Orbital Disease and Surgery

A multidisciplinary approach

COORDINATION

Ana Duarte

João Subtil

João Paulo Farias

Ana Magriço

Orbital Disease and Surgery

A multidisciplinary approach

Orbital Disease and Surgery - A multidisciplinary approach

Editors: Ana Duarte, João Subtil, João Paulo Farias and Ana Magriço

1st Edition - July 2019

ISBN - 978-989-20-9738-1
Legal deposit -

Design and layout: Ricardo Correia
Circulation: 1000 copies

Published by:
Ana Duarte

Orbital Disease and Surgery

A multidisciplinary approach

EDITORS

Ana Duarte
João Subtil
João Paulo Farias
Ana Magriço

SCIENTIFIC SUPPORT

cuf
Academic and Research Medical Center

SPONSORED BY

LABORATOIRES Théa

EDITORS AND AUTHORS

Ana Duarte, MD
Ophthalmology Department, Hospital Cuf Descobertas. Lisbon, Portugal
Ophthalmology Department, Hospital Cuf Torres Vedras. Torres Vedras, Portugal
Orbit and Oculoplastics Unit, Ophthalmology Department, Centro Hospitalar e Universitário de Lisboa Central. Lisbon, Portugal

Ana Magriço, MD
Ophthalmology Department, Hospital Cuf Descobertas. Lisbon, Portugal
Orbit and Oculoplastics Unit, Ophthalmology Department, Centro Hospitalar e Universitário de Lisboa Central. Lisbon, Portugal

João Paulo Farias, MD
Neurosurgery Department, Hospital Cuf Descobertas. Lisbon, Portugal
Neurosurgery Department, Hospital Cuf Torres Vedras. Torres Vedras, Portugal

João Subtil, MD PhD FEB (ORL-HNS)
Rhinology and Cranial Base Surgery Unit, Otorhinolaryngology Department, Hospital Cuf Descobertas. Lisbon, Portugal

AUTHORS

Alcina Toscano, MD
Ophthalmology Department, Hospital Cuf Descobertas. Lisbon, Portugal
Ophthalmology Department, Centro Hospitalar e Universitário de Lisboa Central, Lisbon, Portugal

Benjamin Riesco, MD
Oculoplastics Sector, Hospital del Salvador. Santiago de Chile, Chile
IOPA Clínica Oftalmológica. Santiago de Chile, Chile

Christian Matula, MD PhD
Professor of Neurosurgery
Medical University of Vienna. Vienna, Austria

Diogo Hipólito, MD
Ophthalmology Department, Centro Hospitalar e Universitário de Lisboa Central. Lisbon, Portugal

Guilherme Castela, MD
Orbit and Oculoplastics Unit, Ophthalmology Department, Centro Hospitalar e Universitário de Coimbra. Coimbra, Portugal
Ophthalmology Center, Medical School, University of Coimbra. Coimbra, Portugal

Hae-Ryung Won Kim, MD
Oculoplastics Unit, Hospital Universitario la Princesa. Madrid, Spain
Oculoplastics Unit, Clínica Rementeria. Madrid, Spain

Hugo Pereira, MD
Head and Neck Surgery Department, Hospital Cuf Descobertas. Lisbon, Portugal

João Cabral, MD
Ophthalmology Department, Hospital da Luz. Lisbon, Portugal

Jorge Vasco Costa, MD
Oculoplastics Unit, Ophthalmology Department, Hospital de Braga. Braga, Portugal

Julius Lukas, MD PhD
Professor of Ophtalmology
Medical University of Vienna. Vienna, Austria

Kyle J. Godfrey, MD
Edward S. Harkness Eye Institute, Columbia University Medical Center. New York, USA

Mara Ferreira, MD
Ophthalmology Department, Hospital da Luz. Lisbon, Portugal

Marco Sales-Sanz, MD PhD
Oculoplastics Sector, Hospital Univeristario Ramón y Cajal. Madrid, Spain
Oculoplastics Unit, Clínica Novovisión. Madrid, Spain

Martín Devoto, MD
Clínica Consultores Oftalmológicos. Buenos Aires, Argentina

Michael Kazim, MD
Edward S. Harkness Eye Institute, Columbia University Medical Center. New York, USA

Michelle M. Maeng MD
Edward S. Harkness Eye Institute, Columbia University Medical Center. New York, USA

Nádia Lopes, MD
Oculoplastics Unit, Ophthalmology Department, Centro Hospitalar de Leiria. Leiria, Portugal

Nuno Caçador, MD
Radiology Department, Hospital Cuf Descobertas. Lisbon, Portugal
Radiology Department, Hospital Cuf Infante Santo. Lisbon, Portugal
Radiology Department, Centro Hospitalar e Universitário de Lisboa Central. Lisbon, Portugal

Pedro Oliveira, MD
Head and Neck Surgery Unit, Centro Hospitalar e Universitário de Lisboa Central. Lisbon, Portugal

Renata Rothwell, MD FEBO
Ophthalmology Department, Centro Hospitalar Tâmega e Sousa. Penafiel, Portugal
Opthalmology Department, Centro Hospitalar Vila Nova de Gaia/Espinho. Vila Nova de Gaia, Portugal

Ricardo Figueiredo, MD
Ophthalmology Department, Hospital do Espírito Santo de Évora. Évora, Portugal

Richard Voegels, MD PhD
Otolaryngology Department, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
Ophtalmology and Otorhinolaryngology Department, Universidade de São Paulo, São Paulo, Brazil

Rui Tavares, MD
Ophthalmology Department, Hospital Cuf Viseu. Viseu, Portugal
Centro Cirúrgico de Coimbra. Coimbra, Portugal

Sandra Prazeres, MD
Ophthalmology Department, Hospital Cuf Porto. Porto, Portugal
Orbit and Oculoplastics Unit, Ophthalmology Department, Centro Hospitalar Vila Nova de Gaia/Espinho. Vila Nova de Gaia, Portugal

Sara Filipa Teixeira Ribeiro, MD, PhD, FEBO
Orbit and Oculoplastics Unit, Ophthalmology Department, Hospital de Braga. Braga, Portugal
Ophthalmology Department, Hospital Lusíadas – Porto. Porto, Portugal

Sérgio Cardoso, MD
Radiology Department, Hospital Cuf Descobertas. Lisbon, Portugal
Radiology Department, Hospital Cuf Infante Santo. Lisbon, Portugal

Vera Soares, MD
Otorhinolaryngology Department, Hospital Cuf Viseu. Viseu, Portugal
Centro Cirúrgico de Coimbra. Coimbra, Portugal

BOOK CONTENTS

PREFACE

Orbital disease and its management have been, in recent years, areas in increasing development. Due to a complex anatomy and limited accuracy of its semiology, the orbit was a feared territory for centuries. Its recognition as a distinct field has been naturally emerging, following and integrating the advances of other areas in Medicine. Among all specialties that have always been hand-in-hand with orbital surgeons, two deserve a special reference: Radiology and Pathology. During the last decades, they have opened a new era in the diagnosis of diseases in general, and were the pillars for what we now know and do when treating orbital disease. The emergence of new tools, in the 1970s, such as computed tomography and later magnetic resonance imaging allowed a complete change in orbital disease management. The ability to evaluate and characterize the orbital contents in a non-invasive way, and more recently to make 3D reconstructions and highly detailed vascular analyses became milestones that allowed a better understanding of the normal and abnormal orbit. Also, new insights in Pathology, namely in Surgical Pathology, Cytopathology and the latest discipline, Molecular Pathology, have given a new and improved direction in the prevention, diagnosis and management of orbital diseases. This has also contributed to a growing individualization of treatment, increasingly pathogenesis-based.

Many challenges are still ahead in orbital disease management, however, and facilitated by the refinement of preoperative localization techniques, large steps are being taken in surgical procedures. From the description of the lateral orbitotomy technique in 1888 by Krönlein, to the use of mechanical drills and more recently the endoscopy, piezoelectric technology as well as neuronavigation and intraoperative imaging systems, a long road was already traveled in the search for increased safety margins, effectiveness and better aesthetic results.

The purpose of this book is to bring an update on orbital disease and surgery, in a multidisciplinary perspective. The orbit is bordered by anatomical regions that are usually managed by different medical specialties: superiorly the skull base, medially the ethmoid and nasal cavity, inferiorly the maxillary sinus... It becomes a convergence point of several areas, including Ophthalmology, Maxillofacial Surgery, Neurosurgery, Otorhinolaryngology, and also Internal Medicine, Endocrinology, Oncology. Regardless of the background, those who manage these cases know the importance of an update in techniques commonly used in their specialty but also in neighbor areas.

This book was born from the curiosity and mutual interest of several specialists who already work together on a daily basis. "Learning is by nature, curiosity" said once the Greek philosopher Plato. Let's share this curiosity.

Ana Duarte *João Subtil* *João Paulo Farias* *Ana Magriço*

Section 1

Orbital Anatomy and Evaluation

1. Surgical Anatomy of the Orbit

NEUROSURGERY
João Paulo Farias, MD

Summary

The orbit is a small space with a complex anatomy that encompasses several vital structures such as the optic nerve, muscles, oculomotor nerves, ciliary nerves, vessels and the eye. It has connections with the nasal sinuses, the intracranial space and the pterygo-maxillar fossa and subtemporal region, where lesions can grow from or to the orbit.

Keywords: *Orbit; Anatomy; Surgery*

INTRODUCTION

Orbital surgery is a specific discipline with its own rules and approaches, and the knowledge of its anatomy is of critical importance to surgical success.

For simplification, the following anatomical items will be addressed:

1. Bone walls and orbital rim
2. Muscles, oculomotor nerves and nerve pathways for oculomotor control
3. Surgical spaces and contents
4. Eyelids
5. Superior orbital fissure
6. Optic canal

Anatomical tips for safe and effective surgical approaches will be given along the way *(in italic)*

1 - BONE WALLS AND ORBITAL RIM

The orbit (Fig. 1) is a quadrangular pyramid with its vertex oriented posteriorly, on the anterior part of the optic canal, while its base is located anteriorly. The superior wall comprehends the frontal bone and the inferior aspect of the lesser sphenoid wing. The lateral wall encompasses the zygomatic bone and the greater sphenoid wing. The zygomatic bone also contributes to the inferior wall, which includes the maxillary bone (superior wall of the maxillary sinus), and the orbital process of the palatine bone on its posterior and medial aspect. Finally, the medial wall includes, from anterior to posterior, the frontal process of the maxillary bone, the lacrimal bone, the *lamina papiracea* of the ethmoid and the lateral aspect of the body of the sphenoid bone.

Between the superior and lateral walls, namely between the lesser and greater sphenoid wings, lies the superior orbital fissure (SOF), through which the orbit communicates with the cavernous sinus. The anterior part of the optic canal stands medial to the superior orbital fissure, from which is separated by the optic struct (a bone bridge between the lesser sphenoid wing and the body of the sphenoid bone).

The optic canal runs from the apex of the orbit to the intracranial space below and medial to the anterior clinoid process (Fig. 2); its medial wall is limited by the posterior ethmoidal cells, and its superior wall is in continuum with the orbital roof. *The access to the optic canal and optic nerve inside it can be done either superiorly transcranially by drilling the roof of the optic canal, or medially, transnasally. In the transcranial approach, one can access the whole optic nerve, from the eye to the chiasm.*

Between the lateral and inferior walls (the greater sphenoid wing and the maxillary bone) we find the inferior orbital fissure, which allows communication between the orbit and the pterygomaxillar fossa.

Other relevant anatomical features are (Fig. 1):

- The lacrimal fossa on the anterolateral aspect of the orbital roof
- The lacrimal canal on the anterior part of the medial wall, harboring the lacrimal canal and sac on their way to the nasal fossa
- The anterior and posterior ethmoidal canals in the medial wall
- The infraorbital canal and duct running from posterior to anterior on the inferior wall (with the infraorbital artery, vein and nerve).
- The fossa of the trochlea located on the anteromedial part of the orbital roof, just behind the orbital rim, where the superior oblique tendon pivots from its anterior direction along the superomedial aspect of the orbit to a posterior and lateral direction towards the eye. *If necessary, the trochlea may be desinserted from the bone with a small periosteal elevator. As long as it is not damaged, it will recover its function without the need to reinsert it.*

2 - MUSCLES, OCULOMOTOR NERVES AND NERVE PATHWAYS FOR OCULOMOTOR CONTROL

The eye and eyelids move due to the orbital muscles (Fig. 3). The four rectus muscles and the superior palpebral elevator (SPE) form a common tendon, the tendon of Zinn, inserted in the lateral aspect of the body of the sphenoid, just anterior to the opening of the optic canal. These muscles run anteriorly from the tendon of Zinn and spread over the eye to allow its movements:

- Superior rectus is responsible for elevation and adduction
- Inferior rectus is responsible for depression and adduction
- Lateral rectus is responsible for the abduction
- Medial rectus is responsible for adduction
- SPE goes to the superior eyelid, partially to the skin,

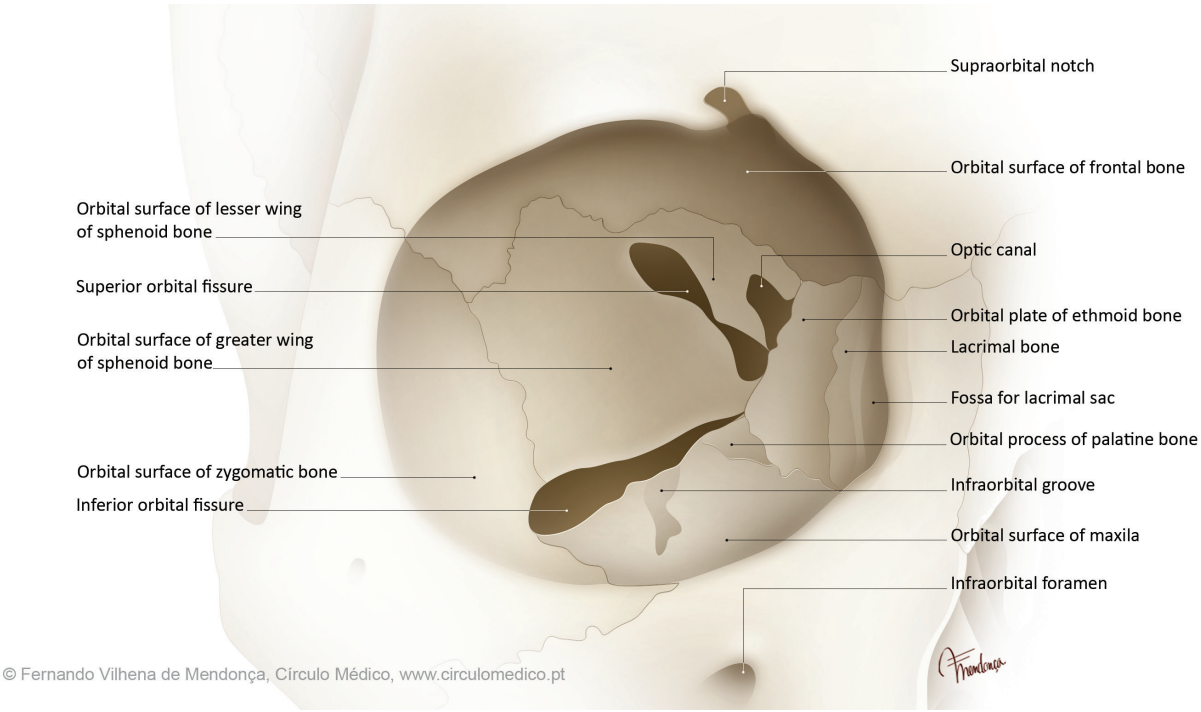


Figure 1. Bone walls of the orbit

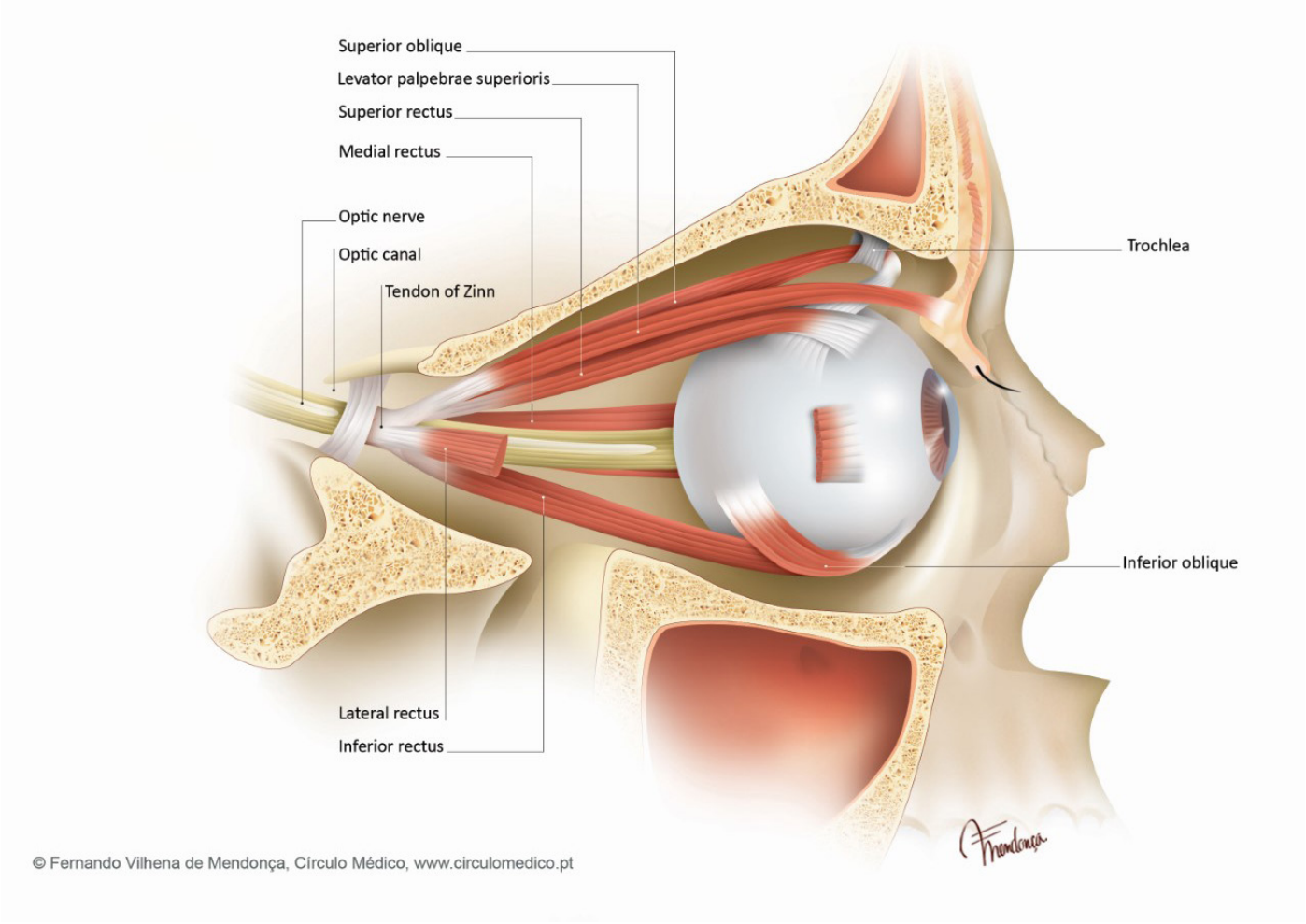


Figure 2. Optic canal

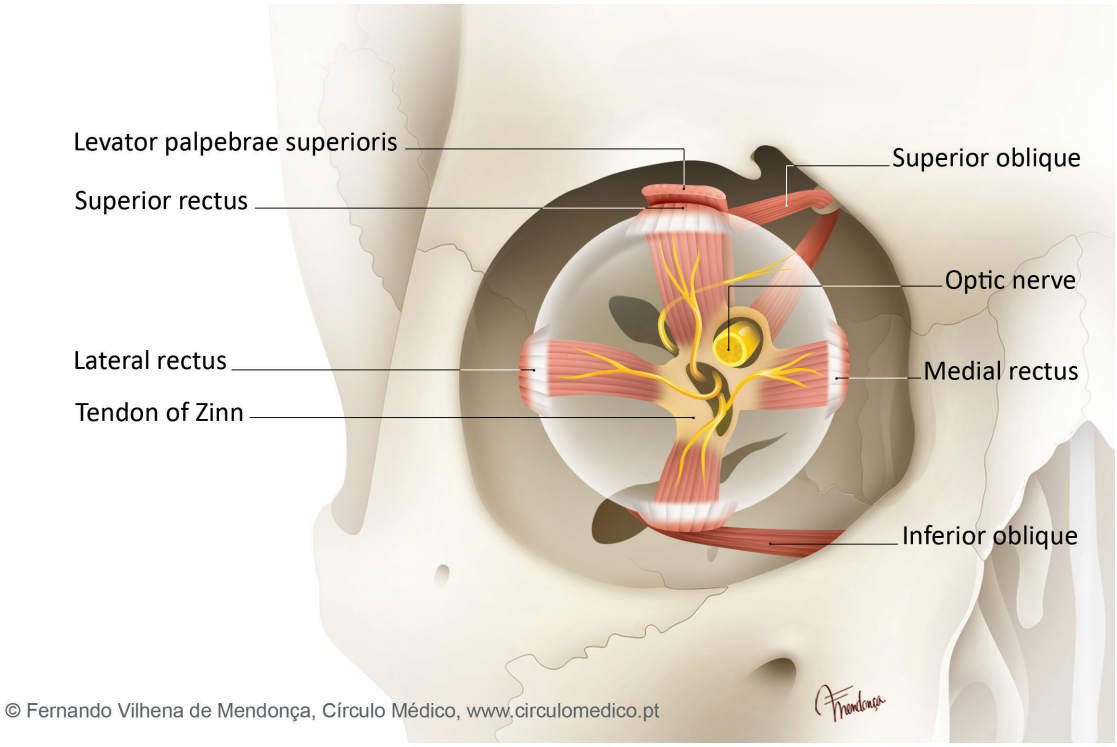


Figure 3. Orbital muscles and cone and tendon of Zinn

partially to the tarsus, and is responsible for the elevation of the superior eyelid

- These five muscles will, with their fascia, create a conus with the apex posteriorly on the tendon of Zinn, and the base anteriorly at the eye, that will divide the orbit into an intraconal and an extraconal space.

The inferior oblique muscle (Fig. 4) comes from the anterior orbital floor and runs in a posterior and lateral direction towards the eye. The superior oblique muscle (Fig. 5) comes from the anterior opening of the optic canal, superior and medial to the insertion of the tendon of Zinn, and runs along the groove between the superior and medial orbital walls until, in the trochlea, its tendon reflects postero-laterally towards the eye.

- Inferior oblique muscle is responsible for elevation and abduction
- Superior oblique muscle is responsible for depression and abduction

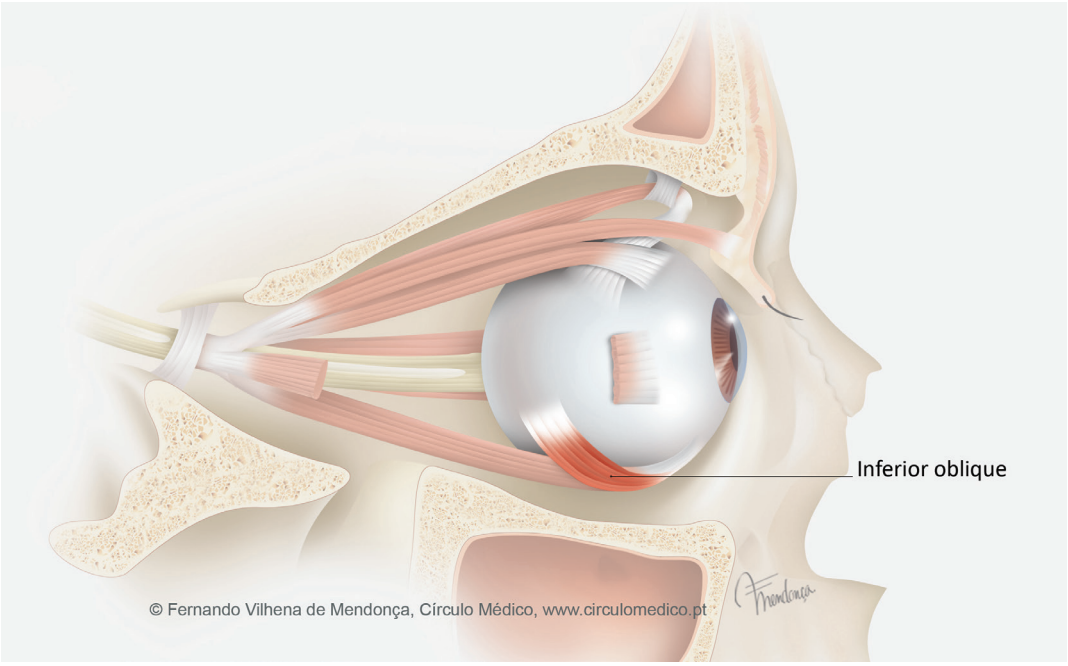


Figure 4. Inferior oblique muscle

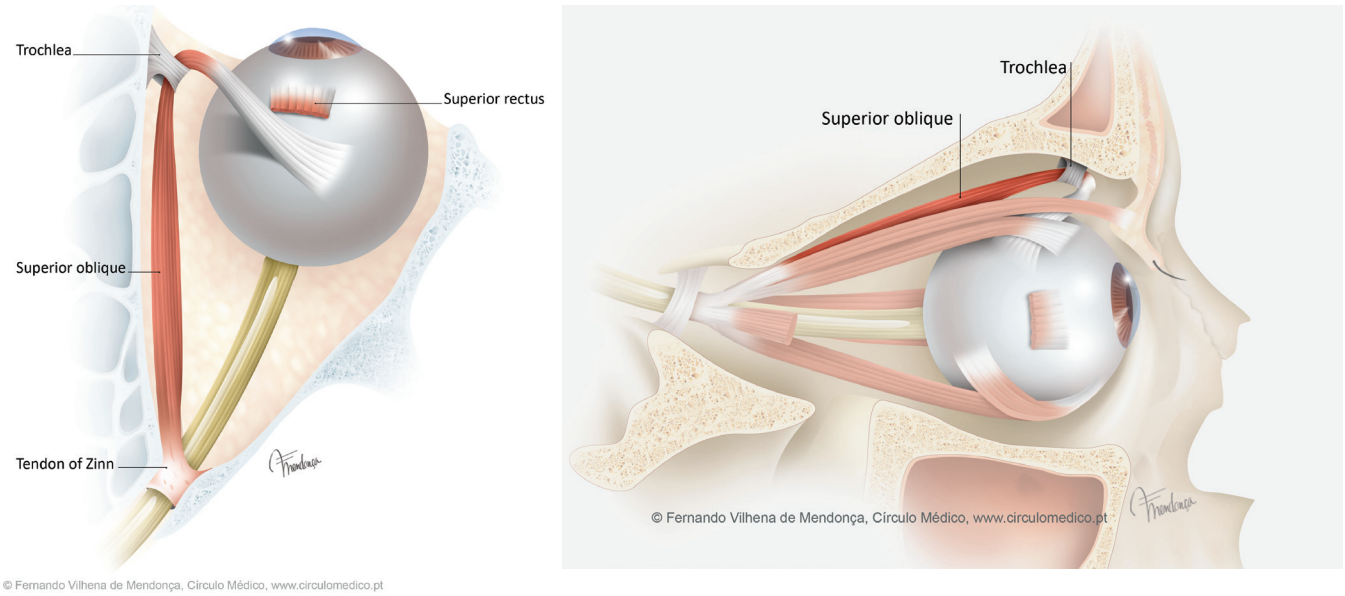


Figure 5. Superior oblique muscle

The IIIrd nerve (oculomotor) is responsible for the motor innervation of the medial, inferior and superior rectus, inferior oblique and SPE muscles, as well as the parassympatic innervation of the eye.
The IVth nerve (trochlear) is responsible for the motor innervation of the superior oblique muscle.
The VIth nerve (abducens) is responsible for the motor innervation of the lateral rectus.

