slowly growing pleomorphic adenoma, however, does not lead to elevated IOP. Elevation of IOP among patients with lacrimal gland tumors is seen in those with rapidly growing malignant lacrimal gland tumors, particularly with adenoid cystic carcinoma.

9. Primary Orbital Melanoma

Primary orbital melanoma in a patient with oculodermal melanocytoma presented as an orbital mass and was associated with secondary open angle glaucoma.[147,257]

10. Invasive (Secondary) Ocular Melanoma

In one study,[164] four out of 15 patients with secondary orbital melanoma had acute attacks of high IOP. A case of invasive melanoma with neovascular glaucoma and orbital cellulitis has also been reported.[2,226]

11. Optic Nerve Meningioma

Meningiomas typically do not lead to space-occupying orbital mass complications because of their slow, longitudinal growth; however, neglected cases may lead to secondary neovascular glaucoma.[229] Sphenoidal ridge meningiomas are also known to develop increased IOP.[277]

12. Optic Nerve Glioma

The optic nerve glioma is another slowly growing orbital tumor that does not characteristically lead to compressive secondary glaucoma, but occasionally glioma patients with other types (congenital, neovascular, or hemorrhagic) of glaucoma have been reported in the literature.[35,115,219]

13. Neurofibromatosis

Proptosis and diplopia in neurofibromatosis type I may be caused by orbital tumors such as optic nerve gliomas, optic nerve sheath meningiomas, and orbital neurofibromas or by orbital bony defects that allow herniation of intracranial tissue into the orbit. Orbital bony defects are usually due to congenital absence of the sphenoid bone or to erosion of the bone by an orbital tumor. In either case, cranial contents may prolapse, and the intracranial pulsation can be transmitted to the orbit, causing pulsatile proptosis and consequently intermittent increase of IOP.[84,233] Orbital and periorbital neurofibromas are the most common soft-tissue tumors in neurofibromatosis type I and may cause proptosis, which tends to be slowly progressive in childhood. Space-occupying schwannomas and meningiomas are much less common in neurofibromatosis type I. If these slow-growing tumors are not treated, they eventually may lead to optic nerve atrophy, optociliary shunt vessels, choroidal folds, and motility disorders. Congenital glaucoma has been reported in neurofibromatosis type I.[44,86,214,232,286] The mechanism of IOP elevation in neurofibromatosis in the absence of an infiltrating orbital mass, such as plexiform neurofibroma, is speculative.[98,154] Glaucoma is not associated with neurofibromatosis type II.

14. Juvenile Xanthogranuloma

High IOP is one of the common, dreaded complications of iris juvenile xanthogranuloma developing secondary to the blockage of the aqueous outflow, but increased IOP may also be experienced in orbital histiocytosis, which is most likely secondary to the intraorbital mass effect.[104,133]

15. Pituitary Adenoma Invading the Orbit

Pituitary adenoma may erode the bony wall of the orbit and cause elevation of the intraocular pressure by globe compression or venous stagnation.[62,134,246]

16. Malignant teratoid medulloepithelioma of the optic nerve

A malignant teratoid medulloepithelioma in the optic nerve of a 6-year-old girl, presented with pain, dilated pupil, hard globe on palpation, and no light perception.[99] The IOP was controlled with paracentesis, miotics, and acetazolamide, then orbital exenteration with removal of the intracanalicular and intracranial portions of the optic nerve.

17. Orbital Metastases (Metastatic Carcinoma)

Breast carcinoma metastatic to the optic nerve, masqueraded initially as a central retinal vein occlusion and later as an optic nerve meningioma.[12] It is most likely that the progressive infiltration of the nerve had enhanced the venous ischemia and resultant neovascular glaucoma.

Another case of bronchoalveolar carcinoma presented with unilateral painless visual loss, retinal detachment, proptosis, and high IOP. The patient was diagnosed clinically as having scleritis, but the symptoms did not improve with steroid therapy. Definitive diagnosis was achieved with histopathological documentation of carcinoma cells in episcleral and orbital tissues.[291] Another case of extensive infiltration of the globe and orbit by metastatic bronchogenic carcinoma that resulted in elevated IOP was also described.[240]

A proptotic patient with a metastatic orbital tumor from a primary focus of small cell lung carcinoma was found to have an IOP of 36 mm Hg.[244] In this patient, the orbital metastasis responded dramatically to chemotherapy. One week after chemotherapy, exophthalmos resolved, and IOP returned to normal.