The vertical eye movements are controlled by the tectal plate of the mesencephalon, through the IIIrd and IVth nerves. A lesion or compression of this area (for ex. in pineal region tumors – Fig. 6) will cause Parinaud's syndrome, with bilateral elevation paresis. Other lesions of the posterior part of the mesencephalon (vascular, trauma,...) can cause skew deviation of the eyes (asymmetrical vertical position of the eyes).

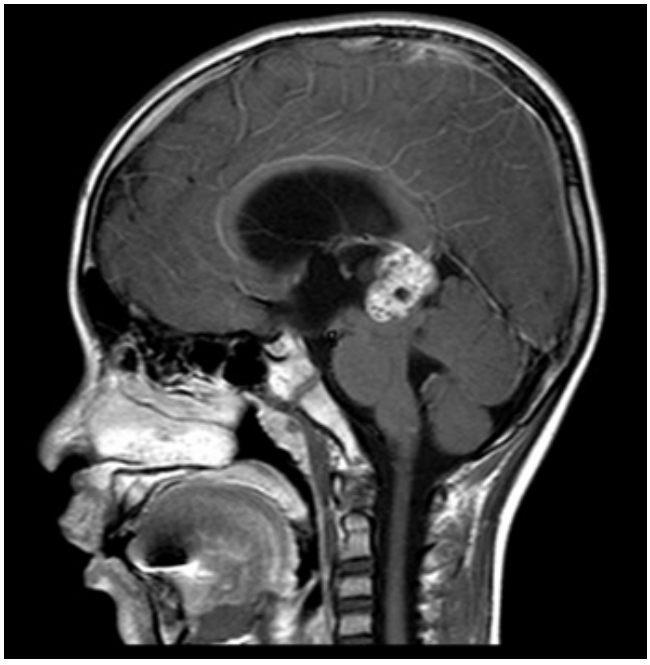


Figure 6. Pineal region tumor

The control of horizontal eye movements is more complex (Fig. 7), and is centered in a pontine nucleus called paramedian pontine reticular formation (PMPRF). This area receives motor information from the contralateral cerebral cortex and sends fibers to the ipsilateral VIth nerve nucleus, in the pons, and to the contralateral IIIrd nerve nucleus in the mesencephalon, through a fiber tract called the medial longitudinal fascicle (MLF), located just paramedially on the IVth ventricle floor. Hence, the left frontal lobe will control eye movements to the right and vice versa. Lesion of the MLF will cause an internuclear ophthalmoplegia (ipsilateral lateral deviation of the eye and contralateral nystagmus), while supranuclear lesions (supranuclear ophthalmoplegia - proximal to PMPRF) will cause a bilateral conjugated eye paresis to the opposite side.

3 - ORBITAL SPACES AND CONTENTS (FIG.S 8 TO 10)

From a surgical point of view, the orbit can be divided into two main spaces: extraconal and intraconal. In the extraconal space we find the lacrimal fossa with the lacrimal gland. The periorbita limits the orbital contents and it is in continuity with the dura of the SOF (postero-laterally) and of the optic nerve (postero-medially). *The subperiosteal space, a virtual space between the periorbita and the bone, can become real in some pathological situations such as hematomas and infections.*
The superior extraconal space is bounded by the orbital roof and the SPE muscle. It contains the frontal and lacrimal divisions of the ophthalmic nerve, and the trochlear nerve crossing form posterolateral (exiting the SOF) to the anteromedial area, until it reaches the superior oblique muscle. *This is importante when entering the intraconal space from above, medial to the SPE and superior rectus muscles (for ex. in optic nerve lesions).*
The intraconal space is bounded by the four rectus muscles and the fascia that unites them. Anteriorly, it is limited by the posterior aspect of the eye. The center contains the optic nerve, the IIIrd, VIth, and ciliary nerves (responsible for the pupillary and accommodation reflexes), the ophthalmic artery (running lateral, then superior and then medial to

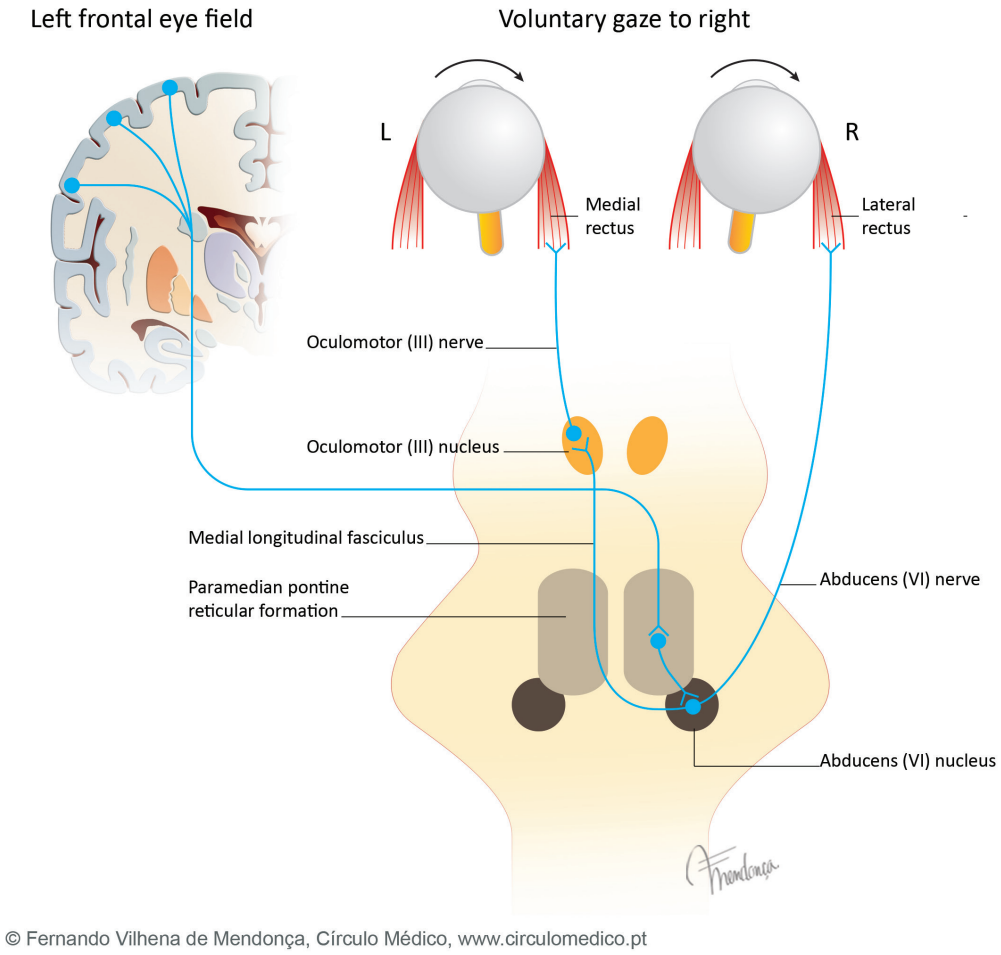


Figure 7. Control of horizontal eye movements

the optic nerve, from posterior to anterior) and ophthalmic veins (the superior and inferior being above and below the optic nerve, respectively). The remaining space is occupied by orbital fat composed of multiple septa - the Korneef septa – through which most vessels and nerves run. *When a mass grows in the intraconal space, the lesion will eventually replace the intraconal fat and cause the septa to form a multilayer, "onion-like" pseudo-capsule surrounding the surface of the lesion. All layers must be crossed to reach the lesion's actual surface. Blunt dissection in the orbit is essential to prevent damaging the nerves and vessels running through these septa.*

The IIIrd nerve enters the intraconal space by the Zinn annulus (a ring in the tendon of Zinn) and immediately divides into two branches: 1) the superior division to the superior palpebral elevator and superior rectus, and 2) the inferior division to the medial and inferior rectus, as well as the inferior oblique muscles. The IIIrd nerve and its divisions run laterally to the optic nerve.

The VIth nerve enters the orbit also through the Zinn annulus, and runs laterally until it reaches the medial part of the lateral rectus muscle.

In addition, there is also the SOF and the optic canal that we will address later.

The orbital rim (Fig. 11), on its superior part, has two grooves, one lateral - supraorbital groove with the supraorbital artery and nerve - and one medial – frontal or supratrochlear, also with the artery and nerve with the same name. These two nerves are responsible for the sensation of the forehead. *Sacrificing them in orbital approaches (mainly lateral or anterior transeptal approaches) will cause numbness of the forehead.*

4 – EYELIDS

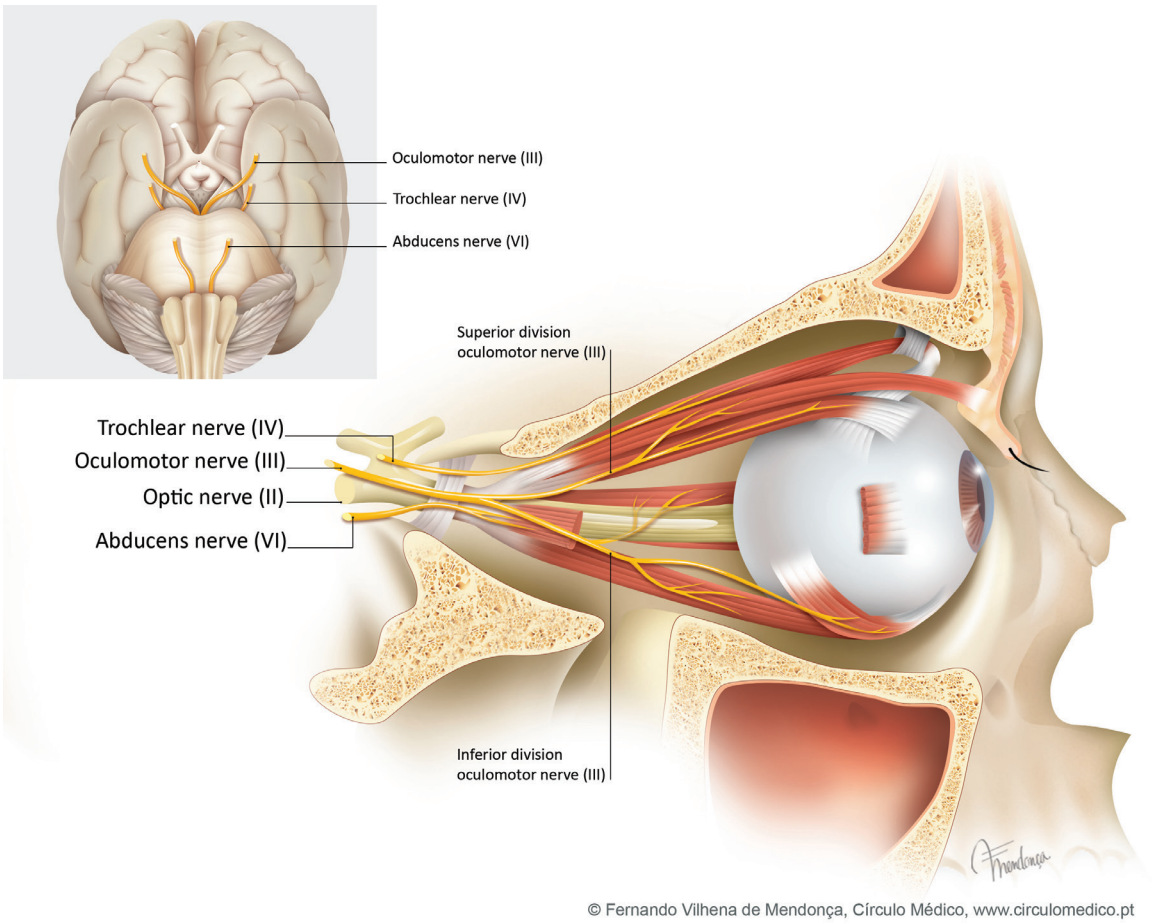
The eyelids (Fig. 12) have seven layers, from the skin to the conjunctiva. The most important layers, from surface to depth, are:

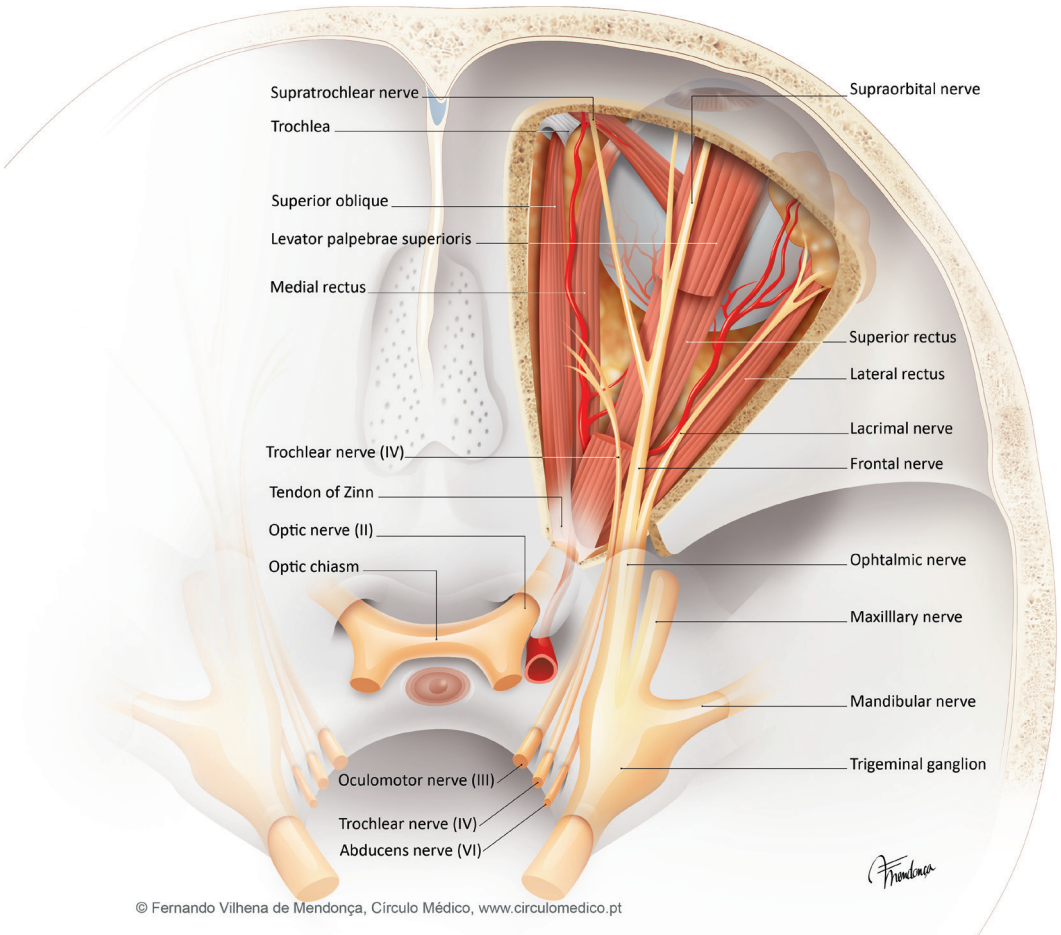
- The orbicularis muscle, responsible for the closure of the eyelids.
- The tarsus (located in the eyelid directly over the eye), which is in continuity with the septum (from the tarsus to the orbital rim) - *the septum is an excellent place to enter the orbit anteriorly.*

Closure of both these structures, after opening them to access the orbit (anterior transeptal or lateral approaches), is essential for the preservation of the eyelid function.

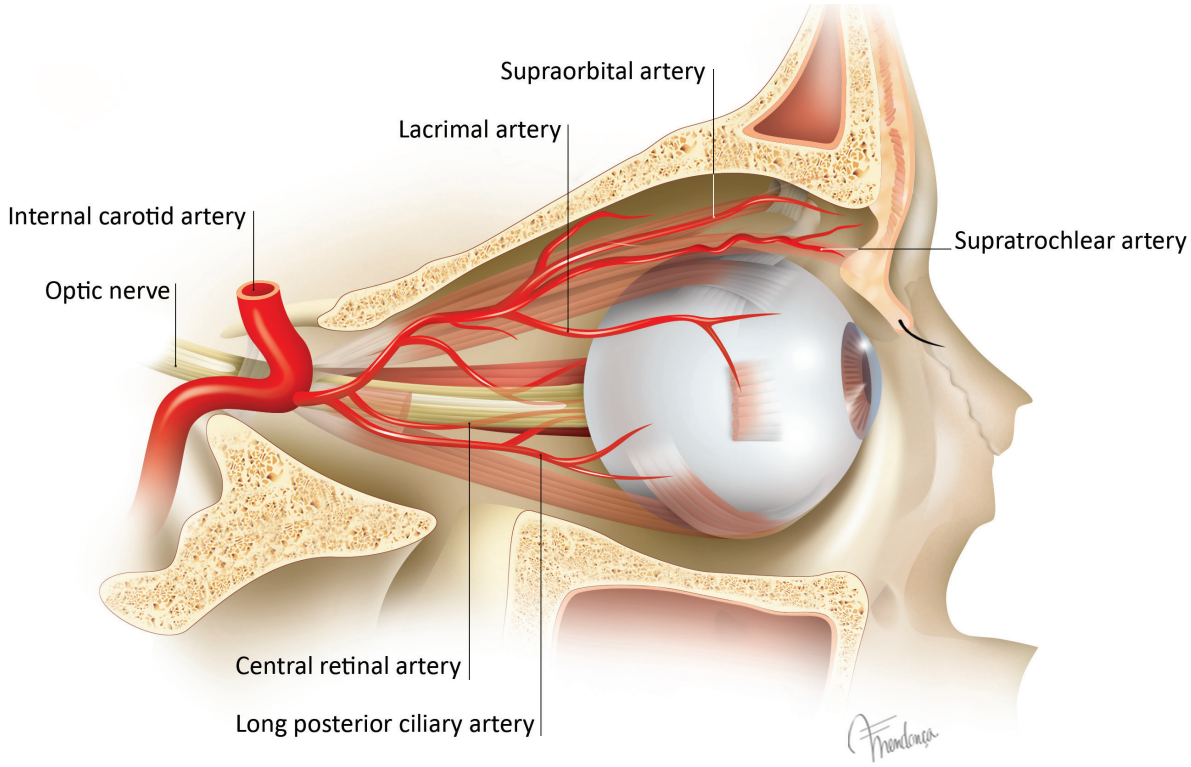
5 - SUPERIOR ORBITAL FISSURE

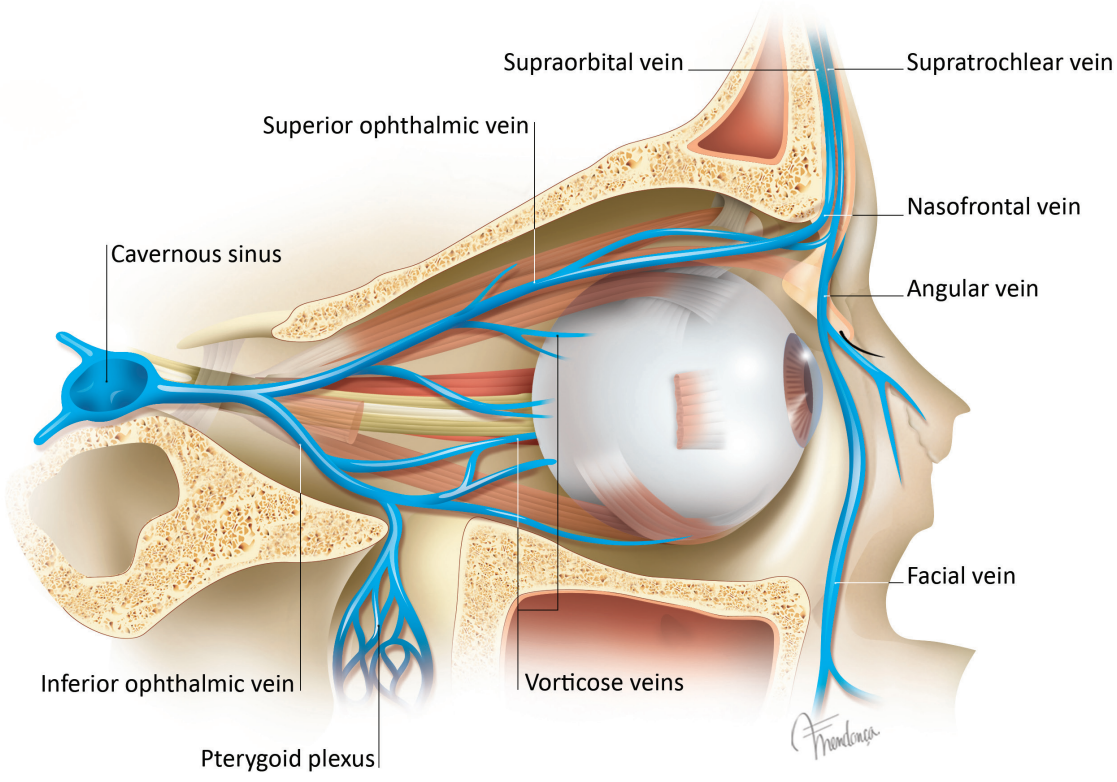
The SOF (Fig. 13) is a fissure between the lesser and greater sphenoid wings that allows communication between the orbit and the intracranial space, namely the cavernous sinus. That is the reason why cavernous sinus diseases (meningiomas, thrombosis, Toulosa-Hunt syndrome) will affect orbital structures and function. It is enveloped by the dura of the cavernous sinus that will be in continuity with the periorbita.





Figures 8 to 10. Orbital contents





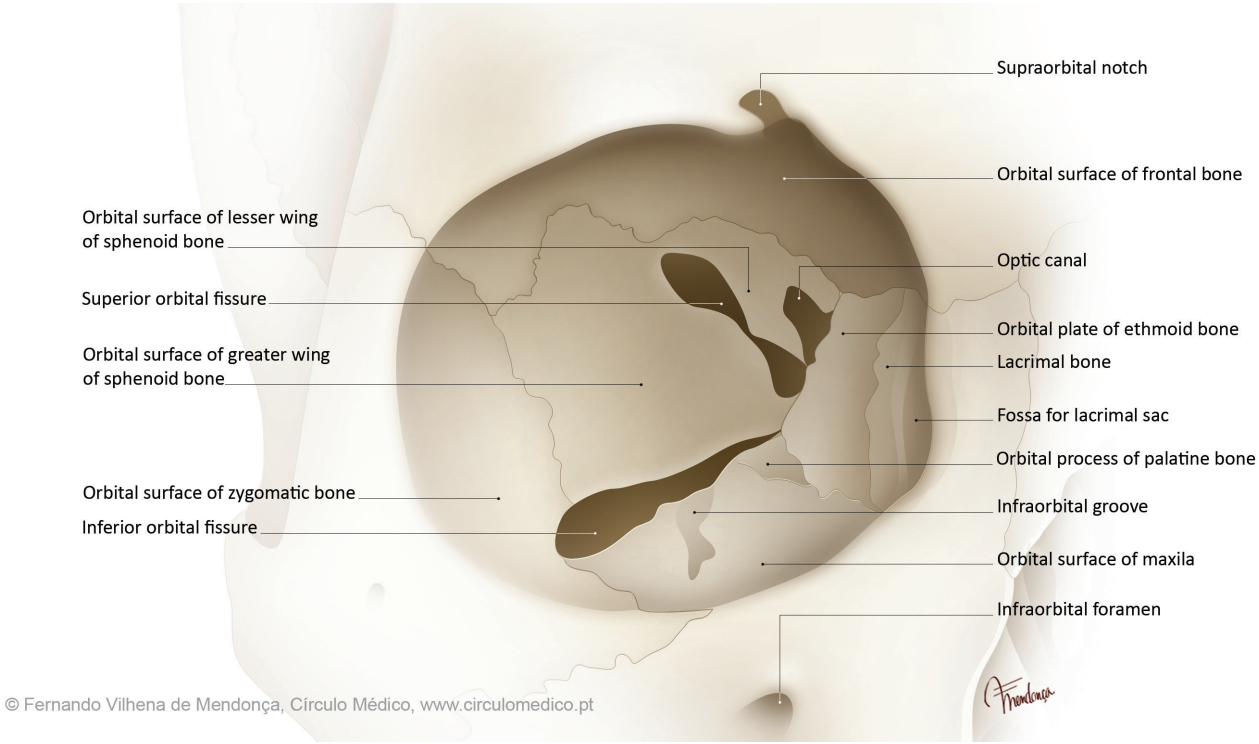


Figure 11. Orbital rim

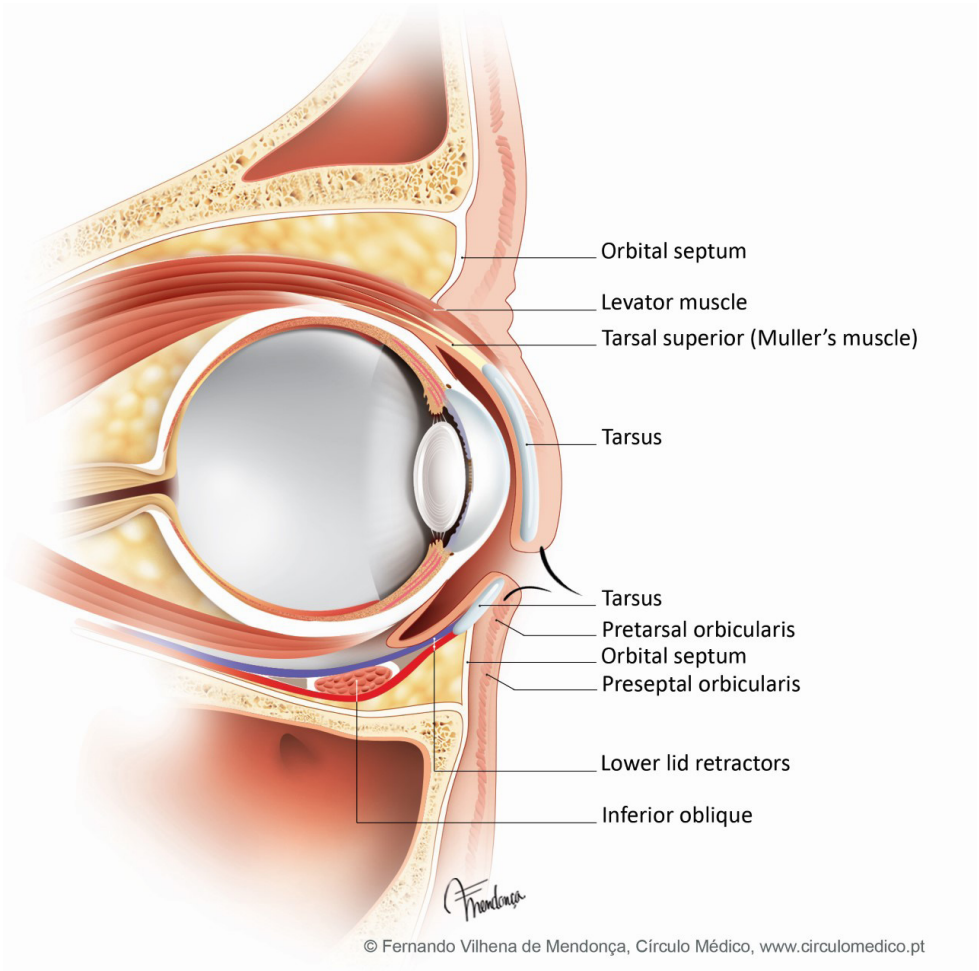


Figure 12. Eyelid anatomy

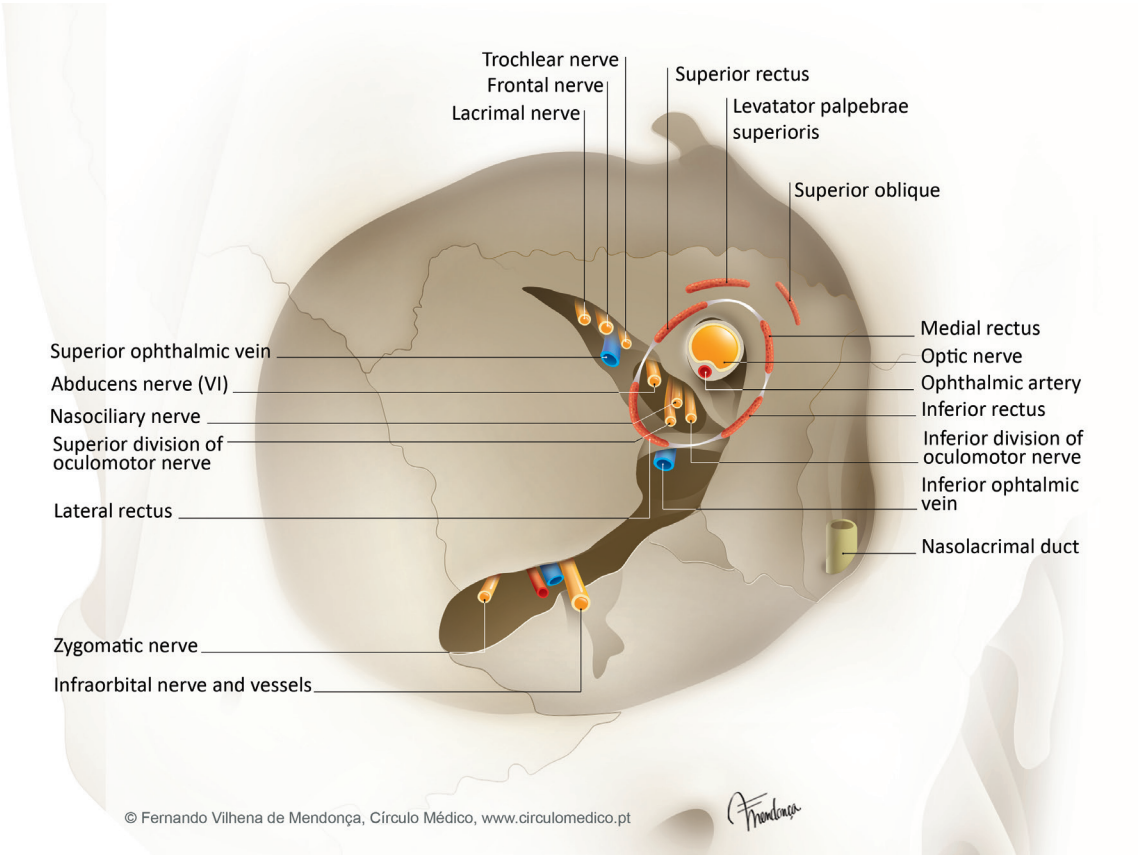


Figure 13. Superior orbital fissure

Important structures extending from the intracranial space to the orbit through the SOF are the IIIrd, IVth, VIth nerves, as well as the three divisions of the ophthalmic nerve (nasociliary, frontal and lacrimal); coming from the orbit to the cavernous sinus, the superior ophthalmic vein.

At the orbital apex, the tendon of Zinn has two rings which allow structures to access the intraconal space directly: the medial one, where the optic nerve and ophthalmic artery cross from the optic canal to the orbit; and the lateral one (Zinn annulus), which is crossed by the IIIrd, VIth and nasociliary nerves entering the orbit. The IVth, frontal and lacrimal nerves enter the orbit outside this annulus, and, as described before, are in the superior extraconal space. Also, the superior and inferior ophthalmic veins exit the orbit outside this annulus, the former towards the cavernous sinus and the latter towards the veins of the pterygomaxillar venous plexuses.

6 - OPTIC CANAL

The optic canal (Fig. 14) runs from the orbital apex towards the intracranial space, where it ends below and medial to the anterior clinoid process. *The optic canal can be accessed from above by drilling its superior wall, which is in continuity with the orbital roof; or medially through a transnasal route. Intracranially, posterior to the bone limits of the optic canal, there is a dural fold that arches over the optic nerve, the falciform ligament. It can be opened to increase the access to the intracranial optic nerve with relative ease.*

When opening the optic canal to reach the optic nerve (ON), the dura/periorbita enveloping the nerve and the falciform ligament need to be incised. The ophthalmic artery that leaves the internal carotid artery on its medial aspect, lateral to the intracranial ON, will immediately enter the optic canal below the ON, from which it is normally separated by a dural layer. From there, the ophthalmic artery will run in a postero-anterior direction until it reaches the orbital apex. After entering the orbit, the ophthalmic artery runs from inferior to superior, lateral to the ON, and then crosses it superiorly in an anterior direction, onward to the superomedial aspect of the orbit. Here, it anastomoses with the angular artery, a terminal branch of the facial artery.

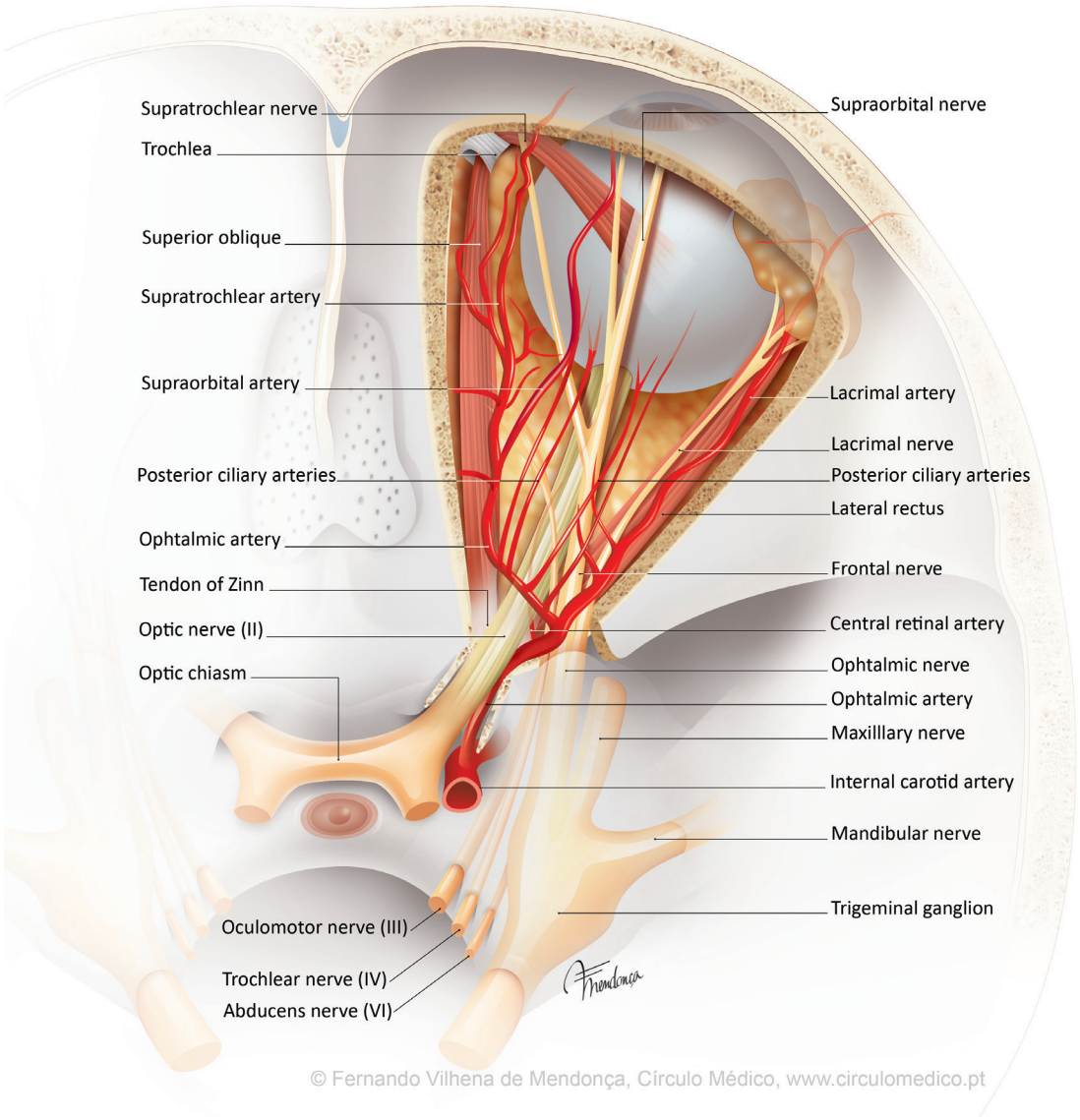


Figure 14 - Optic canal and contents

Ethical Disclosures
Conflicts of Interest: The author has no financial conflicts.

Corresponding author
João Paulo Farias
joao.farias@jmellosaude.pt

REFERENCES

1. McNab AA. Surgical anatomy of the orbit and lacrimal system. In: Manual of orbital and lacrimal surgery. 2nd ed. London: Elsevier Health Sciences; 1998. p. 31-73.
2. Rhoton AL Jr. The orbit. Neurosurgery. 2002;51(4 Suppl): S303-34.

2. Orbital Clinical Evaluation

OPHTHALMOLOGY

Ricardo Figueiredo, MD; Ana Magriço, MD

Summary

Orbital disease has several possible causes. A thorough clinical history and knowledge of both routine ophthalmic examination and specialized orbital examination techniques are required to properly diagnose and treat orbital conditions, many of which can be sight- or even life-threatening.

Keywords: *Diagnostic Techniques, Ophthalmological; Orbital Diseases/diagnosis*

INTRODUCTION

Orbital disease can have inflammatory, vascular or neoplastic causes. The evaluation of a patient with orbital disease should include a complete history and clinical examination, and should also be validated by imaging techniques for a better definition of the characteristics, location, and relations of the abnormal areas with adjacent structures. Only an accurate and thorough clinical evaluation allows a correct diagnosis and treatment of diseases that can be sight- or even life-threatening.

The assessment of a patient with orbital disease includes routine ophthalmic and specialized orbital examination techniques.

1. OPHTHALMIC EXAMINATION

- **Visual acuity.** Central distance and near best corrected visual acuity should be measured to have a baseline that can be used to assess the progression of the disease. Orbital and adnexal conditions may affect visual acuity through optic nerve involvement, keratopathy or visual axis occlusion.
- **Color vision.** An acquired color vision defect may occur due to compressive optic neuropathy, which in some diseases such as thyroid eye disease, may precede the loss of visual acuity.
- **Peripheral vision.** Confrontation fields may identify large field defects due to compressive optic neuropathy.
- **Pupillary exam.** Examination of the pupils provides information regarding optic nerve function. A relative afferent pupillary defect may be the only sign of optic nerve involvement before visual acuity reduction. Anisocoria can occur with any lesion along the pupillary pathways.
- **Anterior segment examination.** The integrity of the corneal and conjunctival epithelium should be checked, as they can be exposed secondarily to proptosis or lid retraction. Chemosis, dilation and tortuosity of the conjunctival vessels can also be caused by orbital disease.
- **Intraocular pressure.** Orbital disease may increase intraocular pressure by several mechanisms. The elevation of episcleral venous pressure in carotid cavernous fistulas or restrictive myopathies (blowout fractures, thyroid eye disease) are two possible causes.
- **Fundus examination.** The papilla should be evaluated for the presence of optociliary shunt vessels (may occur in optic nerve meningioma or glioma cases) and signs of compression or infiltration (edema, pallor). Space-occupying masses can also manifest with chorioretinal folds and dilated and tortuous retinal veins.
- **Ocular motility.** Ocular deviations should be assessed by the cover-uncover and alternate cover tests in all gaze positions. In an incomitant strabismus due to muscle restriction, the largest deviation is usually away from the side of restriction. Eye movements, either monocular (ductions) or binocular (versions and vergences) should also be evaluated (Fig.1). Ductions are usually assessed in six positions of gaze and can be quantified on a scale from -4 (underaction) to +4 (overaction), 0 being considered normal. The forced duction test, in which the conjunctiva is grasped with forceps and the globe is moved to multiple positions, can be used to evaluate any globe restriction, helping to distinguish between a nerve paralysis and a mechanical restriction.

Figure 1. Ocular motility - the 9 diagnostic positions of gaze (photography provided courtesy of António Ramalho, MD).

2. ORBITAL EXAMINATION

An external general examination should be performed before a more detailed periocular assessment, including facial features, symmetry, visible deformities and displacement of the ocular, eyelid and orbital structures.

- **Orbital hyper and hypoplasia and dystopia** should be noted, and the distance between the two medial canthi -**intercanthal distance**- should be measured (mean value 29-32 mm in adults).
- **Periocular tissues** should be evaluated for changes in color, edema, and tenderness, as they may provide clues to the underlying orbital pathology. While edema combined with erythema suggests inflammation, isolated eyelid edema may be caused by allergic, lymphatic or congestive disorders. Bruises can be caused by trauma, but may be also associated with orbital bleeding due to various diseases.
- The assessment of an axial or nonaxial **globe displacement** is one of the most important evaluations in orbital disease. Axial displacement of the globe is determined by measuring the axial distance between the coronal plane of the corneal apex and the plane of the anterior margin of the zygomatic arch (the lateral orbital rim). This is determined through exophthalmometry, for which the Hertel exophthalmometer is the standard method of quantification (Fig.2). Normal values range from 12 to 21 mm in Caucasian adults, with up to 2 mm of asymmetry. Values greater than 21 mm are considered proptosis or exophthalmos (Fig.3) while values lower than 12 mm are described as enophthalmos. Horizontal displacement can be assessed by measuring the distance from a point between the eyebrows to each medial limbus, while vertical displacement is measured as the distance from this horizontal line to the pupil.

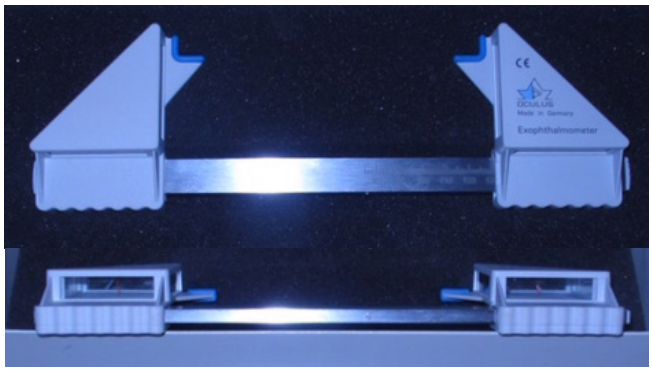


Figure 2. Exophthalmometer

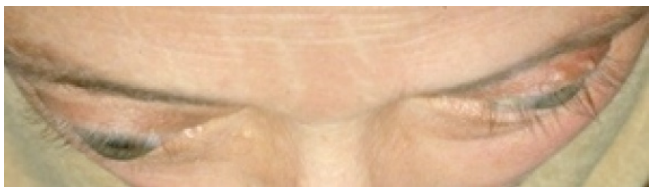


Figure 3. Proptosis of the right eye (photography provided courtesy of António Ramalho, MD).

- **Orbital palpation** is of limited value, but it may reveal discontinuities along the orbital rim and anteriorly located tumors, as well as evaluate for pulsation and retropulsion of the globe, through gentle ballottement of the eye through closed eyelids – a firm lesion located posteriorly to the globe will resist retropulsion. The evaluation of periorbital sensation is also useful for assessing the integrity of the first and second divisions of the trigeminal nerve. **Ocular auscultation** may reveal bruits from carotid cavernous fistulas or arteriovenous malformations.
- **The palpebral fissure height** is the distance between the upper and the lower lid margin (measured with open eyelids), the average being 9-11 mm in adults (Fig.4). The **margin reflex distance** (MRD) is the vertical distance between the corneal light reflex in the center of the pupil and the eyelid margin. MRD1 corresponds to the distance from the light reflex to the upper eyelid while MRD2 corresponds to the distance from the light reflex to the lower eyelid. In primary gaze, the upper lid margin should lie 1-3 mm below the upper limbus (MRD1 of 3-5 mm), and the lower lid margin should be at the level of the lower limbus (MRD2 of around 6 mm). Upper eyelid ptosis is defined as an upper eyelid margin lying low in the primary position (MRD1 ≤3 mm), whereas upper eyelid retraction is an elevation of the upper eyelid margin in the primary position (MRD1 ≥5 mm). No sclera should be visible between the limits of the cornea and the eyelid margin. Lower lid retraction is defined as an MRD2 >6 mm or any inferior scleral show in primary gaze.

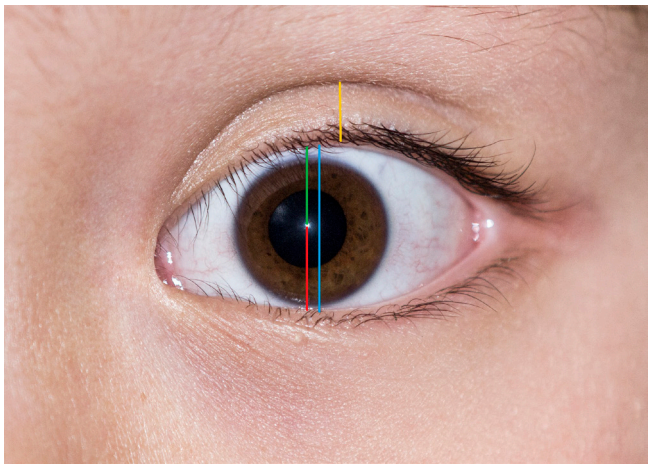


Figure 4. Clinical anatomy. Blue: palpebral fissure height; green: MRD1; red: MRD2; yellow: upper eyelid crease height.

- **Lagophthalmos** corresponds to an incomplete closure of the eyelids, being evaluated by asking the patient to close the eyes –no visible space should exist between the upper and lower eyelid margins.
- **The upper eyelid crease** is an important anatomical landmark created by cutaneous attachments of the aponeurosis of the levator palpebrae superioris (LPS) muscle. In non-Asian individuals, it should lie close to the upper tarsal border, 8-10 mm height, being 1 mm higher in females. Asians may have a lower or no visible crease. Involutional ptosis can result in a high lid crease duo to the disinsertion of the LPS aponeurosis, while floppy eyelid

syndrome can result in a lower or absent eyelid crease.

- **Eyelid laxity** can be evaluated through the lid distraction test (considered positive if the lower lid can be pulled away from the ocular surface by more than 10 mm), through the snap-back test (which evaluates the lower lid response after distraction – from no laxity if it snaps back instantly, to severe laxity if it does not snap back even after blinking), and through eversion and distraction of the upper eyelid.
- **The levator palpebrae superioris function** is assessed after frontalis muscle stabilization, by measuring with a ruler the vertical displacement of the upper eyelid margin from the maximum downgaze to the maximum upgaze, the normal value being 12-16mm. Measurements of less than 10mm are abnormal and suggest myogenic, neurogenic or neuromuscular junction dysfunctions.

3. LACRIMAL EXAMINATION

Lacrimal examination should be performed when evaluating a patient with tearing. Eyelid pathology (ectropion, entropion, floppy eyelid) and eyelash (trichiasis, distichiasis) should also be assessed.

- **Evaluation of the tear lake.** The tear meniscus height can be assessed after instillation of a drop of fluorescein into each conjunctival fornix. The average height is normally around 0.2-0.25mm. Lower values are associated with dry eye, while higher values can indicate reflex tearing and/or deficient tear drainage. The dye disappearance test can also be performed, consisting in checking how much dye is retained after 5 minutes. In a normal case, the dye will clear completely.
- **Evaluation of the anatomic position of the lacrimal puncta.** The lacrimal puncta, the openings of the lacrimal pathways, are located around 5mm from the medial canthus in each eyelid margin, sitting on small elevations called the lacrimal papillae. The lower lacrimal punctum cannot be usually observed without manual eversion of the eyelid margin, as it sits in the tear meniscus. Lacrimal puncta should be evaluated for malposition (eyelid eversion), atresia, stenosis or obstruction (Fig.5).
- **Evaluation of the lacrimal pathway patency** A lacrimal cannula or a Bowman probe can be used. The lid should be stabilized with a finger while the probe is place vertically in the punctum for 1-2mm. The eyelid is then pulled temporally, directing the probed toward the lacrimal sac. Care should be taken if the eyelid moves while probing, as a false passageway can be created – the eyelid should be pulled temporally again and the probe redirected. A hard stop should be felt (contact of the probe against the lacrimal bone). If a soft tissue obstruction is present, a soft stop is noticed. **Lacrimal irrigation** using saline or water should then be performed using a lacrimal cannula. Fluid should flow easily into the nasal cavity without any reflux. Reflux, if present, suggests resistance in the nasolacrimal drainage system – either partial or complete obstruction. If the patient cannot taste the fluid in the throat, occlusion of the opposite punctum or increased pressure in the syringe can be performed, which may help to differentiate a partial from a complete obstruction.