18. Orbital Cystic Lesions

a. Encephalocele, Meningocele, and Meningoencephalocele

Herniation of brain and/or meningeal tissue into the orbit has been found to be associated with congenital glaucoma in a case of neurofibromatosis type I.[172] Encephalocele has also been reported in association with high IOP, microphthalmia, hydrocephalus, agyria, retinal dysplasia, and cataract. It has also been reported in patients with Peter's anomaly and Walker-Warburg syndrome.[91,221]

b. Arachnoidal Cyst

Ipsilateral elevation of IOP has been reported in a case of temporal lobe arachnoidal cyst invading the orbit posteriorly and creating a mass effect adjacent to the optic nerve. Following intracranial rupture of the arachnoidal cyst, the IOP dropped significantly.[155]

F. OTHER ORBITAL DISORDERS

1. Orbital Amyloidosis

Orbital involvement in primary amyloidosis is uncommon; however, a 71-year-old man with primary amyloidosis developed painless proptosis and restricted extraocular motility. Histopathologic examination confirmed the presence of amyloid deposits in the orbit. The patient had no intraocular amyloidosis, family history of amyloidosis, or systemic disease. Several years later, he developed intracranial amyloidosis and elevation of IOP.[14,272] The mechanisms that may cause IOP elevation in amyloidosis include increased episcleral venous pressure, angle closure, and infiltration of the trabecular meshwork with amyloid material.[197]

2. Mucopolysaccharidoses

a. Hurler Syndrome

The facial features of this syndrome include shallow orbits, hypertelorism, prominent supraorbital ridges, heavy brows, and puffy lids. Corneal clouding takes place early on and is progressive. Associated retinal degeneration includes arteriolar attenuation, decreased foveal light reflex, pigmentary changes, and abnormal electroretinogram. Glaucoma has been reported in many cases with Hurler syndrome; younger patients develop higher IOP measurements than normal population.[138,201,209,245,248] Development of glaucoma in Hurler syndrome is most likely attributable to mucopolysaccharide-containing macrophage entrapment within the trabecular meshwork interfering with aqueous drainage.[245] In a 3-year-old child with Hurler syndrome, IOP was reported to return to normal after bone marrow transplantation.[53]

b. Morquio Syndrome

Progressive pseudoexophthalmos due to shallow orbits has been described in a patient with Morquio disease.[137] High IOP has also been reported in patients with this syndrome.[40] Glaucoma in Morquio disease has been attributed to structural alterations in the trabecular meshwork.[96]

c. Hunter Syndrome

Progressive pseudoexophthalmos as the result of shallow orbits and hypertelorism with glaucoma are the usual features of this type of mucopolysaccharidosis as well.[1,128]

3. Phakomatoses

The phakomatoses (neurocutaneous syndromes) include neurofibromatosis types I and II, tuberous sclerosis, von Hippel-Lindau disease, ataxia telangiectasia, oculodermal melanocytosis (Ota's nevus), and Sturge-Weber, Klippel-Trenaynay-Weber, and Wyburn-Mason syndromes. These hereditary disorders are characterized by the formation of hamartomas in the eye, adnexa, skin, central nervous system, and other organs. Unilateral or bilateral and pulsating or non-pulsating proptosis have been described with almost all phakomatoses.[191] Some of these disorders, such as Sturge-Weber syndrome and neurofibromatosis type I, are commonly associated with glaucoma (Fig. 13). Others, including von Hippel-Lindau syndrome, tuberous sclerosis, and oculodermal melanocytosis, are occasionally associated with increased IOP. Ataxia-telangiectasia (Louis-Bar syndrome) and racemose angioma of the retina (Wyburn-Mason syndrome) are generally not associated with glaucoma, except when the latter presents with orbital vascular lesions.[175,283]

In patients with Sturge-Weber syndrome and glaucoma, medical therapy to lower the IOP is usually ineffective. Young patients with elevated IOP may be treated with goniotomy or trabeculotomy, as a temporizing measure. Filtration surgery may be complicated by choroidal effusions, shallow anterior chamber, and suprachoroidal hemorrhage. These problems may be minimized by two-stage drainage implant surgery, which avoids early postoperative hypotony.

Fig. 13. A patient with Sturge-Weber disease with nevus flammeus primarily presents on the right side (*upper frame*); glaucoma was only detected in the right eye and treated with a drainage valve (*lower frame*).

4. Collagen Tissue Diseases

Ocular and orbital manifestations of collagen tissue diseases with particular emphasis on proptosis and IOP changes are summarized in Table 3.

5. Treatment-related Causes of Elevated Intraocular Pressure

a. Corticosteroids

Elevation of IOP with the chronic use of topical and systemic steroids is a well known compli cation in a variety of orbital disorders including inflammatory, autoimmune, and neoplastic diseases. However, the general discussion of steroid-induced glaucoma is beyond the scope of this review and the reader is referred to related literature.[176,222]

Acute rise of IOP with the use of steroids in treatment of proptosis has also been reported. In one unusual case of iatrogenic Cushing syndrome an emergency orbital decompression was performed.[29] This was necessary because of acute, severe ocular hypertension and significant bilateral exophthalmos with rapid loss of vision. It is believed that steroids alone can produce exophthalmos with elevation of IOP in subjects treated for systemic conditions like Addison disease.[208]

b. Antineoplastic Agents

Chemotherapy-induced glaucoma in relation to proptosis have been described with the use of etoposide, carboplatin, tamoxifen, and other antimetabolites such as immunopotentiation agents.[157,254,275] Painful proptosis and acute angle-closure glaucoma secondary to choroidal detachment have been reported in tamoxifen treated patients. IOP resolves to normal following discontinuation of tamoxifen therapy.[237]

c. Radiotherapy

Elevated IOP has been documented following radiotherapy of many orbital and periorbital tumors.[24,242] Neovascular glaucoma is one of the complication of high-dose irradiation of the eye due to the vascular damage in the anterior segment, which can cause ischemia of the iris, ciliary body, or retina. Anterior segment ischemia leads to the