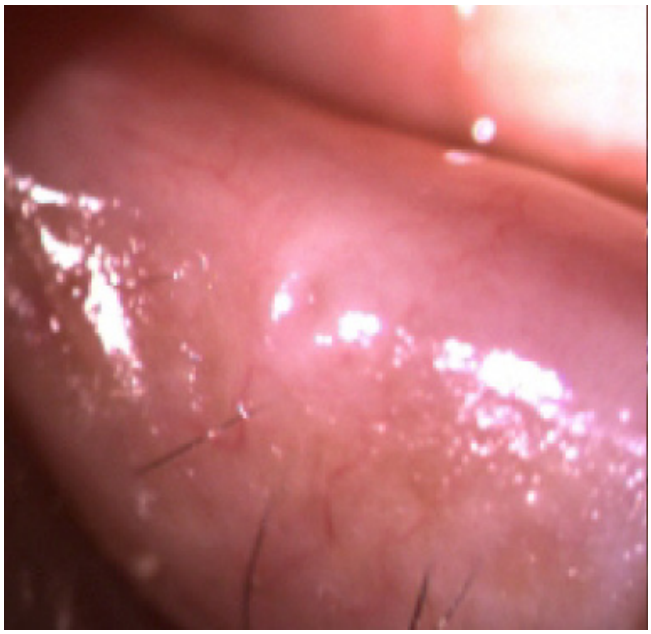


Figure 5. Lower lacrimal punctum stenosis (photography provided courtesy of António Ramalho, MD).

Photographic documentation is a very important aid in the diagnosis and follow-up of orbital disease. A frontal, lateral and inferior view should be taken sequentially at the first visit and all follow-ups.
On some occasions, **nasal examination** or even a **neurological** and **systemic evaluation** is needed to aid the diagnosis.

Conclusion

When evaluating patients with suspected orbital disease, a systematic approach should be performed, including a complete history and physical examination, both ocular and orbital, that can be complemented with laboratory and imaging exams. It is important to keep in mind that, due to the close relationship between orbital structures, different conditions may exhibit similar symptoms and signs.

Ethical Disclosures

Conflicts of Interest: The authors have no financial conflicts
Confidentiality of Data: Patient consent obtained.

Corresponding author

Ana Magriço
anamagricoboavida@gmail.com

REFERENCES

1. Dolman P, Goold L. Clinical Evaluation and Disease Patterns. In: Fay A, Dolman P, editors. Diseases and Disorders of the Orbit and Ocular Adnexa. Amsterdam: Elsevier; 2016. p. 35-55.
2. Karcioglu Z. Clinical Evaluation of the Orbit. In: Karcioglu Z, editor. Orbital Tumors: Diagnosis and Treatment. Berlin: Springer; 2005. p. 51-60.
3. Vásquez L. Basic Concepts in Orbital Examination. In: Medel R, Vásquez L, editors. Orbital Surgery. ESASO Course Series. Berlin: Karger; 2014. Vol 5; p. 1-17. 7, p. 27-80.
4. Nerad J. Clinical Anatomy. In: Nerad J, editor. Techniques in Ophthalmic Plastic Surgery: A Personal Tutorial. Amsterdam: Elsevier; 2010.

5. McKeag D, Lane C, Lazarus JH, Baldeschi L, Boboridis K, Dickinson AJ, et al. Clinical features of dysthyroid optic neuropathy: a European Group on Graves' Orbitopathy (EUGOGO) survey. Br J Ophthalmol. 2007;91:455-8.

3. Orbital Imaging: Diagnostic Tools

RADIOLOGY

Nuno Caçador, MD; Sérgio Cardoso, MD.

Summary

Diagnosing orbital diseases may become a complex process, and often requires imaging studies in order to provide an accurate anatomical characterization and structural involvement.

Keywords: *Magnetic Resonance Imaging; Orbit/diagnostic imaging; Orbital Diseases/diagnostic imaging; Tomography, X-Ray Computed; Ultrasonography*

INTRODUCTION

The main imaging modalities used to evaluate the orbit are ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). Ultrasonography is useful to evaluate intraocular lesions and is frequently performed by ophthalmologists. MRI and CT provide additional information, and both are vital for evaluating more complex disease.

In a high number of cases, CT is the first imaging modality for patients presenting external/ periorbital symptoms, being very useful in the evaluation of bony involvement. MRI is more accurate for evaluating retrobulbar disease, such as lesions of the optic nerve-sheath complex. MRI is also very important to understand the intracranial extension of some orbital lesions.

There are several potential causes for an imaging abnormality, which may justify the need for several complementary techniques.

1. COMPUTED TOMOGRAPHY

Computed tomography (CT) scan was introduced in 1973,[1] revolutionizing the neuroimaging scenario (Fig. 1). With the evolution to spiral CT, it became possible to study the head and orbit in multiple planes and in better detail compared to the previous single slice scanners.

Spiral systems with 16 slices or more can deliver high quality images in multiple planes. In trauma and postoperative studies, 3D bone reconstructions may also be useful.

CT angiography is currently very important in the detection of aneurysms and other vascular malformations [2] (Fig. 2). In cases of trauma or bone tumors, CT is preferred to evaluate the facial bones and orbital canal. CT also becomes the first choice in emergencies and when MRI is contraindicated.

The use of intravenous contrast, by filling the vascular compounds of any structure, including lesions, allows to improve accuracy and detail of images. The use of ionizing radiation is, however, an important disadvantage of CT, especially in children and young patients.

2. DIGITAL SUBTRACTION ANGIOGRAPHY

Digital subtraction angiography (DSA) is performed primarily for vascular pathology (Fig. 3). The commercialization of DSA began in 1980,[3] starting a new era for diagnostic and endovascular therapy. It also uses X-rays, allowing a more dynamic study compared to CT angiography. It is however an invasive procedure, and requires a large volume of intravenous contrast.

It can be used to complete the characterization of an imaging finding, either CT or magnetic resonance angiography.

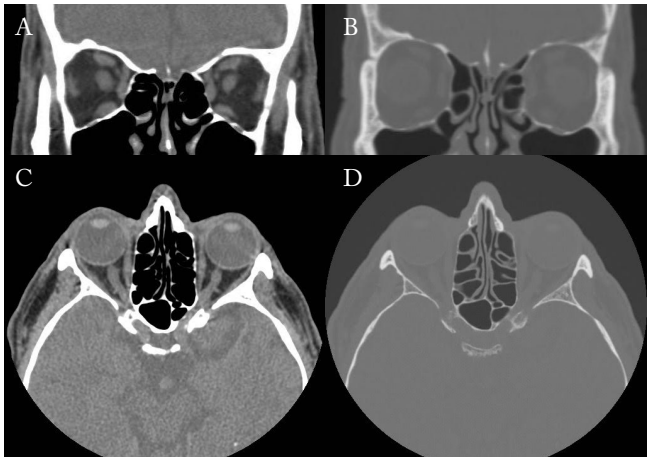


Figure 1. Normal CT images in the coronal plane (A,B) and axial plane (C,D)

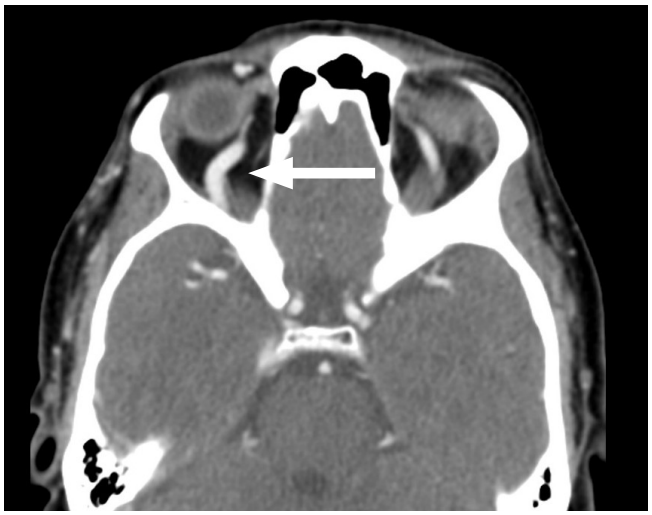


Figure 2: Axial plane CT angiography showing a dilated right superior ophthalmic vein (white arrow), secondary to an ipsilateral carotid-cavernous fistula

3. MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) was first performed on a human in 1977.[4] It has evolved since then, with increased

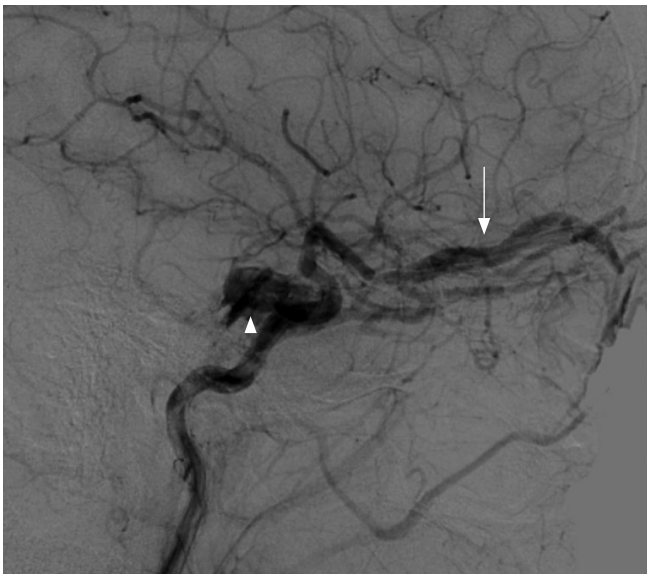


Figure 3: Lateral view of a digital subtraction angiography showing a dilated right superior ophthalmic vein (white arrow) and an ipsilateral carotid-cavernous fistula (white arrowhead)

strength to the magnetic field, new sequences and better image quality (Fig.s 4 and 5).

It is the modality of choice for imaging the brain and orbit, mainly because it allows a better discrimination of soft tissue, higher resolution and has multiplanar capability. The magnetic field strength is also important as the resolution improves with increasing field strength; machines of 1.5 Tesla and above give high quality images, with better anatomic detail.

There are some special sequences in MRI that are very useful in orbital imaging:

- Fat suppression sequences (Fig. 4 C, D): highlight intra-orbital structures surrounded by the bright fat sign (both on T1 and T2 sequences).[5]

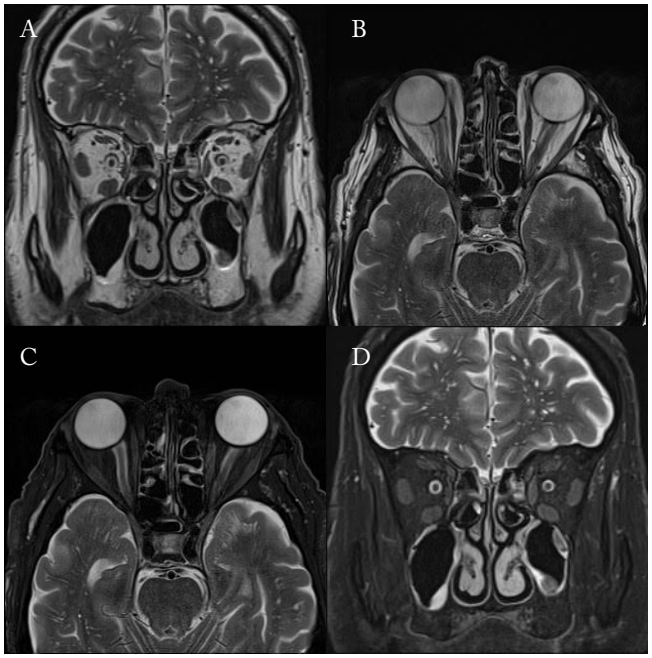


Figure 4. Normal T2 weighted images without fat suppression (A,B) and with fat suppression (C, D)

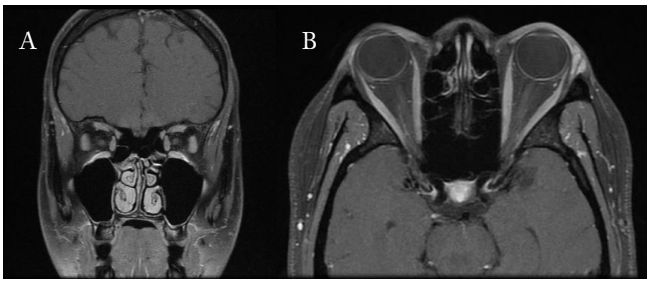


Figure 5. Normal T1 weighted images with fat suppression and contrast-enhanced in the coronal plane (A) and axial plane (B)

- Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC): useful to distinguish highly cellular lesions from other lesions.[6]
- Dynamic contrast enhanced (DCE) MR imaging: allows perfusion studies.[7]
- Optic nerve tractography: used to study possible neural injury.[8,9]
- Functional magnetic resonance imaging (fMRI): analyzes the activation of the visual cortex.
- Susceptibility weighted imaging (SWI): identifies hemorrhage and calcification.

MR angiography may be an alternative to CT angiography, avoiding exposure to radiation.

CONCLUSION

There are several imaging tools for orbital disease characterization. CT or MRI are initially used to determine the location and nature of lesions. The use of contrast material is also indicated in most cases. In MRI, performing special sequences may become very useful, allowing the distinction between specific types of lesions.

Ethical Disclosures

Conflicts of Interest: The authors have no financial conflicts

Corresponding author

Nuno Caçador

nuno.cacador@jmellosaude.pt

REFERENCES

1. Cierniak R. X-Ray Computed Tomography in Biomedical Engineering. London: Spronger-verlag; 2011.
2. Fleischmann D, Chin AS, Molvin L, Wang J, Hallett R. Computed tomography angiography: a review and technical update. Radiol Clin North Am. 2016;54:1-12.
3. Crummy AB, Strother CM, Mistretta CA. The history of digital subtraction angiography. J Vasc Interv Radiol. 2018;29:1138-41.
4. Edelman RR. The history of MR imaging as seen through the pages of radiology. Radiology. 2014;273(2 Suppl):S181-200.
5. Gokharman D, Aydin S. Magnetic Resonance Imaging in Orbital Pathologies: A Pictorial Review. J Belg Soc Radiol. 2018;101:5.
6. Drake-Pérez M, Boto J, Fitsiori A, Lovblad K, Vargas MI. Clinical applications of diffusion weighted imaging in neuroradiology. Insights Imaging. 2018;9:535-47.
7. Jittapiromsak N, Hou P, Liu HL, Sun J, Schiffman JS, Chi TL. Dynamic contrast-enhanced MRI of orbital and anterior visual pathway lesions. Magn Reson Imaging. 2018;51:44-50.
8. Hales PW, Smith V, Dhanoa-Hayre D, O'Hare P, Mankad K, d'Arco F, et al. . Delineation of the visual pathway in paediatric optic pathway

glioma patients using probabilistic tractography, and correlations with visual acuity. NeuroImage. 2017;17:541-548. d

9. Naismith RT, Xu J, Tutlam NT, Lancia S, Trinkaus K, Song SK, et al. Diffusion tensor imaging in acute optic neuropathies: predictor of clinical outcomes. Arch Neurol. 2012;69:65-71.

Section 2

Surgical Approaches to the Orbit and Optic Nerve

4. Surgical Approaches to the Orbit and Optic Nerve

OPHTHALMOLOGY

Ana Duarte, MD

Summary

A thorough knowledge of orbital diseases and their management, a meticulous surgical technique, and the flexibility to adapt to any intraoperative contingencies are critical qualifications for an orbital surgeon. The orbit may be divided into distinct areas in the axial and coronal planes, and a large set of transcutaneous and transconjunctival incisions and access planes exist for each one of them. Every procedure should be adapted to its specific indications, final goals and surgeon's experience.

Keywords: *Ophthalmologic Surgical Procedures; Optic Nerve/surgery; Orbit/surgery; Osteotomy; Orbitotomy*

INTRODUCTION

It is essential to have a detailed characterization of the disease and the patient´s profile when planning orbital surgery. As Rootman states, "surgery remains, in essence, a controlled violent intrusion"[1] and, therefore, this option should involve a thorough pre-planning that weighs down its risks and benefits reliably. In this chapter, we will address some technical concepts of orbital surgery while emphasizing the importance of its proper contextualization in a specific clinical setting. The goal is to provide a conceptual and systematic review of the main indications and techniques used in orbital surgery.

GENERAL INDICATIONS FOR ORBITAL SURGERY

There are many indications for orbital surgery. The most common are conditions causing compression of orbital structures (acute or chronic) with associated optic neuropathy, venous congestion and ischemia; biopsies; trauma repair; excision of solid or cystic lesions; management of vascular lesions or congenital abnormalities.[1]

For diagnostic purposes and surgical planning, it is useful to divide the orbit into distinct anatomical areas in the coronal and axial planes, and distinguish soft tissue compartments.[2] Each one of them has not only a set of more frequent conditions, but also specific approaches. We may consider four quadrants on the coronal plane, that extend from the corneal apex to the optic canal: the superomedial, superolateral, inferomedial and inferolateral (Fig.s 1 and 2). In the axial plane, three anteroposterior areas may be accounted: anterior,

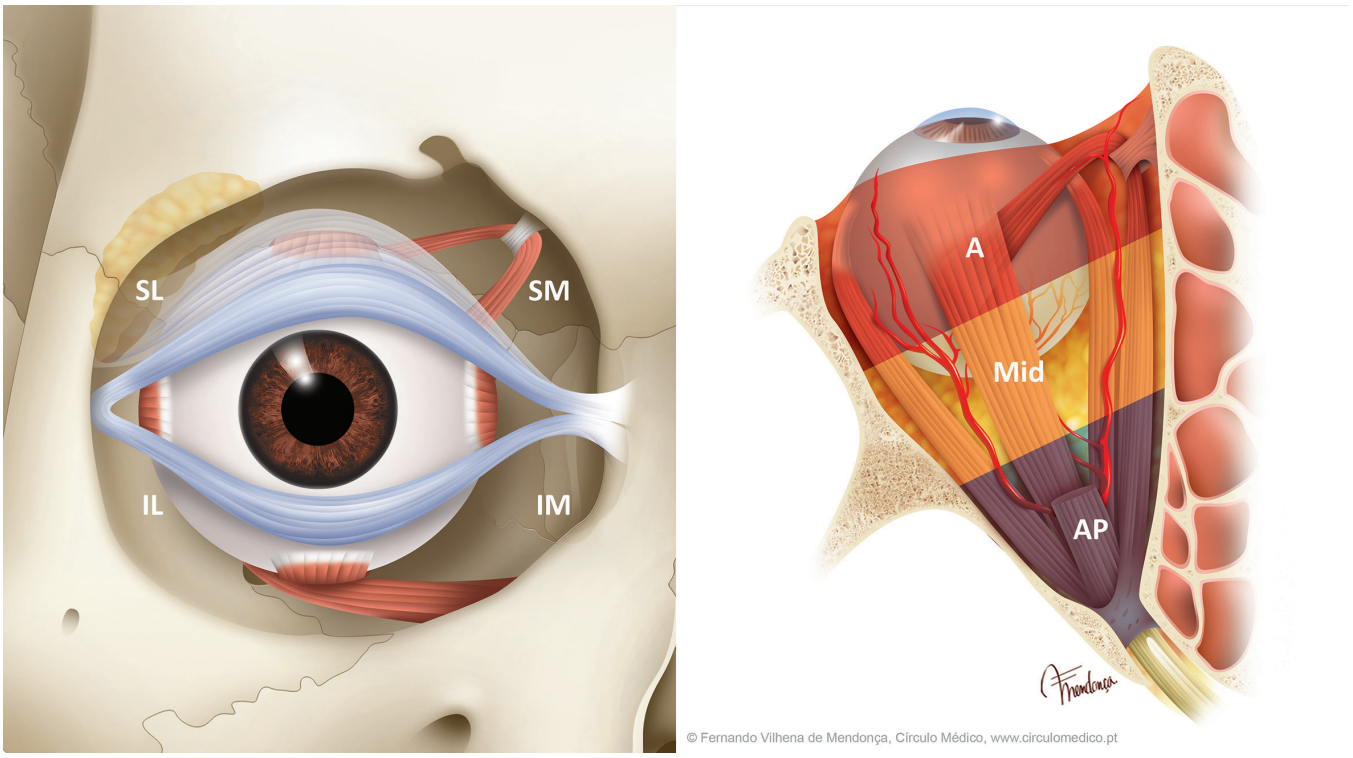


Figure 1. Anatomic divisions of the orbit in the coronal (left) and axial (right) planes. SL indicates superolateral orbit SM, superomedial orbit; IM, inferomedial orbit; IL, inferolateral orbit; A, anterior orbit; Mid, middle orbit; AP, apex.

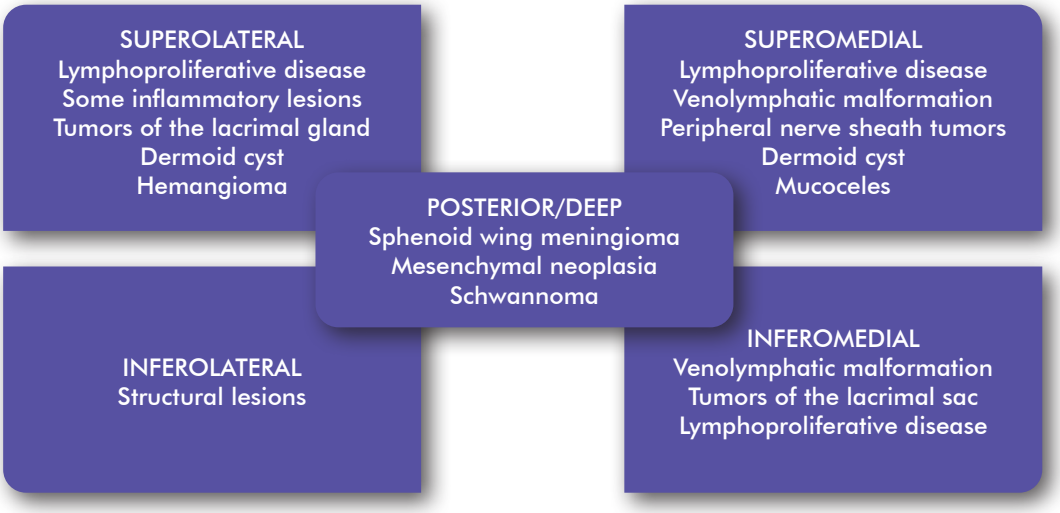


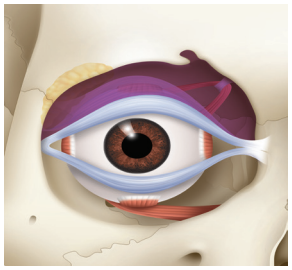
Figure 2. Common orbital diseases by location (adapted from Rootman J.[1]

middle orbit and the apex (Fig.1). The anterior area originates from the septum, anteriorly, and proceeds until reaching just behind the equator of the globe. From this point, the middle orbit extends until reaching an imaginary limit that can be estimated radiographically by connecting a line that goes from the posterior aspect of the trigone to the posterior ethmoidal foramen.[2] The orbital apex is found behind this plane. Four spaces comprise the soft tissues compartments: the subperiosteal, extraconal (between the intraconal space and the periorbita), intraconal (bounded by the globe and extraocular muscles), and the sub-Tenon space. Describing a surgical area in these three manners becomes extremely useful for reference and planning. See Chapter 1 for more anatomical details.

SURGICAL APPROACHES TO THE ORBIT

The orbit is a pyramidal structure that shields the ocular globe, extraocular muscles, fat, the lacrimal gland, several arteries, veins and nerves, and a complex system of ligaments and fascias.[3] There are numerous surgical approaches to this area, each presenting its own risks and benefits. The most appropriate approach is one that allows good exposure, better aesthetic result and lowers morbidity, avoiding areas with a higher risk of complications such as visual loss, paresthesias, and hemorrhages. An anterior access to the orbital contents can be achieved using either a transcutaneous or a transconjunctival approach, or through one of its sides by using osteotomies to increase exposure.

The access decision mainly depends on the location of the disease (whether it is anterior or deep), its relation to the optic nerve, and the surgical area involved. Without compromising exposure and thus the surgical goal, the incision should be as small as possible. Equally important, incisions should be made in places that limit their identification after surgery.
Lesions anterior to the equator of the eye can be addressed by an anterior orbitotomy. Deep lesions involving the posterior 1/3 of the orbit and/or the optic canal may need a more complex technique such as a transcranial orbitotomy (see Chapter 6). Deep lesions lateral to the optic nerve require a lateral orbitotomy, whereas deep medial lesions should be accessed through an anterior deep medial orbitotomy or a transnasal endoscopic approach (see Chapter 5). Moreover, whether the goal is to excise a lesion, fracture repair or decompression, the knowledge of the local anatomy is essential to surgical success and to avoid complications.



1. SUPERIOR ORBIT

To access the superior orbit, an anterior approach should be preferred if possible, as it doesn´t require an osteotomy and gives a fast and less invasive access to the subperiosteal, extraconal and intraconal spaces. Common indications are lacrimal gland diseases, biopsy/excision of extraconal lesions, subperiosteal hematomas and abscesses.[2] Transcutaneous approaches are commonly used (Fig. 3A). The **upper eyelid crease** is an excellent way to hide an incision[4] while allowing a broad access to the entire supraorbital rim (Fig. 3B). The incision may be extended laterally to also access the lateral orbit.[5] Technique: The incision is made through the skin and orbicularis muscle. The surgeon then proceeds superiorly in a plane between the muscle and the septum, towards the upper orbital rim. At this point, the surgeon may choose to open the septum to access the preaponeurotic extraconal space or to incise the *arcus marginalis* and access the subperiosteal plane, depending on the indication. In the latter case, the incision should stop lateral to the supraorbital neurovascular bundle to avoid injuries.[2]
Despite a lesser cosmetic result, another option is to use a **supraorbital sub-brow incision** (Fig. 3A).[4]
The **coronal incision** is a more invasive option that allows a wide exposure of the superior, lateral and medial wall of the orbit (Fig. 3C). It is made behind the hairline, with a postauricular extension, proceeding anteriorly in the subperiosteal plane towards the orbital rim. Care should be taken to protect the facial and supraorbital nerves.[4] Major risks include injury to the facial nerve, scalp hematoma, scalp pain, paresthesia or anesthesia.[5]

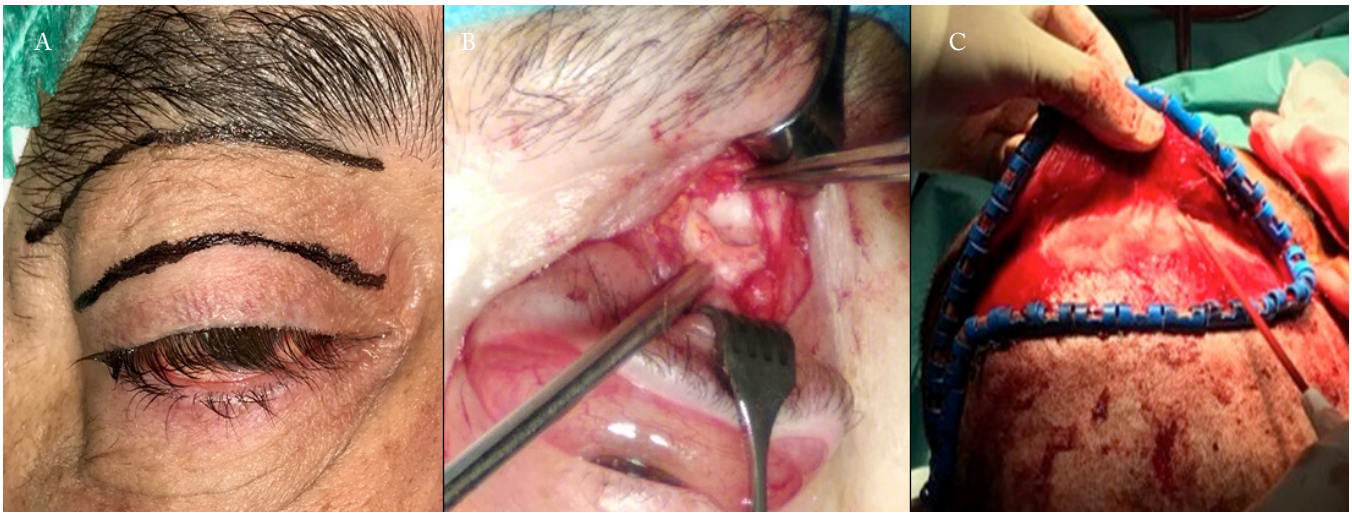
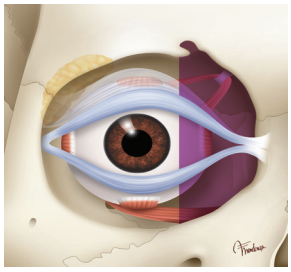


Figure 3. A. Various skin incisions used to approach the superior orbit. B. Biopsy of an inflammatory lesion of the superior orbit using a lid crease incision. The superior orbital rim is visible immediately above the lesion. C. Coronal incision with supraperiosteal dissection.



2. MEDIAL ORBIT

The access to the superomedial and inferomedial quadrants of the orbit is enabled by conjunctival or cutaneous incisions. The most common indications for this approach are inferomedial orbital decompression, fracture repair, and incisional or excisional biopsies.[2]

The **transcaruncular approach** is preferred by many orbital surgeons. Technique: The incision is placed between the plica semilunaris and the caruncle and extended into the superior and inferior fornices. Dissection is performed toward the posterior lacrimal crest, using either a Stevens or Westcott scissors in a spreading motion (Fig. 4A). Care should be taken to avoid any injury to the inferior oblique muscle, medial canthal tendon or lacrimal apparatus. Depending on the indication, the periorbita may be incised just behind the posterior lacrimal crest, using a monopolar microdissection needle or scalpel blade, to expose the medial bony wall. Whether in the extraconal or subperiosteal planes, the anterior and posterior ethmoidal neurovascular bundles should be identified and preserved, if possible.[2] If needed, the inferior oblique may be deinserted to improve exposure.[5] In the end, the conjunctival incision is closed with absorbable sutures.

When accessing the intraconal space/anterior optic nerve, a **medial peribulbar conjunctival incision**, followed by medial rectus muscle release, allows a good exposure with minimal intraorbital dissection (e.g., for optic nerve fenestration, optic nerve sheath biopsy or biopsy/excision of medial intraconal lesions).[2]

The **medial upper eyelid crease incision**, the **vertical upper eyelid split incision** or the **frontoethmoidal (Lynch) incision** (vertical and anterior to the medial canthus, over the frontal process of the maxilla) are transcutaneous alternatives to access the medial orbit (Fig. 4B). [6] The first two approaches allow adequate access to the deep superior intraconal and extraconal spaces, medial to the optic nerve, with the advantage of not needing medial rectus deinsertion. Usually, the scar becomes nearly imperceptible, the contour of the eyelid margin remains stable, and the risk of ptosis is very low. These two approaches are however inadequate for lesions in the posterior 1/3 of the orbit. Finally, the Lynch incision is now rarely performed as it leaves unaesthetic scarring and requires the reattachment of the medial canthus when released. Nevertheless, Lynch incision may be used when a drain is left after surgery (ex. orbital abscesses not

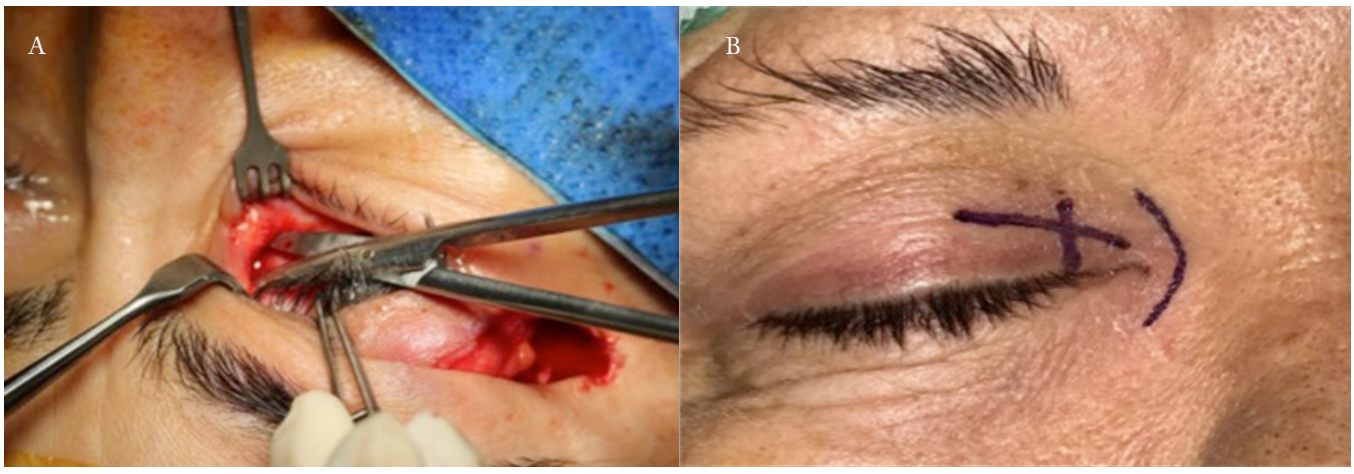
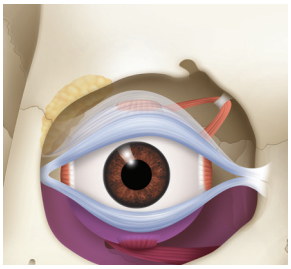


Figure 4. A. Transcaruncular access to the medial orbit B. Skin incisions used to approach the medial orbit.

suitable for endonasal surgery). Chapter 4 describes in more detail the endonasal endoscopic access to the medial orbit.



3. INFERIOR ORBIT

Two types of incisions can be used to access the inferior quadrants of the orbit: transconjunctival or transcutaneous.

Transconjunctival incisions gain favor due to the absence of skin scars and the lower risk of eyelid ectropion (Fig. 5). We may divide the accesses used for an inferior orbitotomy in:

1. Transconjunctival preseptal
2. Transconjunctival postseptal
3. Transcutaneous sub ciliary

Sometimes, an inferior transconjunctival incision may be combined with a lateral canthotomy and inferior cantholysis to improve exposure (the swinging eyelid extension), or with a medial transcaruncular incision to access the medial orbit.[2]

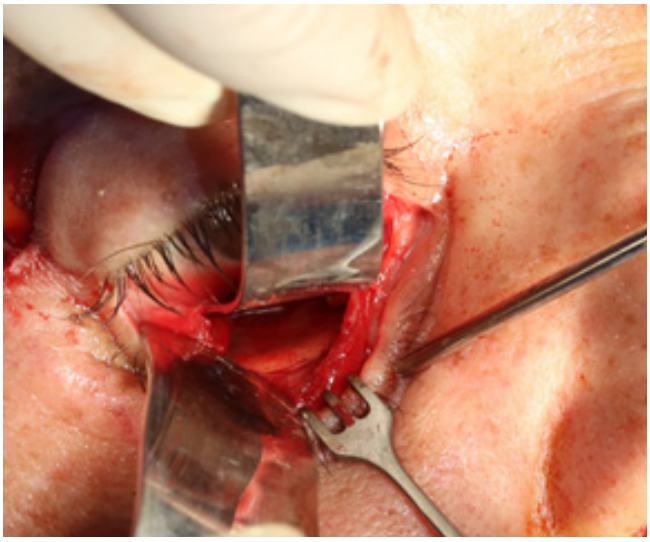


Figure 5. Transconjunctival access to the orbital floor

TRANSCONJUNCTIVAL INFERIOR ORBITOTOMY

Technique: Based on the surgeon´s preference, the transconjunctival incision may be performed in the preseptal or postseptal plane (Fig. 6A). The **preseptal approach** is performed using a conjunctival incision parallel to the eyelid margin, 3 to 4 mm inferior to the tarsus. Dissection is carried through the lower eyelid retractors and continued inferiorly, between the orbital septum and the orbicularis muscle, up to the inferior orbital rim. In the **postseptal approach**, the incision is lower, 6 to 7.5 mm below the tarsus, and the conjunctiva and retractors are promptly incised to access the extraconal space. Even though the postseptal approach carries a low risk of lower eyelid retraction and entropion (as the septum and orbicularis are spared), the major disadvantage is the prolapse of orbital fat into the surgical field.

When accessing the inferior orbit, care should be taken medially to avoid injuring or deinsert the inferior oblique muscle unintentionally.[4] If the medial orbital floor needs to be exposed, the periosteal incision should be prolonged anteriorly to the origin of the inferior oblique to elevate the muscle´s insertion along with the periosteum. At the end of the procedure, the surgeon may choose to close the conjunctival incision with continuous or interrupted resorbable sutures. Complications related with the incision, whether or not it is closed, are very low.[7]

When the goal is to have a direct access to the bony orbital floor (e.g., in fractures), a direct transconjunctival postseptal approach as originally described by Tenzel and Miller may also be chosen.[8] Here, a monopolar microdissection needle is used to make a single incision over the orbital rim through the conjunctiva, retractors, and the periosteum at the posterior limit of the *arcus marginalis*, allowing the direct exposure of the bony rim. The periorbita is then elevated using a Freer elevator, and with malleable retractors a hand-over-hand technique is used for orbital floor exposure.

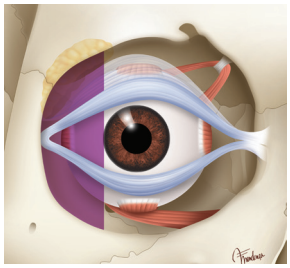
As described for the medial orbit, an **inferior peribulbar conjunctival incision** may also be used to access anterior peribulbar structures like the inferior rectus muscle (Fig. 7).

TRANSCUTANEOUS INFERIOR ORBITOTOMY

The most often used transcutaneous approaches are the subciliary and subtarsal incisions (Fig. 6B). The infraorbital incision should be avoided as it leaves an unaesthetic scar.[5]

Technique: A **subciliary incision** is created about 2 mm below the lower eyelid margin. The surgeon proceeds inferiorly in the plane between the orbicularis and the septum, generally using a "stepped skin-muscle flap," trying to preserve the pretarsal orbicularis muscle.[5] Depending on the indication, the periosteum may be incised at the inferior orbital rim. The **subtarsal incision** is made about 6-7 mm below the eyelid margin following a skin crease. A major disadvantage of these incisions, especially the subciliary, is that skin and septal scarring may be associated with vertical eyelid shortening and scleral show.[9] In the last few years, some controversy has developed over the effect of this skin-muscle flap on the zygomatic branch innervating the orbicularis muscle.[10] However, recent anatomic and clinical studies have shown that the risk of postoperative eyelid retraction and scleral show are not related to the simple denervation of this branch,[11-13] and that buccal branch preservation and careful hemostasis are crucial to lower the risk of lid malposition.

Compared with the transconjunctival approach, the author´s preference, the transcutaneous incisions allow access to the same compartments and areas of the orbit. However, transcutaneous incisions leave skin scars, are more limited when exposure of the lateral and medial orbit is needed, and subciliary incisions carry a higher risk of lower eyelid malposition.[2]



4. LATERAL ORBIT

Lateral orbitotomy gives access to the extraconal, intraconal or subperiosteal spaces of the superolateral and inferolateral quadrants of the orbit. Depending on the required exposure and the goal of the surgery, lateral orbitotomy may or may not involve bone removal.[2] It is used for lateral

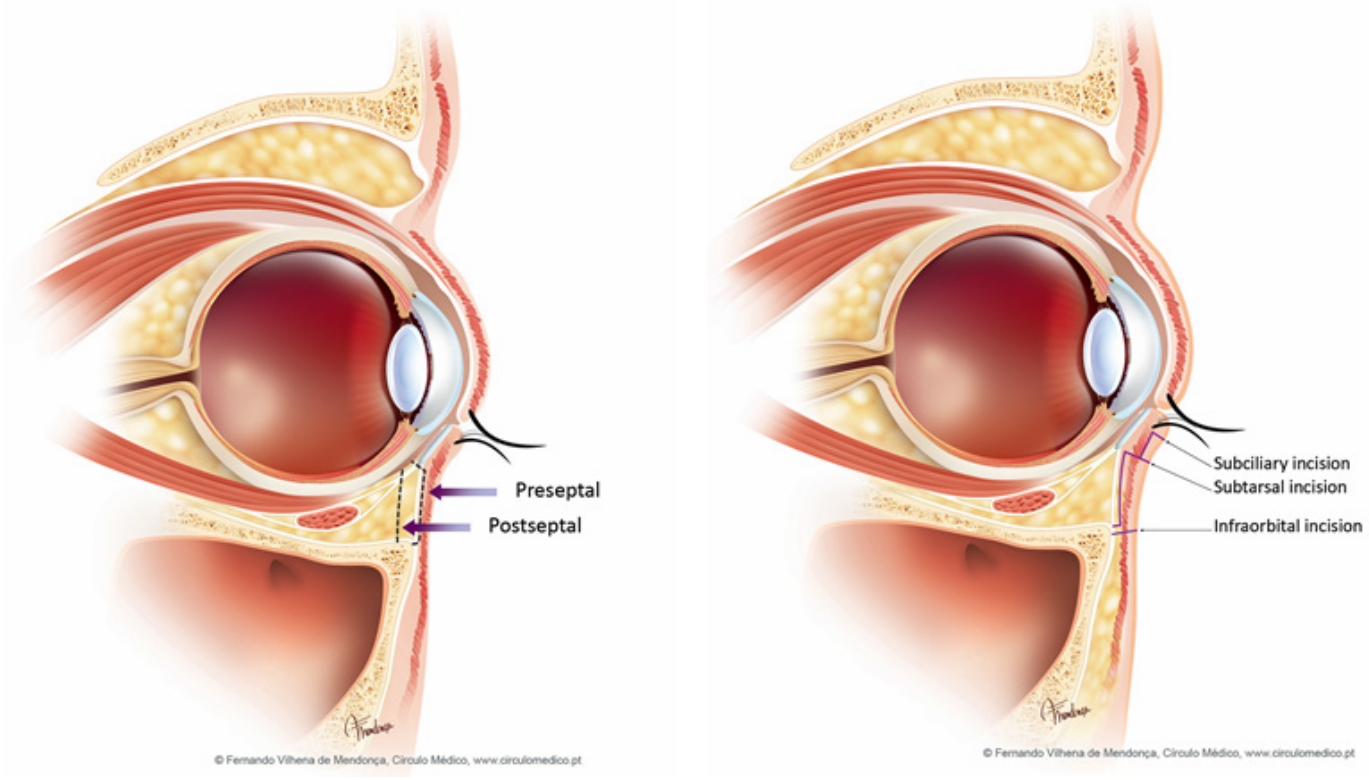


Figure 6. A. Transconjunctival and B. transcutaneous approaches to the inferior orbit. Figure adapted from Drolet et al.[14]

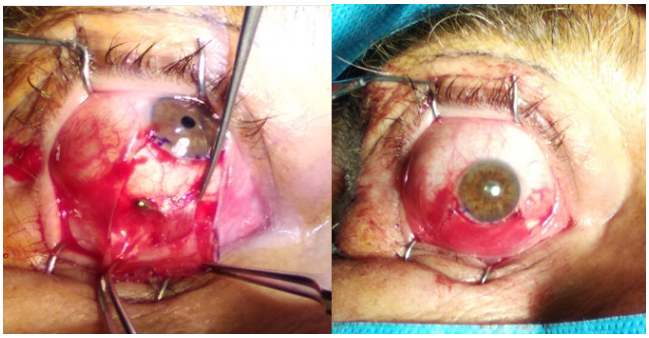


Figure. 7 Inferior peribulbar conjunctival incision used for biopsy of an enlarged inferior rectus. Histopathology revealed a marginal zone lymphoma of mucosal associated lymphoid tissue (MALT lymphoma).

orbital decompression, lacrimal fossa lesions, or tumors lateral to the optic nerve. Transcutaneous incisions are generally used (Fig.s 8 and 9), being the most frequent the lateral upper lid crease incision (the author´s preference), the lateral canthotomy with superior and inferior cantholysis - which allows the direct extension of the incision through the subtarsal conjunctiva of the inferior eyelid (swinging eyelid approach) - or the sub brow (Stallard Wright) incision.[2] While the latter allows direct access to the superolateral orbital rim, it also leaves a more visible scar on the skin.

Technique: Incisions on the **lateral lid crease** or through **canthotomy** should extend approximately 1 cm lateral to the orbital rim using a natural rhytid, being tissue dissection carried through the orbicularis and connective tissue toward the lateral orbital rim. Then, the procedure is adapted in accordance to the indication. After exposure of the lateral orbital rim, the periosteum may be incised and reflected to expose the subperiosteal plane from the internal surface of the lateral orbital wall, lateral roof, or inferiorly the zygomatic portion of the orbital floor. In this region, we may find the zygomaticofacial and zygomaticotemporal vessels, which can be cauterized and transected. At this point, an osteotomy may be created using a surgical drill system, whether for decompression or to better access the intraorbital space. In this case, the periosteum from the external surface of the zygoma and the temporalis muscle are also elevated and two horizontal osteotomies are created: one just superior to the frontozygomatic suture and another immediately above the level of the zygomatic arch. A rongeur and a drilling system allow the surgeon to create a bone window, after which the periorbita may be incised to access orbital contents. At this stage, care should be taken to avoid injury to the recti muscles by opening the periorbita beyond the limits of the muscle belly. In the end, the orbital rim can be repositioned using nonabsorbable sutures or titanium microplates. Soft tissue is closed using buried absorbable sutures (including lateral canthus reformation when canthotomy is performed), and the skin is sutured using 6-0 nylon or prolene.

5. ORBITAL APEX

As stated previously, lesions located in the posterior 1/3 of the orbit sometimes require a more complex approach. When an anterior orbitotomy is insufficient in enabling a good and safe access to the deep orbit, alternatives such as the transcranial or endonasal endoscopic approaches become excellent options (see Chapters 5 and 6).

CONCLUSION

Orbital surgery starts way before entering the operating room. It is important to consider the specificities of each clinical case, and to establish the primary goal of the intervention

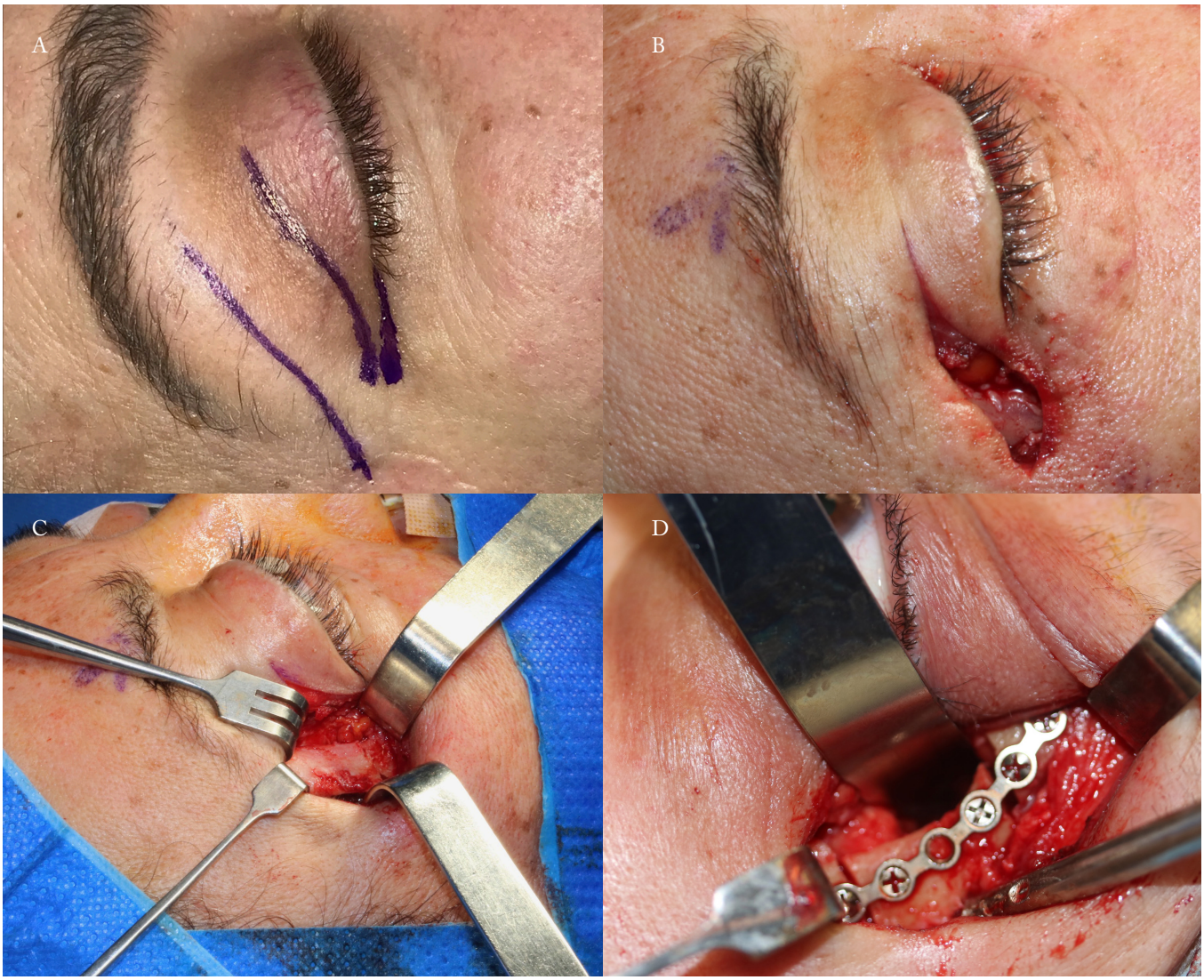


Figure 8. A. Various incisions used to approach the lateral orbit. B. Lateral eyelid crease incision. C. Exposure of the lateral orbital rim. D. Repositioning of the orbital rim using titanium microplates.