TABLE 3

Ocular Manifestations of Collagen Diseases

Disease	Ocular Manifestation
Lupus erythematosus	Open-angle glaucoma and angle-closure glaucoma[273,284]
Dermatomyositis	Orbital vasculitis and high IOP[238]
Polymyositis	Orbital vasculitis and high IOP[159,263]
Rheumatoid arthritis	Keratoconjunctivitis sicca, anterior uveitis, episcleritis, scleritis, scleromalacia perforans, sclerosing keratitis with or without marginal thinning of cornea, choroiditis, optic neuritis, choroidal nodules, and secondary retinal detachment[23,220] Orbital lesions including posterior scleritis,[80,276] orbital myositis,[41,78,192,207] orbital pseudotumor,[173] orbital apex syndrome,[151] orbital thrombophlebitis,[283] and orbital lymphoid lesions[193]Elevated IOP in juvenile rheumatoid arthritis and as a steroid induced complication of long term treatment of adult rheumatoid arthritis[81,270,282]
Scleroderma	High IOP[7,46,68,212,250] Lens opacities, vitreous frosting, skin stiffness and telangiectasis of the eyelids, deficient tear secretion, chronic conjunctivitis, keratoconjunctivitis sicca, and superficial retinal hemorrhages[111,280] Exophthalmos[9] and/or enophthalmos[144]
Polyarteritis nodosa	Neovascular glaucoma, iris neovascularization stimulated by release of angiogenic factors from hypoxic retina[182] Optic atrophy, diffuse choroiditis, retinal detachment, iritis, central retinal artery occlusion, and scleral necrosis[194] Orbital vasculitis with exophthalmos[122,148]
Behçet disease*	Anterior or posterior uveitis that may be associated with hypopyon, necrotizing retinitis with retinal and macular edema, disc edema, retinal pigmentary changes, exudative retinal detachment, retinal vaso-occlusive disease, cranial nerve palsies, optic neuropathy, and high IOP secondary to intraocular inflammation[60,71,255,289] Orbital inflammation in the form of myositis.*
Wegener granulomatosis	Necrotizing inflammation and glomerulonephritis[158] Exophthalmos and visual loss if granulomatous disease spreads from sinuses to the orbit[258]
Churg-Strauss syndrome[54,180]	Possible orbital inflammation and exophthalmos[228,231] Neovascular glaucoma secondary to central retinal artery and vein occlusion in rare cases[103,231]

*Data from Al-Malki A, Hussain H, Al-Ma'ani J, Karcioglu ZA. Extraocular myositis in Behçet's syndrome. Presented at the VI International Symposium on Ocular Inflammation, June 2000, Istanbul, Turkey.

release of angiogenic growth factors and new blood vessels that invade the iridocorneal angle and may block the trabecular meshwork causing a dramatic increase of IOP.[19,135]

d. Sinoendoscopy

Sinoendoscopy can lead to a rise in IOP associated with orbit compartment syndrome (see Orbit Compartment Syndrome, section III. B.3).

e. Interventional procedures

Acute angle-closure glaucoma has been reported following embolization of carotid-cavernous and dural-cavernous fistulas.[94,150] Superior ophthalmic vein embolization in the management of carotid-cavernous fistulas may be associated with acute vision loss and/or neovascular glaucoma.[100,185]

IV. Conclusion

Elevated IOP can be seen in conjunction with a variety of orbital disorders and is sometimes the presenting manifestation. Glaucoma may develop with open or narrow angles, and its onset may be insidious or acute. IOP should be measured in patients with any suspected orbital condition; measurements should be taken in different directions of gaze. A gonioscopic examination is also necessary. Because the mechanism of IOP elevation is usually secondary to increased episcleral pressure or ocular compression, the treatment may be different than primary glaucoma and should address the underlying condition.

V. Method of Literature Search

The authors conducted a Medline search using the PubMed database (National Library of Medicine) and EMBASE search using OVID (Walters Kluwer). The literature search had no start date limitation and continued through December 2007. A combination of key words was used, including *intraocular pressure, intraocular tension, glaucoma,* and *glaucomatous* combined with orbital keywords (using the "AND" Boolean) like *proptosis, exophthalmos, orbit, orbital, periorbita,* and *periorbital.* The search was confined to articles written in English and other-language publications with English-language abstracts. Cross-references cited in the bibliography list of the retrieved articles and from the "related articles" link on PubMed were included if found to be relevant.

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Outline

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  1. Orbital amyloidosis
  2. Mucopolysaccharidosis
     - a. Hurler syndrome
     - b. Morquio syndrome
     - c. Hunter syndrome
  3. Phakomatoses
  4. Collagen tissue diseases
  5. Treatment-related causes of elevated intraocular pressure
     - a. Corticosteroids
     - b. Antineoplastic agents
     - c. Radiotherapy
     - d. Sinoendoscopy
     - e. Interventional procedures

IV. Conclusion

V. Method of literature search