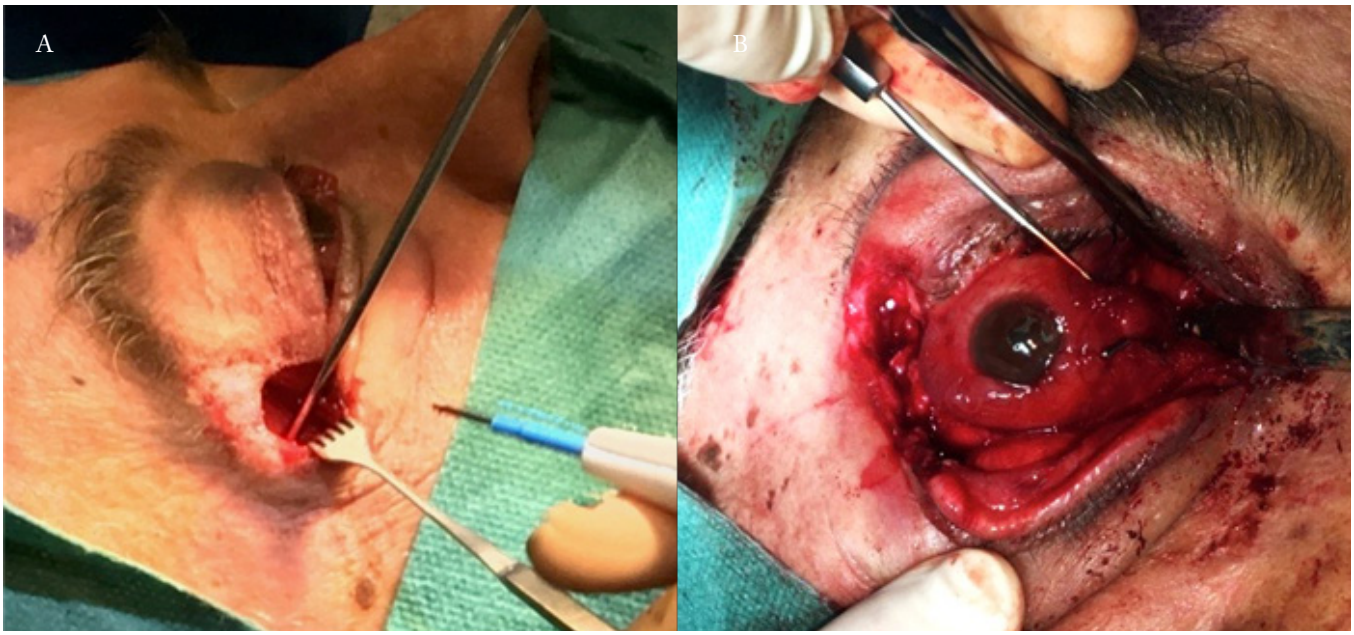


Figure 9. Three-wall orbital decompression for thyroid orbitopathy presenting with marked proptosis, optic neuropathy, orbital congestion, and ocular surface exposure. A lateral canthotomy (A) combined with a swinging eyelid approach and a medial transcaruncular incision (B) were used to access the lateral, inferior and medial orbital wall, respectively.

taking into account the patient´s needs and the possibility of other, less invasive alternatives. Once the surgical indication is established, the next step should be to define the surgical area and the most effective and safe way to approach it. The fundamentals presented here are just a fraction of the conceptual framework that the orbital surgeon must master. In all cases, the surgical outcome will depend heavily on a combination of anatomical knowledge, technical ability, and flexibility to adapt to intraoperative adversities.

Ethical Disclosures
Conflicts of Interest: The author have no financial conflicts
Confidentiality of Data: Patient consent obtained.

Corresponding author
Ana Duarte
anaf. duarte@hotmail.com

REFERENCES

1. Rootman J. Orbital Surgery. A conceptual approach. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2014.
2. Weller CL, Tabor MH, Ryan LE, Leyngold IM. Orbital Surgery: Approaches and Techniques. Int Ophthalmol Clin. 2018;58:61-84.
3. Hayek G, Mercier P, Fournier HD. Anatomy of the orbit and its surgical approach. Adv Tech Stand Neurosurg. 2006;31:35-71.
4. Turvey TA, Golden BA. Orbital anatomy for the surgeon. Oral Maxillofac Surg Clin North Am. 2012;24:525-36.
5. Markiewicz MR, Bell RB. Traditional and contemporary surgical approaches to the orbit. Oral Maxillofac Surg Clin North Am. 2012;24:573-607.
6. Timoney PJ, Sokol JA, Hauck MJ, Lee HB, Nunery WR. Transcutaneous medial canthal tendon incision to the medial orbit. Ophthalmic Plast Reconstr Surg. 2012;28:140-4.
7. Mullins JB, Holds JB, Branham GH, Thomas JR. Complications of the transconjunctival approach. A review of 400 cases. Arch Otolaryngol Head Neck Surg. 1997;123:385-8.
8. Tenzel RR, Miller GR. Orbital blow-out fracture repair, conjunctival approach. Am J Ophthalmol. 1971;71:1141-2.
9. Holtmann B, Wray RC, Little AG. A randomized comparison of four incisions for orbital fractures. Plast Reconstr Surg. 1981;67:731-7.
10. Griffin G, Azizzadeh B, Massry GG. New insights into physical findings associated with postblepharoplasty lower eyelid retraction. Aesthet Surg J. 2014;34:995-1004.
11. Choi Y, Kang HG, Nam YS, Kang JG, Kim IB. Facial Nerve Supply to the Orbicularis Oculi around the Lower Eyelid: Anatomy and Its Clinical Implications. Plast Reconstr Surg. 2017;140:261-71.
12. Kim YK, Kim JW. Evaluation of subciliary incision used in blowout fracture treatment: pretarsal flattening after lower eyelid surgery. Plast Reconstr Surg. 2010;125:1479-84.
13. McCord CD. Commentary on: New insights into physical findings associated with postblepharoplasty lower eyelid retraction. Aesthet Surg J. 2014;34:1005-7.
32. Drolet, B. C., Sullivan, P. K. Evidence-based medicine: Blepharoplasty. Plast Reconstr Surg. 2014;133:1195-1205.

5. Surgical Approaches to the Orbit and Optic Nerve

OTORHINOLARYNGOLOGY

João Subtil, MD Phd FEB; Richard Voegels, MD PhD

Summary

Orbital surgery has greatly developed during the last few years, and one of its major advances was the introduction of endoscopic approaches. The transnasal route and endoscopy have reduced surgical morbidity, especially when dealing with pathology medial to the optic nerve, both in the orbit or in the optic canal. In this chapter, we discuss the use of endoscopes and detail our technique of endoscopic transnasal orbitotomy and optic nerve decompression.

Keywords: *Decompression, Surgical; Endoscopy; Optic Nerve/surgery; Orbit/surgery*

INTRODUCTION

The surgical approach to the post-septal orbit presents several difficulties: the incision must not be obvious, relevant structures must be avoided (eye, muscles and lacrimal sac), nerves and vessels must be preserved (ophthalmic artery, oculomotor nerves), and finally the "navigation" through the orbital fat, which interposes and hinders vision and manipulation of orbital structures.

Thus, and depending on the indication, various pathways have been used, most commonly the transconjunctival pathway, the transcranial pathway, and lateral orbitotomy.[1] More recently, the endoscopic transnasal access has been used for medial orbit pathology.

USE OF ENDOSCOPES IN ENDONASAL SURGERY

Endonasal surgery had a tremendous development in the last 50 years, after the introduction of the nasal endoscope (Fig. 1).[2] During this time, several instruments were gradually introduced into the surgeon's table, allowing endoscopic surgery. The nasal endoscope has several advantages over other traditional approaches: it allows nasal and transnasal surgery through the nostril (the orbit, in this case) without cutaneous incisions; gives an expanded view of the operating field; projects the "point of view" into the nasal fossa, placing it near the surgical field; angled lenses allow a "sideways" view and to see "around the corners", that is, to see behind anatomical structures without mobilizing them; and finally, the endoscope itself transports the light by optical fiber, therefore making visualization no longer dependent on external illumination.

We may point out some difficulties of this approach, such as changes in our tridimensional perception (the projection of the "point of view" twists the surgeon's anatomic perception, that now "looks" to the surgical field from a point of view inside the nasal fossa), and the permanent care with cleaning the lens during surgery, which may cause a slower learning curve.

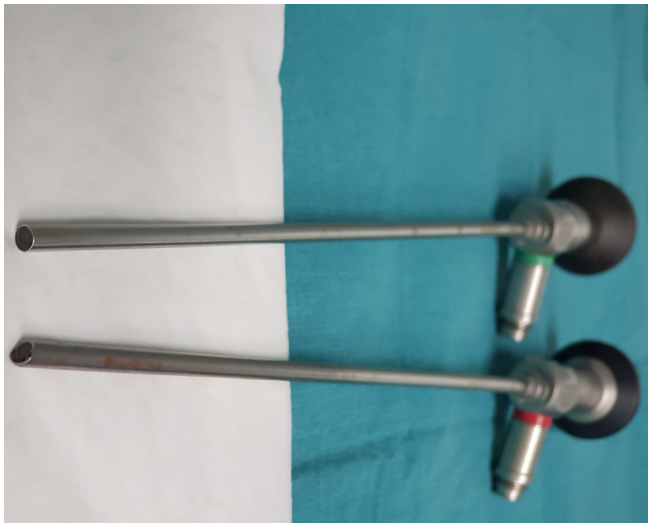


Figure 1. Rigid nasal endoscope, and common angulations

Surgery for nasal inflammatory pathology has long been almost entirely endoscopic,[3] being a very common procedure in Otolaryngology. For the otolaryngologist, it is therefore natural to use endoscopes. Currently, surgery for inflammatory disease respects the natural physiology of the naso-sinusal system, aiming for the enlargement of the natural ostia, without rupture of other structures. With surgical training, the surgeon learns to orient himself in the nasal cavity, respecting relevant structures and identifying their limits, namely the orbital wall (Fig. 2).

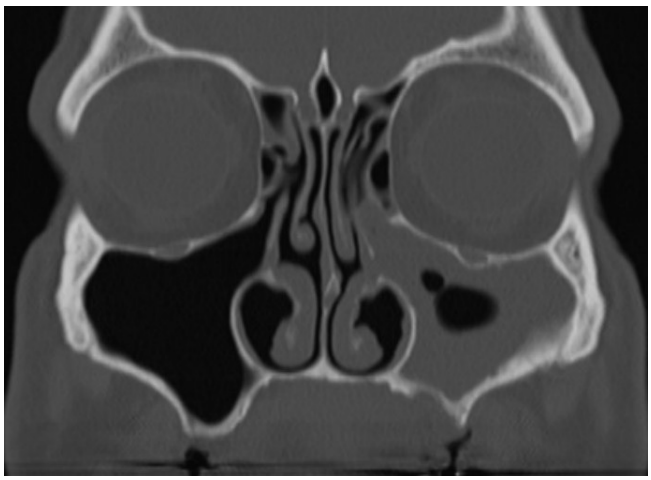


Figure 2. Coronal tomography of ethmoid showing inflammatory pathology and its relationship with the orbit and skull base

1. TRANSNASAL APPROACH FOR INFLAMMATORY ORBITAL DISEASE

The orbital wall is a limit in endonasal surgery with which the surgeon is familiar. We must recognize, and even anticipate it, during the dissection of the ethmoid. Orbital inflammation often emerges as a complication of sinusitis, and thus its resolution must include the resolution of the underlying cause as well. Consequently, Otolaryngology is often called to assist these situations. In cases where medical therapy is not effective, surgery is required.

Since the beginning of the 90s of the last century, the transnasal approach to the orbit has been used to solve abscesses (Fig. 3).[4] In addition to the advantages presented before, the transnasal route also allows the establishment of a drainage path without needing a drain (which when placed externally has a unfavorable cosmetic effect, leaving a noticeable scar). It also directly addresses the abscess focus and simultaneously solves the underlying sinus pathology (Fig. 4).

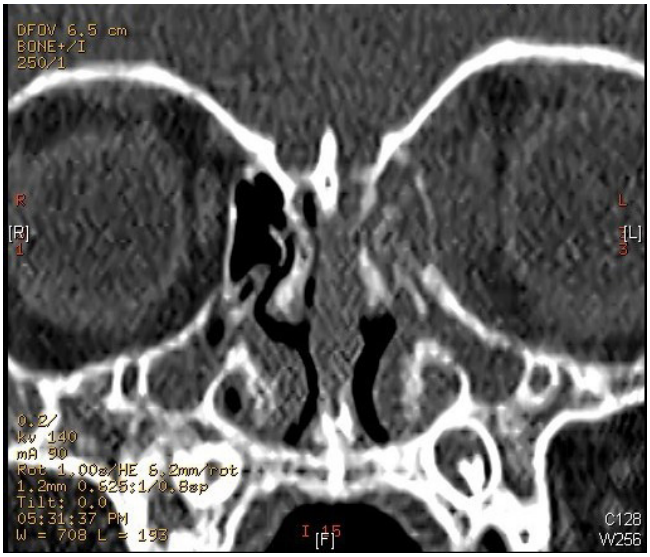


Figure 3 Subperiosteal orbital abscess

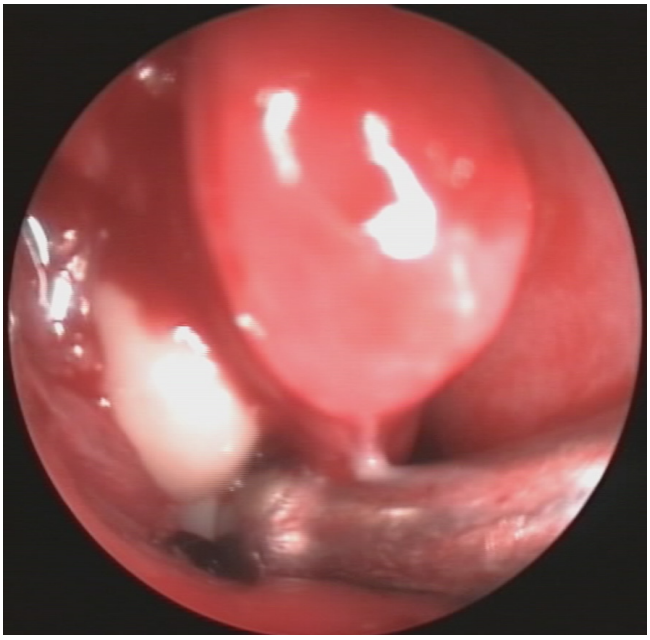


Figure 4. Endonasal drainage of subperiosteal orbital abscess

2.TRANSNASAL APPROACH FOR NON-INFECTIOUS ORBITAL DISEASE

Decompression of the orbit due to exophthalmos in Graves' disease is a well known procedure. The transnasal endoscopic medial wall decompression was first described in the 1990s, [5] having as an advantage the much larger nasal cavity generated by ethmoidectomy, made with endoscopic dissection, as a preparation for orbital decompression (Fig. 5). Another significant advantage is that it is easier to identify the skull base, making it safer. We describe these aspects in Chapter 11.

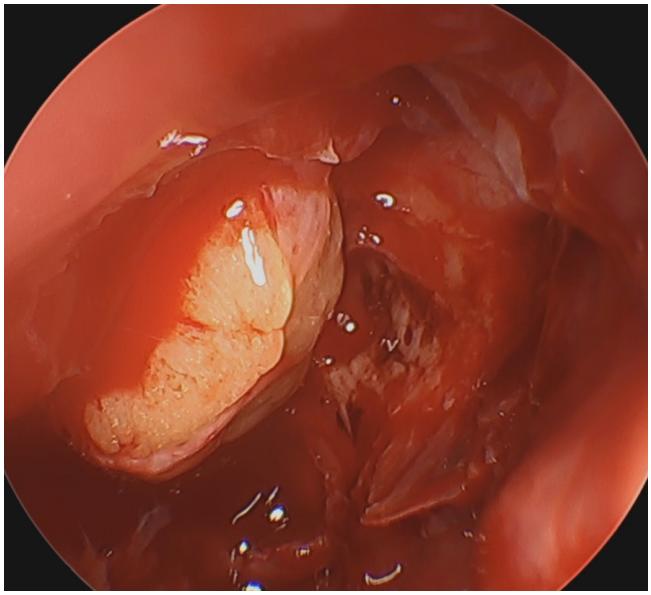


Figure 5. Orbital fat exposure in the nasal fossa

Optic nerve decompression was only possible after the introduction of endonasal drills, which allowed the removal of the bony wall of the optic canal (Fig. 6).[6] The advantages were considerable compared to the traditional transcranial route - craniotomy was no longer necessary, considerably shortening the surgical time and eliminating its inconveniences.

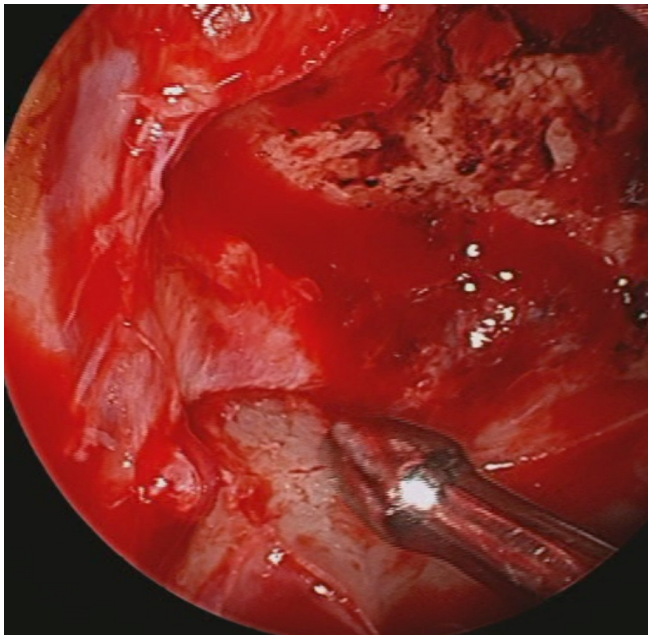


Figure 6. Decompression of the optic nerve

3. TRANSNASAL APPROACH FOR NEOPLASTIC ORBITAL DISEASE

Only recently the neoplastic pathology of the orbit started to be approached by a transnasal route.[1] The benefit derives from the lower morbidity of surgery in medially located lesions. The transnasal approach allows easy access to medial extraconic tumors in the same way as described before for the abscessed collections. A significant development was the access to intraconic tumors, medial to the optic nerve, making possible a direct approach to the tumor without mobilizing the eyeball or disturbing the vessels and nerves. Also, as visualization and magnification are better, surgery became safer. Several instruments and techniques have recently been developed for this purpose, such as the trans-septal endonasal route (giving greater parallax and better vision), four hand (two surgeons) surgery, and medial rectus muscle suspension. In our experience, the presence of a second surgeon is fundamental, collaborating in exposing the surgical field, and keeping the orbital fat away from view.

Approaching these tumors using the endonasal route has yet another advantage, namely in unresectable lesions, in which the surgery has a diagnostic purpose. In this scenario, it also allows orbital wall removal, decompressing the structures with immediate clinical improvement. For example, a benign, slow-growing tumor, nonresectable without functional compromise, is allowed to grow and expand without a functional repercussion.

SURGICAL STEPS IN THE APPROACH OF THE ENDONASAL ORBIT

In our experience, orbital surgery imposes frank endonasal exposure in order to have a wide working channel, allowing multiple instruments to pass simultaneously, room to keep the optics clean, and a better visualization. Contrary to surgery for inflammatory conditions (functional, with preservation of structures and widening only natural drainage pathways), the endonasal orbital approach is an anatomical dissection, focusing first at exposure and making room. Thus, in our practice, the steps of endonasal dissection after preparation and decongestion are as follows:

1. Dissection of the anterior ethmoid (uncinectomy, supraturbinal antrostomy, dissection of the anterior ethmoid with exposure of the lamina papyracea, extension of the dissection to the frontal recess). In cases of subperiosteal abscess, the lamina papiracea may be removed at this stage, allowing immediate drainage. No further surgery is required.
2. Partial middle turbinectomy (amputation of the lower half of the middle turbinate to allow wide exposure of the orbit, leaving a stump of about 5-10 mm for olfactory preservation).
3. Dissection of the posterior ethmoid with exposure of the spheno-ethmoidal recess and sphenoid rostrum, ethmoidal roof, and posterior lamina papiracea.
4. Posterior extension of the antrostomy to the posterior wall of the maxillary sinus, with open exposure of the orbital floor.
5. Dissection of the ethmoidal foveae with identification (and cauterization if necessary) of the ethmoidal arteries. Sometimes the roof is located a few millimeters above the emergence of the anterior ethmoidal artery (and vice versa), which must be previously recognized in the tomography, not to inadvertently damage the artery.
6. Sphenoidotomy, when necessary, with exposure of the upper lateral wall of the sphenoid sinus, namely the osseous path of the optic canal and identification of the sphenoid carotid and carotid-optic recesses. In cases where there is only indication for decompression of the nerve, we dissect the optic canal and expose the nerve, and no further orbit dissection is necessary.
7. Complete removal of the lamina papiracea, carefully preserving the periosteum, (so that the fat does not interfere with the surgical field). It should extend from near the fronto-ethmoidal suture superiorly, lacrimonasal duct anteriorly, and annulus of Zinn posteriorly (where the periosteum becomes thicker, with vertical fibers). We think that a longitudinal bony beam must be preserved between the orbital floor and the lamina papiracea (at least its anterior 2/3), in order to avoid postoperative strabismus.
8. In some cases (orbital decompression) it is necessary to remove the orbital floor, up to the infraorbital canal, although this step is often easier through a transconjunctival approach. Especially on this case, we believe that the anterior portion of the beam described above should be preserved.
9. Incisions in the periosteum of the orbit with frank exposure of fat. The incisions are made longitudinally, from posterior to anterior, and to get a full effect, the periosteum is completely removed. The fat can then be gently manipulated and pulled to debride its septations and allow a more significant decompressive effect. Here the surgeon's experience is relevant, to not inadvertently pull muscle or vascular structures, using his anatomical knowledge, and feeling the natural consistency and firmness of the tissues when clamping, taking small steps at a time.
10. In cases of intraconic pathology, we identify the medial and inferior rectus muscles, which are easily identifiable in these cases; comparing with fat, they present a very different consistency, orientation, and coloration. This identification is easier posteriorly, where there is less fat. Sometimes it helps to remove fat (avoidable, in our opinion) or folding it, if possible.
11. Dissection of the gap between the two muscles with exposure of the intraconic space. Sometimes at this stage, the neoplasia is identified and biopsied.
12. In cases where further dissection is required, for example for excision of apical tumors, a septal fenestra is created for instrumentation through the opposite nasal fossa. It will allow a greater parallax for the instruments or the endoscope, relative to the orbit. This window is made about 2 cm posterior to the caudal edge of the septum, with an approximately square aperture of 2cm^2. The mucoperiosteum and septal skeleton are removed so as not to hinder access and not to have persistent bleeding during surgery that would soil the endoscope. This opening later heals as a posterior septal perforation without functional impact.
13. Strut the medial rectus muscle to expose the lesion. This exposure is often extended posteriorly, to near the annulus of Zinn in the apex of the orbit, and in our experience, is more easily done through the septal fenestra and using cotton pads.
14. The lesion is then dissected, identifying and preserving the neurovascular structures when close to the apex. At this stage we do not use diathermy or vasoconstrictors, only warm lavage and procoagulants.
15. After surgery, the structures are carefully repositioned (muscle and fat), and hemostasis is reviewed in the nasal fossa. We do not apply any dressing or packing, and the

healing is done by second intention.

CONCLUSION

In our experience, the endonasal approach is the least invasive and most effective way to address inflammatory disease of the orbit, namely abscesses, while simultaneously solving the underlying sinus pathology.

The endonasal approach is also already consensually the most accessible and most effective route for medial orbit or optic nerve decompression.

More recently, we have gained experience in the approach to neoplastic disease of the medial orbit, both extra and intraconic, a field in frank expansion.

The use of endoscopy is not easy and has a long learning curve, and for this reason, otolaryngologists, trained for endoscopic surgery for inflammatory nasal disease, may find the orbital access as a natural next step. However, this should always be a teamwork centered in the ophthalmologist, for diagnosis, surgery and post-surgical treatment. This has been our experience, with a great gain for our patients.

Ethical Disclosures

Conflicts of Interest: The authors have no financial conflicts

Confidentiality of Data: Patient consent obtained.

Corresponding author

João Subtil

joaosubtil@gmail.com

REFERENCES

1. Castelnuovo P, Turri-Zanoni M, Battaglia P, Locatelli D, Dallan I. Endoscopic endonasal management of orbital pathologies. Neurosurg Clin N Am. 2015;26:463-72.
2. Messerklinger W. Die endoskopie der nase. Monatsschr Ohrenheilkd Laryngorhinol. 1970;104:451-6.
3. Stammberger H. Endoscopic surgery for mycotic and chronic recurring sinusitis. Ann Otol Rhinol Laryngol Suppl. 1985;119:1-11.
4. Manning SC. Endoscopic management of medial subperiosteal orbital abscess. Arch Otolaryngol Head Neck Surg. 1993;119:789-91.
5. Michel O, Bresgen K, Rüssmann W, Thumfart WF, Stennert E. Endoskopisch kontrollierte endonasale orbitadekompression beim malignen ophthalmus. Laryngorhinootologie. 1991;70:656-62.
6. Chow JM, Stankiewicz JA. Powered instrumentation in orbital and optic nerve decompression. Otolaryngol Clin North Am. 1997;30:467-78.

6. Surgical Approaches to the Orbit and Optic Nerve

NEUROSURGERY

João Paulo Farias, MD

Summary

In this chapter, I will address four approaches commonly used by neurosurgeons to access the orbit:
1 - Lateral
2 - Anterior transseptal
3 - Transcranial
   i. Supraorbital frontal
   ii. Pterional (with its multiple variations, depending on the purpose and disease involved).
In the end, some tips on common rules of orbital surgery and post-operative period will be discussed.

Keywords: *Neurosurgical Procedures; Optic Nerve/surgery; Orbit/surgery; Orbital Diseases/surgery*

INTRODUCTION

As described in previous chapters, the choice of approach is critical to surgical success with minimum risk and morbidity, and depends mainly on the location of the lesion to be addressed:
1 - Lateral approach - for lesions lateral to the optic nerve (including the optic nerve) and in the anterior 2/3 of the orbit.
2 - Anterior transseptal approach - for lesions in the anterior 1/2 of the orbit, excluding the optic nerve (especially adequate for lesions with anterior subpalpebral extension, and extraconal lesions).
3 - Transcranial approach
   i. Supraorbital frontal approach - for lesions above the optic nerve and in the anterior 2/3 of the orbit.
   ii. Pterional approach - for lesions superior, lateral and medial to the optic nerve; for optic nerve lesions that involve the optic canal, orbital apex lesions, and lesions that affect more than one space in the orbit; for lesions that extend to and from the intracranial space.

Examples (Fig.s 1 to 4).

1 - LATERAL ORBITAL APPROACH. SURGICAL TECHNIQUE (FIG.S 5 TO 7)

The head is fixed with a Mayfield head holder with a 30º rotation to the contralateral side. The incision is marked on the skin beginning over the eyebrow immediately lateral to the supraorbital groove, which is easily palpable under the skin, to spare the supraorbital nerve. Then, the marking follows laterally along a line joining the palpebral lateral cantus to the superior limit of the insertion of the ear on the head. This allows the scar to be hidden by the eyeglasses' temple. The posterior limit of the skin incision should never go beyond a vertical line 4 cm

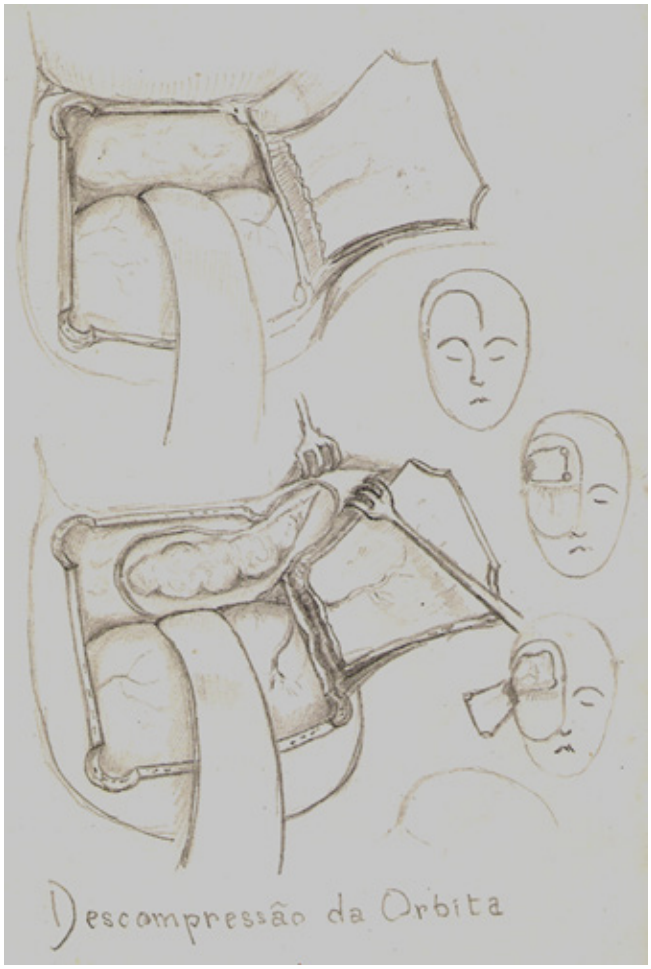


Figure 1. Orbital decompression drawing circa 1960 – Dr. Imaginário

in front of the tip of the tragus in order to avoid damaging the frontal branch of the facial nerve that innervates the frontalis muscle (as it crosses the zygomatic arch and runs anterior and superiorly to the forehead). Sharp dissection should be used to expose the orbital rim superiorly and laterally until below the fronto-zygomatic suture. A small periosteal elevator can be used to finish this exposure.
The periorbita is also dissected from the bone along the exposed orbital rim for at least 1 cm in depth.
The temporalis muscle fascia should then be sharply cut behind the orbital rim, leaving a small cuff to reinsert the fascia at the end. The temporalis muscle can then be dissected from the bone and retracted posteriorly: - one can use a Faraboeuf retractor with one end retracting the muscle and the other end on the bar of the Greenberg retractor system.
The orbital rim is then cut with an oscillating saw at the supero-medial and infero-lateral limits of the exposure. After

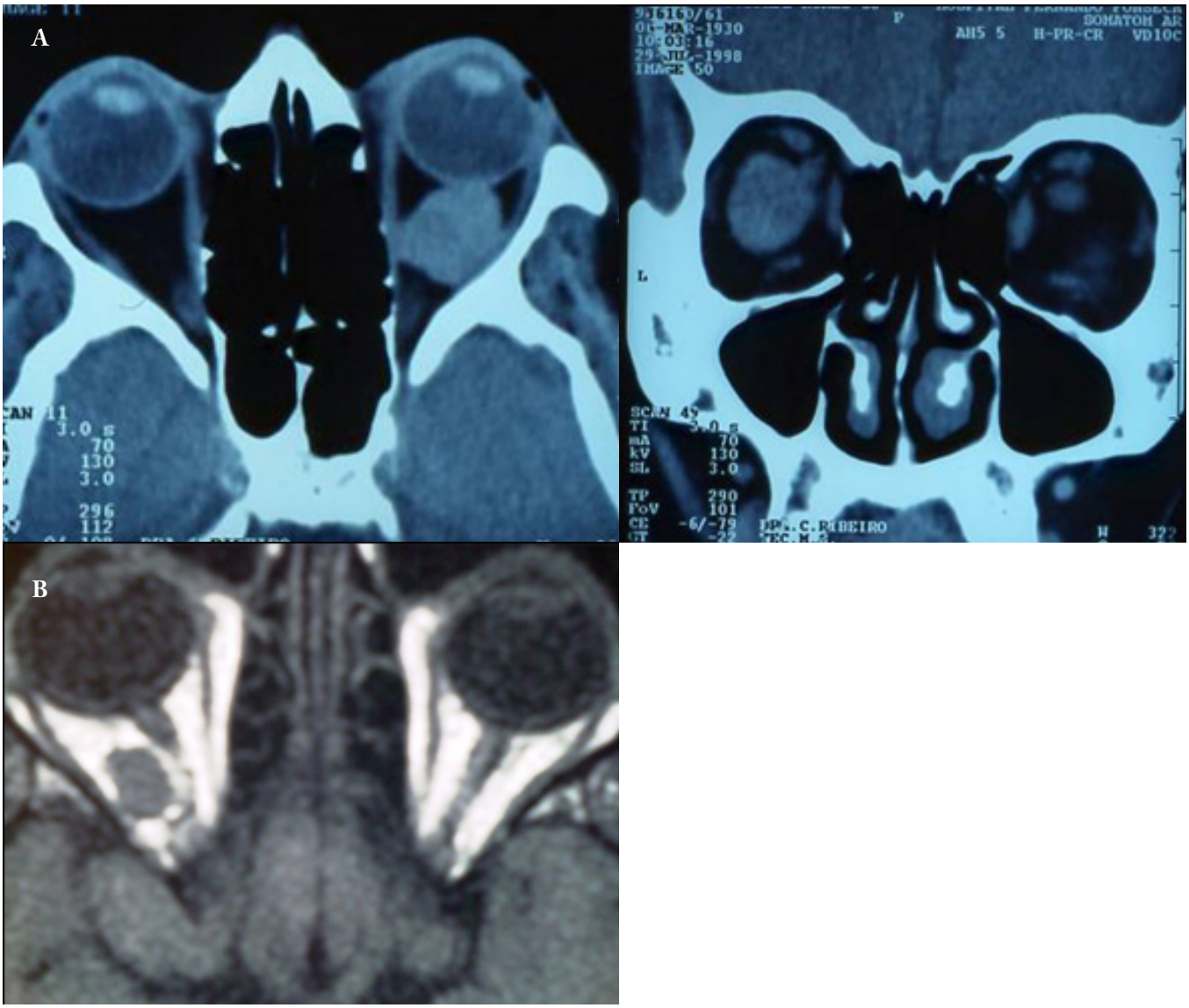


Figure 2. A,B Cavernous hemangiomas – for lateral approach

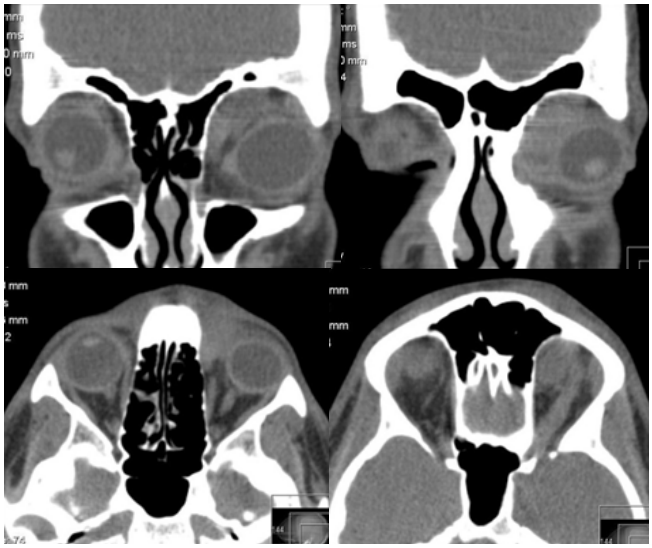


Figure 3. Anterior Lymphangioma – for transseptal approach

bending it anteriorly, the lateral wall of the orbit will break, and the orbital rim can be removed. The exposure is increased posteriorly by removing the lateral orbital wall to the pterion. These steps will expose the lateral periorbita and the lacrimal gland. The lateral orbital approach makes access to the lacrimal gland tumors relatively straightforward.
For intraconal lesions, enter the intraconal space by opening the periorbita antero-posteriorly above or below the lateral rectus.
When closing, there is no need to close the periorbita, and the orbital rim can be fixed with two titanium microplates (Fig. 7). However, to prevent dysfunction of the eyelid closure, special attention should be paid to the closure of the temporalis fascia behind the orbital rim, as well as the orbicularis layer. Subcutaneous and intradermal sutures are also used, ending with liquid tissue adhesive over the skin.

2 - ANTERIOR TRANSSEPTAL APPROACH

Neurosurgeons use the anterior transseptal approach mainly for superior orbital lesions, entering in the orbit laterally or medially to the supraorbital nerve (Fig. 8). A skin incision is

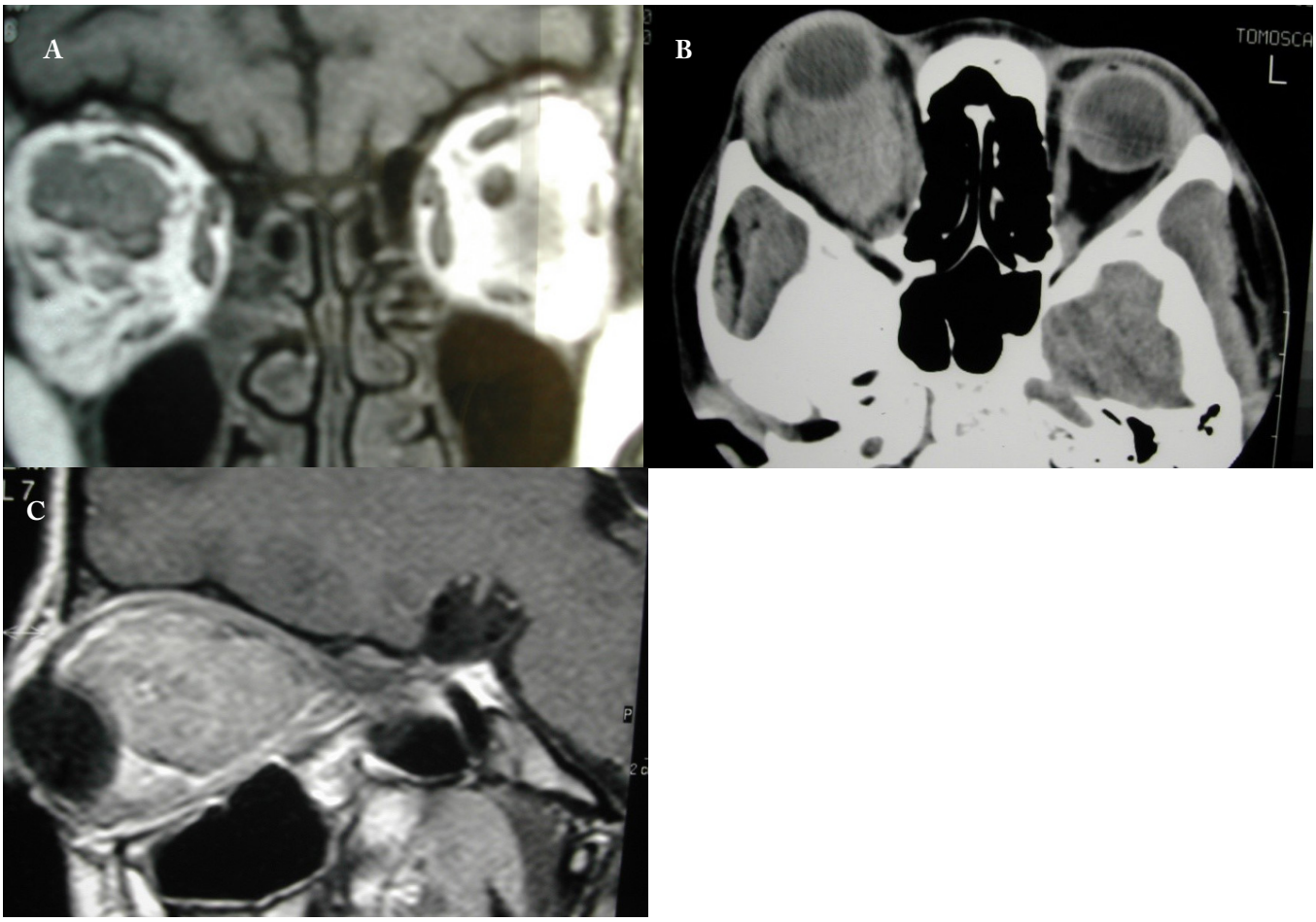


Figure 4. A,B,C. Lymphangioma – for transcranial approach

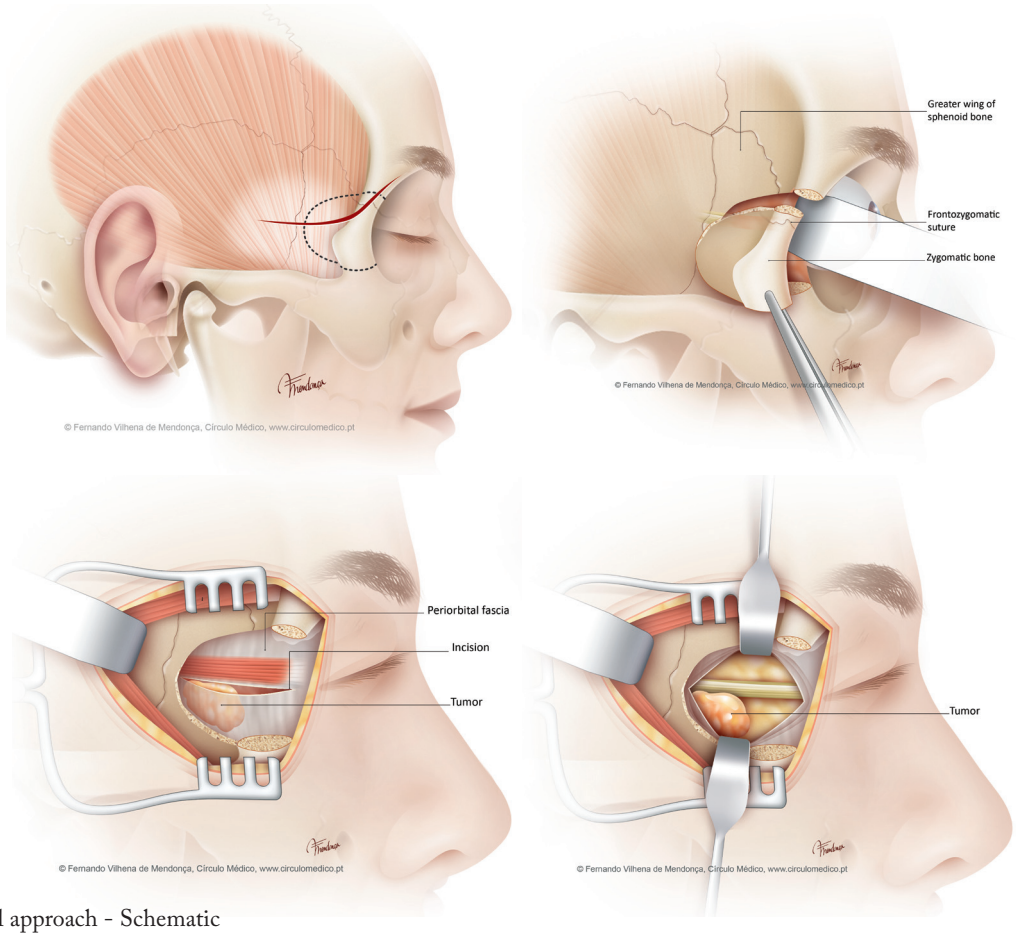


Figure 5. Lateral approach - Schematic

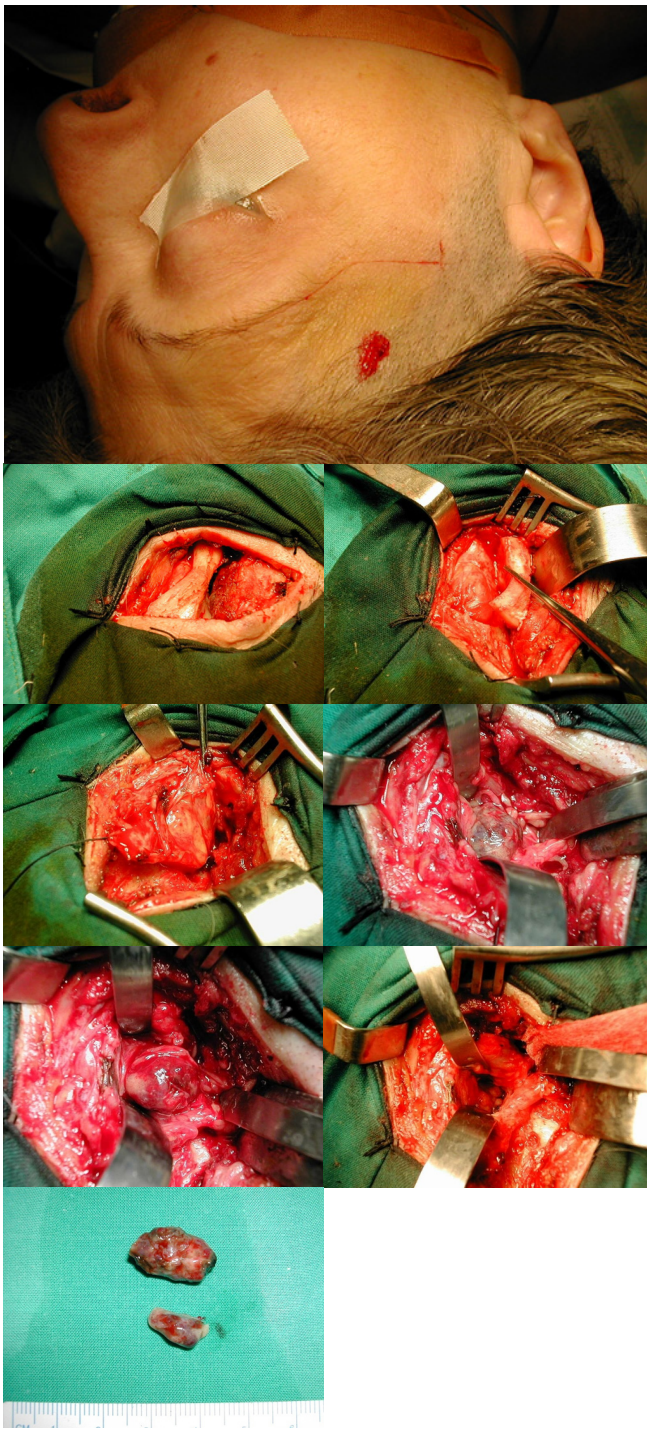


Figure 6. Lateral approach – operative photos (cavernous hemangioma of fig 2b)

created over the orbital rim, and the septum is opened on its insertion (Fig. 8). This is a very simple and quick approach, allowing access mainly to anterior lesions of the orbit, weather extraconal or subperiosteal, such as orbital roof fractures with muscle entrapment, subperiosteal abscesses, anterior lymphangiomas, or biopsies of lesions. When accessing the superomedial orbit with this approach, the superior oblique muscle's trochlea can be disinserted from the bone with a small periosteal elevator, taking care not to damage it (cautery for cutting or coagulation should not be used in this location). If the trochlea is not damaged, there is no need to reinsert it, as it

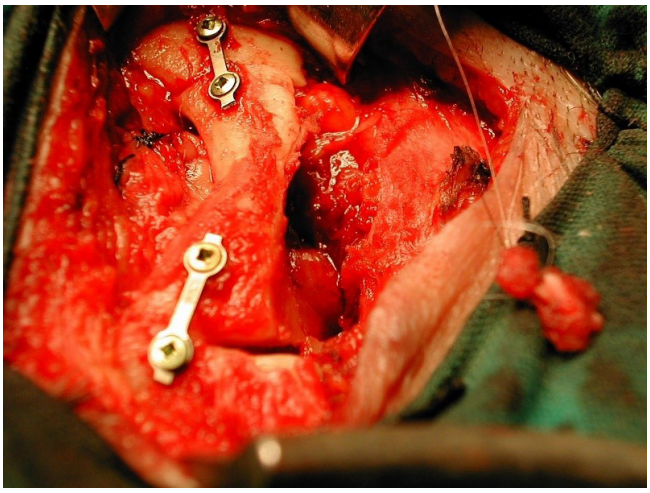


Figure 7. Titanium plates - lateral approach

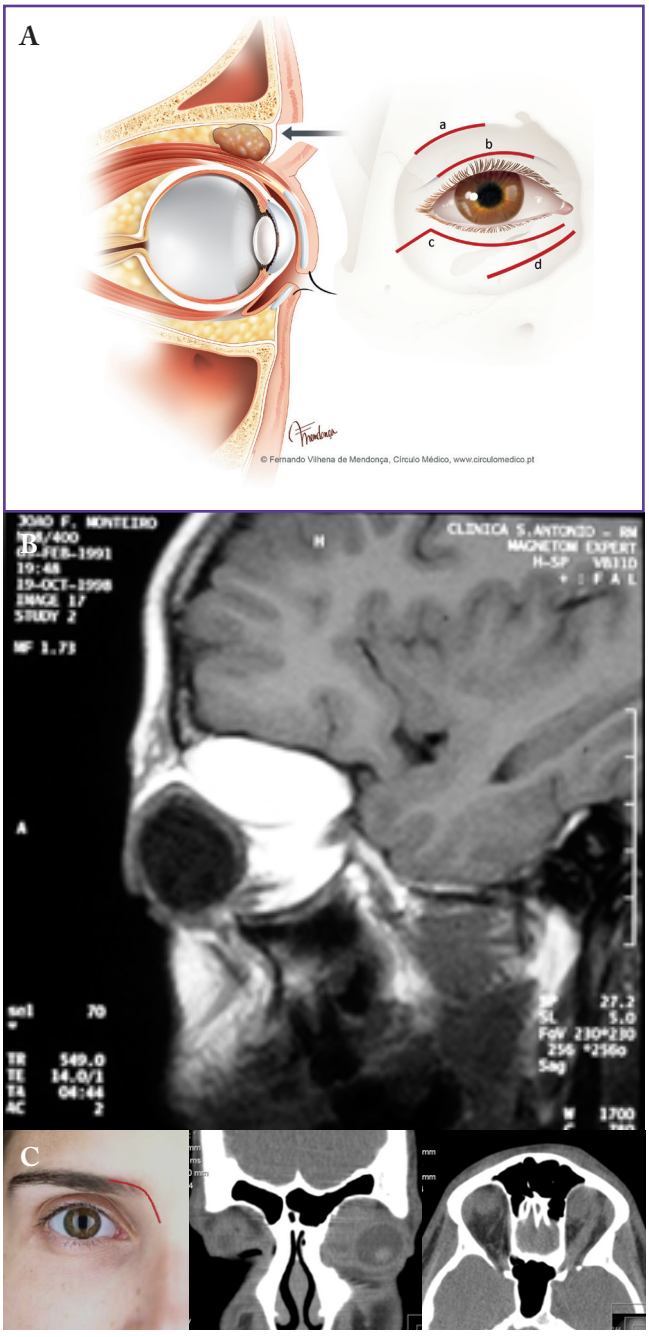


Figure 8. Transseptal approaches. a. Abcess; b. lymphangioma

will recover its function uneventfully.
When closing, one should be especially careful with the closure of the orbicularis, for the same reason previously explained in the lateral approach.

3 - TRANSCRANIAL APPROACHES

a) Supraorbital frontal approach (Fig. 9)

This approach described by Hassler *et al*. in 2009[1] uses an eyebrow incision to expose the frontal bone and superior orbital rim. A small supraorbital frontal craniotomy is performed, with or without removal of the superior orbital rim, allowing an epidural access to the orbital roof, which can be removed with small Kerrison rongeurs.

Depending on the location of intraconal lesions, the surgeon may choose to proceed lateral or medial to the superior palpebral elevator (SPE) and superior rectus muscles. The former provides a wider access and is less risky compared to the latter, where one risks injuring the trochlear nerve.

The supraorbital frontal approach has several drawbacks. Firstly, it is limited to lesions above the optic nerve (ON). Also, there is a frequent need to open the frontal sinus, increasing the risk of infection and cerebrospinal fluid (CSF) leak if the dura is opened. In addition, although likely temporary, the supraorbital nerve may be injured, with the consequent numbness of the forehead; and the manipulation and retraction of the SPE and superior rectus muscles can cause ptosis and monocular elevation paresis.

b) Pterional approach

One of the most used approaches in neurosurgery, pterional craniotomy, will only be summarized in this chapter. It is a fronto-temporal craniotomy with removal of the lateral 1/3 of the lesser sphenoid wing (pterion). After the craniotomy (Fig. 10), the orbital roof and lateral wall are removed either by high-speed drill and/or with small Kerrison rongeurs (or both) to expose the periorbita. The lesion defines the limit of the bone removal. For example, to widen the exposure anteriorly, the superior and lateral orbital rim can also be removed. With this approach the access is epidural: all the orbital roof and roof of the optic canal; the superior 2/3 of the lateral orbital wall; and, if necessary, the superior rim (lesser sphenoid wing with or without anterior clinoid process) and inferior rim (greater sphenoid wing) of the superior orbital fissure (SOF) are removed. This manoeuver allows decompression of the SOF or access to lesions in the orbital apex. Drilling the roof of the optic canal and opening the dura from the orbit to the falciform ligament will then allow exposure of the ON, and with intracranial subarachnoid dissection, one can access the ON from the eye to the chiasm (Fig. 11).

After exposure of the periorbita, the intraconal space may be accessed laterally or medially to the SPE and superior rectus muscles (Fig. 12). The lateral approach offers safe access to the intraconal space because it is wider and has no critical structures between the SPE/superior rectus and the lateral rectus. The medial approach is preferred for lesions medial to the ON and of the ON itself. The trochlear nerve found superiorly, en route to the superior oblique muscle, should be preserved (Fig. 12).

To expose the ON completely, the Zinn annulus has to be opened superiorly. After removing all the bone and opening the dura over the optic canal and exposing the ON, one should dissect from posterior (optic canal) to anterior (orbit) over the ON until the thickening of the dura that represents the Zinn annulus is found. With a micro nerve hook, the annulus should be separated from the ON, and with a small blade (ophthalmology blades are very useful at this point), it should be cut to expose the ON. If cut this way, reconstruction is not necessary.

This is an excellent approach for all superior lesions, lateral or medial to the ON, lesions of the ON itself, and lesions of the orbital apex and SOF, as well as for all lesions extending from or to the intracranial space.

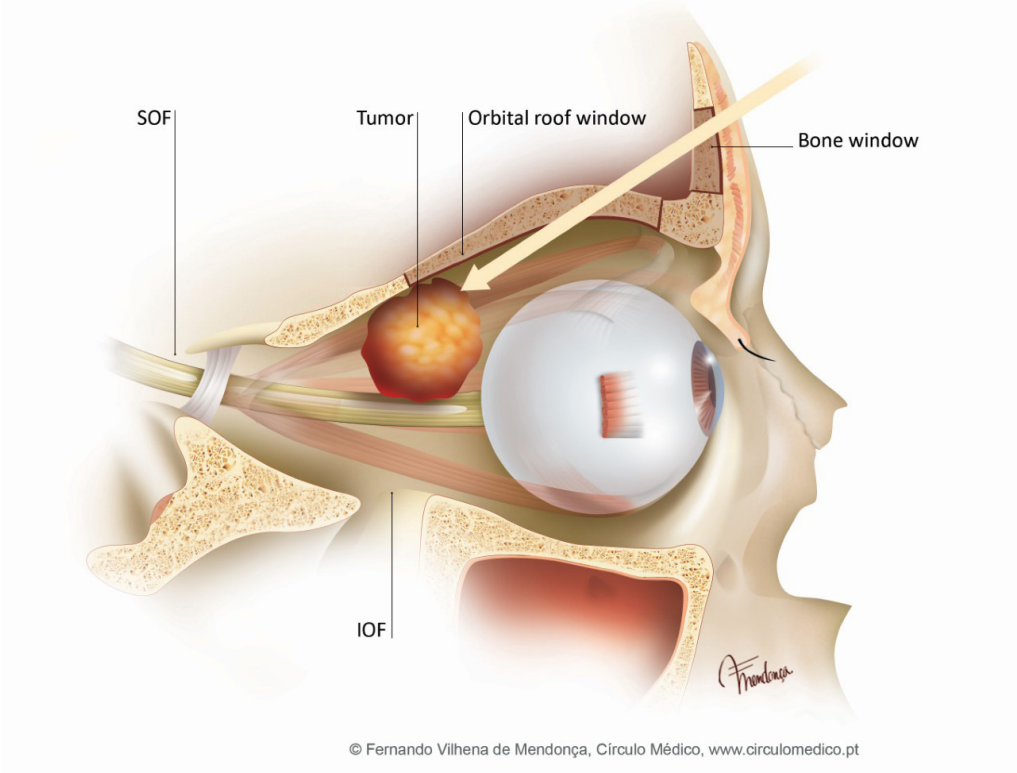


Figure 9. Fig from Hassler et al, Acta Neurochir (2009) 151:601-612

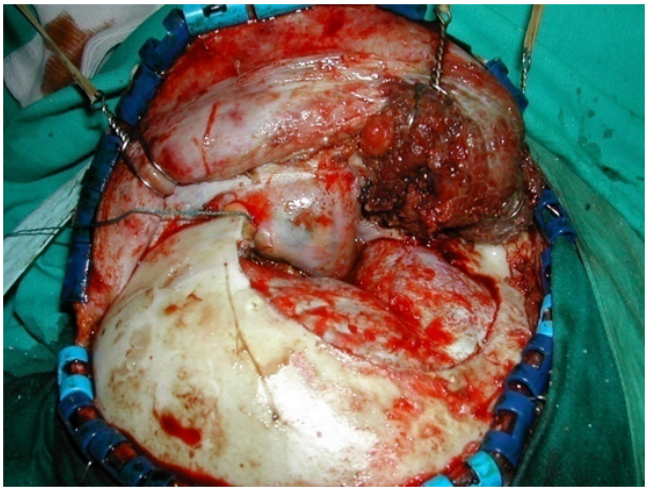


Figure 10. After pterional craniotomy and superolateral orbitectomy on the right (with orbital rim removal)

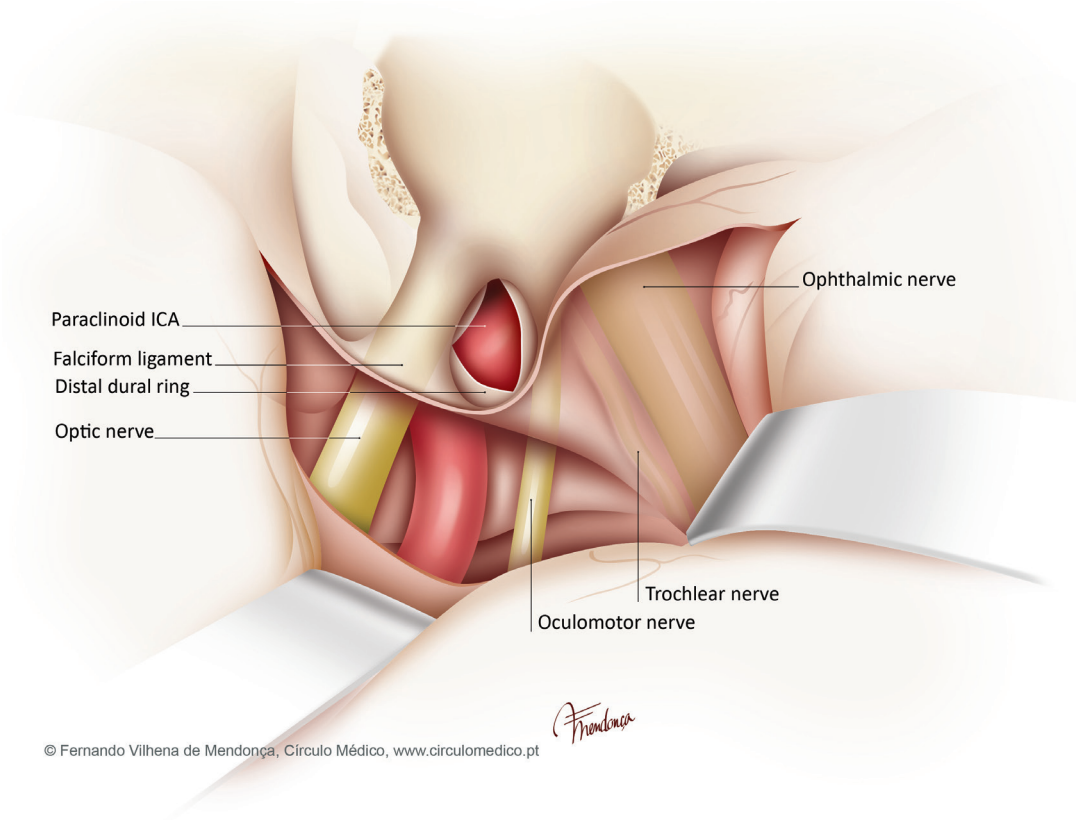


Figure 11. Optic nerve exposure from the eye to chiasm

GENERAL CONSIDERATIONS ON ORBITAL SURGERY:

Surgical technique

1. Always use the surgical microscope when performing intraconal surgery or when drilling the optic canal.
2. Inside the orbit, blunt dissection should be used most of the times, to avoid damaging the vessels and nerves.
3. Generally, only a few surgical instruments are needed when operating inside the orbit: suction, microdissector, micro nerve hook, microscissors, small Metzenbaum scissors, and a bipolar electrocautery.
4. Gentle finger palpation and/or ultrasound can be used to locate tumors and the posterior aspect of the eye.
5. Use three 5 mm retractors with the Greenberg retractor system to prevent orbital fat getting into the eyesight and covering the surgical field. To allow for even better visualization, verify that there are no important structures, and then carefully coagulate to shrink the fat .
6. Most of the intraconal lesions will occupy the space of the orbital fat. The Korneef septa envelop the lesions in concentric, onion-like layers which must all be opened to reveal the actual surface of the lesion.
7. In transcranial approaches, gain additional space without having to retract the brain by allowing CSF to drain through a small 1 cm opening of the dura, in front of the frontal lobe, and inserting a cottonoid into the subarachnoid space.
8. Bone removal achieves the surgical goal with minimum

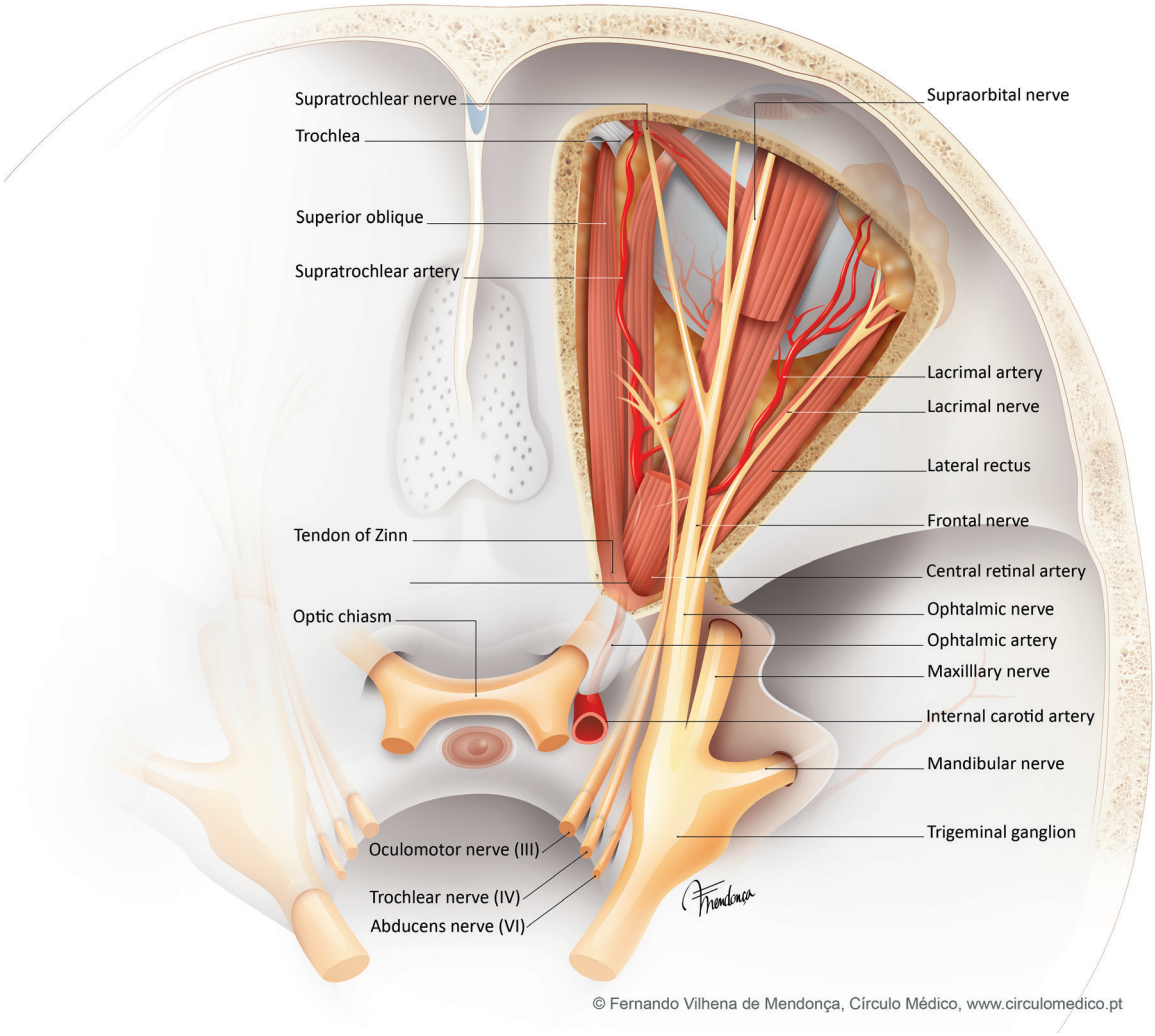


Figure 12. Access medial or lateral to the superior rectus muscle and superior palpebral elevator

retraction of noble structures such as the eye, brain, ON, etc. It is always better to remove more bone than to retract more because retracting may jeopardize vital structures. Besides, bone defects may be reconstructed at the end of surgery for functional or aesthetic reasons, if needed.

Postoperative period - what to be expected (depending on the type of surgery):

1. Palpebral edema/ecchymosis, worse in the first 48-72 hours
2. Conjunctival and ciliary congestion
3. Subconjunctival hemorrhage
4. Chemosis
5. Transient diplopia
6. Transient paresis of muscles manipulated during dissection
7. Transient mydriasis (ciliary nerves manipulation)
8. Temporary worsening of visual acuity

Ethical Disclosures
Conflicts of Interest: The author has no financial conflicts
Confidentiality of Data: Patient consent obtained.

Corresponding author
João Paulo Farias
joao.farias@jmellosaude.pt

REFERENCES

1. Hassler W, Schick U. The supraorbital approach--a minimally invasive approach to the superior orbit. Acta Neurochir. 2009;151:605-11; discussion 611-2.
2. McNab AA. Surgical anatomy of the orbit and lacrimal system. In: Manual of orbital and lacrimal surgery. 2nd ed. London: Elsevier Health Sciences; 1998. p 31-73.
3. Gardner PA, Maroon JC, Stefko ST. 161 Tumors of the orbit. In: Winn R, editor. Youmans and Winn Neurological Surgery. 7th ed. Amsterdam: Elsevier; 2016. Vol 4. p. 1310-21.

7. Combined Sino Orbital and Cranio Orbital approaches

OPHTHALMOLOGY
Michelle M. Maeng MD, Kyle J. Godfrey MD, Michael Kazim MD

Summary

Surgical treatment of complex, multi-compartmental orbital tumors requires a step-wise approach, in which tumor anatomy, pathology, and physiologic behavior guide preoperative surgical planning and postoperative management. First, a thorough clinical history and examination are preeminent in diagnosing and understanding the nature and potential sequelae of orbital disease. Radiographic imaging is essential, as radiographic appearance and location narrow the differential diagnosis, and guide further planning. A surgical approach is defined by tumor location and extension, with room for a multidisciplinary approach, when appropriate. Finally, surgically obtained histopathologic diagnosis suggests biologic behavior and informs subsequent medical and surgical management.

Keywords: *Orbit/surgery; Orbital Neoplasms/diagnosis; Orbital Neoplasms/diagnostic imaging; Orbital Neoplasms/surgery*

1. ORBITAL AND OPHTHALMIC EXAMINATION

Quality clinical evaluation is essential in defining parameters for timing and type of intervention necessary. Particular attention should be paid to cranial nerve function, including the optic nerve. Optic nerve function can be evaluated in the office setting through physical examination, visual field testing, and imaging modalities such as optical coherence tomography. Visual acuity evaluates only central visual function, and should always be performed with best correction (spectacles, contact lenses, or manual refraction). In the cases where refraction is not possible, vision improvement with a pinhole occluder can screen for uncorrected refractive error.[1] Pupils should be assessed for size, symmetry, regularity, reactivity, and measures of afferent and efferent function. The swinging light test assesses for the presence of an afferent pupillary defect, which can give additional information on asymmetric optic nerve dysfunction. Color vision testing complements visual acuity assessment and can be assessed grossly by evaluating differences in red color desaturation between eyes. The Hardy-Rand-Rittler (HRR) color plates can be used to screen for deutan (red-green) and tritan (blue-yellow) defects, which often accompany an optic neuropathy. Ishihara color plates are generally thought to be inferior in screening for dyschromatopias associated with acquired optic neuropathies.[2] Manual or automated perimetry provides a detailed evaluation of visual field, providing insight into degree and laterality of visual field loss as well as localizing information along the optic pathway. Visual evoked potential (VEP) testing measures electrical signals produced in response to a visual stimulus via electrodes placed on the scalp overlying the occipital cortex. This type of testing is clinically useful for evaluation of the visual pathway in a nonverbal patient or in verification of intact visual pathways in a patient with suspected nonorganic disease. Evaluation of remaining cranial nerves' function provides additional information on the extent and location of disease. Motor nerves include cranial nerves III, IV, VI, and VII, which can be assessed by function of extraocular movements and orbicularis oculi muscles. In the proper setting, eye muscle motility dysfunction can be quantified by prism measurements to monitor subtle changes over time. Sensory innervation can be evaluated by the ophthalmic, maxillary, and mandibular division of cranial nerve V, which can be evaluated by the degree of sensation in the subsequent areas innervated. Location and extent of pain can give further information on possible intraneural invasion. For example, orbital lesions may infiltrate nerves and produce pain, paresis, or loss of function, which can aid in localizing the lesion and informs the urgency of treatment. Additional clinical features may provide clues to how a tumor may behave intraoperatively and assist in stratifying risk for collateral damage. Globe displacement is the most common clinical manifestation of a space-occupying orbital abnormality. Visual inspection of proptosis can be made quickly from the "worm's-eye view" position, in which the examiner looks up from below the patient with the patient's head tilted back to assess relative position of the corneas. Further characterization can be made as to whether globe displacement is axial or nonaxial. Axial displacement is generally caused by intraconal masses posterior to the globe, whereas nonaxial displacement is indicative of lesions causing mass effect outside of the muscle cone. Exophthalmometry can be used to quantitatively measure the anterior-posterior position of the globe. The stand-alone measurement is not as important as the difference between the two eyes, as an asymmetry of greater than 2 mm suggests pathologic proptosis or enophthalmos. Quantitative measurements over time may also be helpful in surgical planning. Palpation of the globe is important as increased resistance to retropulsion suggests the presence of a retrobulbar mass or decreased compliance of orbital contents. Proptosis elicited or worsened by Valsalva movements is a particularly specific sign pointing towards distensible orbital lesions such an orbital varix. Lastly, auscultation with a stethoscope over the globe or mastoid bone may detect bruits in the cases of carotid-cavernous fistulas.

2. CHOOSING THE RIGHT IMAGING

The development of diagnostic radiologic modalities has allowed for more precise characterization of the nature

and extent of orbital lesions, aiding in medical and surgical management of disease. Computed tomography (CT) scanning can be rapidly acquired and provide excellent bone detail. Image quality and protocols are largely uniform across institutions and outpatient imaging facilities, providing ease of comparison. Despite the convenience, CT scans do expose patients to ionizing radiation. This is of particular concern in children or patients who may be exposed to numerous repeat scans for chronic or recurrent conditions. In all cases, one should ascertain appropriate protocols to minimize undue radiation risks, as well as weigh the risks and benefits of available imaging modalities, any necessary sedation, contrast solutions, timing, and cost to enable selection of the most appropriate imaging modality for the patient and the pathology.

Magnetic resonance imaging (MRI) offers highest soft tissue resolution, which allows for the best characterization of tumor masses when not associated with significant bony involvement. In general, masses that reside in the orbital apex or those that span into the cranium are better visualized with MRIs. While the study does not put the patient at risk for radiation, gadolinium-based contrast agents may cause nephrogenic systemic fibrosis (NSF) in patients with preexisting renal disease, and have been shown to accumulate in the brain with unknown clinical significance.[3,4] Patients with metallic foreign bodies or implants are also precluded from obtaining MRI imaging. MRI imaging can take anywhere from 15-90 minutes to perform, with the potential added risk of claustrophobia in some patients. Furthermore, imaging protocols, magnets, and interpretations can vary very across institutions, so care should be given when comparing different images over time.

Ultrasonography is another useful imaging modality that is relatively fast, cost-effective, noninvasive, and does not expose patients to ionizing radiation. With the added benefit of real-time imaging, it allows dynamic scanning to evaluate functional movement of the globe and surrounding contents. This imaging modality can be used as a screening modality for the anterior 2/3rd of the orbit.[5] With Doppler imaging, vascular pathology can be identified, such as orbital varix, arterio-venous malformations, carotid cavernous fistulas and capillary hemangiomas. Generalized soft tissue inflammation and trauma can also be evaluated by ultrasound.[6] However, it is generally not favored due to its poor resolution and lack of diagnostic accuracy. Ultrasound is a poor study to evaluate bone involvement, apex lesions, or intracranial extension.[5]

When evaluating radiographic imaging, a differential diagnosis is constructed based on the radiographic appearance of the lesion and surrounding tissues. Then, surgical planning is aided by localizing the mass in relation to the optic nerve as well as extension into intracranial and sinus compartments. The lesion margins, whether well demarcated or diffuse, will indicate how easily the lesion can be dissected away from surrounding structures and delivered through the surgical approach of choice. Additionally, signs of lesion consistency, whether solid, cystic, vascular, encapsulated, infiltrative, or heterogeneous, will have implications for intraoperative tumor handling and instrument choices. As such, orbital surgeons should always review their scans in preparation and planning. Clinical correlation should be assessed and aligned with imaging results. When imaging modality is called into question, CT scan is the preferred modality for screening, and dedicated orbit scans with contiguous thin slices (between 1-3 mm) should always be ordered.[5]

3. BIOPSY

Appropriate management of orbital lesions relies heavily on having the correct diagnosis. In an open biopsy, orbital exposure is made through various direct approaches described in this chapter to gain access to a portion of the mass to be biopsied, at the minimum. In such cases, a small portion of the lesion is obtained for histopathologic studies. Incisional biopsies are usually performed for lesions that are large, ill-defined, infiltrative, or near vital structures that need to be preserved. In contrast, excisional biopsy entails the removal of the lesion en bloc, both for diagnostic and treatment purposes. This approach has the best results for anteriorly located, well-circumscribed, small lesions. To date, incisional and excisional biopsies have been considered the gold standard for diagnosis of orbital lesions.[7]

Fine needle aspiration biopsy (FNAB) requires no incision and involves traversing a 22- to 25-gauge needle attached to a pistol type syringe to obtain samples for cytologic studies. This is an option for patients with deep or posteriorly located orbit tumors, in which open biopsies cannot be performed safely. FNABs can also be considered in patients with presumed metastatic disease in whom rapid minimally invasive technique is desirable.[8] Kennerdell *et al*. introduced CT-guided fine-needle aspiration biopsy for optic nerve tumors in 1980 and percutaneous biopsies have since been safely performed for hard-to-reach tumors, evading possible morbidity associated with major operative surgery.[9] FNAB is a less invasive approach, but the amount of tissue obtained can be much less than that of excision of incisional biopsy approaches, leading to a slightly lower diagnostic accuracy rate. More invasive biopsy approaches may need to be pursued when FNAB results are inconclusive or negative.

Whenever a lesion exists outside the confines of the orbit, the surgeon should consider the opportunity for safer and easier extraorbital biopsy locations. Exposure through the lateral wall, sphenoid bone, or infraorbital fissure can provide biopsy sites that may decrease the risk to intraorbital contents and optic nerve endangerment. Lymph nodes or other organs with metastases of malignant lesions may also provide additional biopsy locations in appropriate settings.

4. DEFINING THE SURGICAL APPROACH

The physiologic nature of the tumor in question can define the extent of the surgical procedure needed. Encapsulated lesions are best to resect in total if located in a safe location for surgical resection. Infiltrative and scirrhous lesions are generally approached with biopsy first in advance of further planning.

Traditional orbital approaches include anterior, medial, and lateral approaches. Tumors that span the orbital, sinus and intracranial spaces have been refined throughout the years and now largely encompass endoscopic transnasal and superior approaches, respectively. By thus approaching tumors directly through these various approaches, the surgeon can optimize exposure and minimize residual deficits.

Endoscopic transnasal approaches, as often performed

with otolaryngology experts, are useful in medially based lesions and can be used in isolation or in conjunction with transcaruncular orbitotomy. Endoscopic approaches have the benefit of avoiding skin incisions and brain retraction through a minimally invasive technique to the ventral skull base, orbit, and orbital apex regions.[10,11] Lesions with extension into the ethmoidal, maxillary, or pterygopalatine fossas may be considered for this approach. Anatomically, medial or inferomedial masses are most easily assessable. Additional exposure can be made through a transantral approach or in conjunction with orbital floor removal. Tumors of the superior and lateral orbit are generally difficult to access transnasally because the optic nerve lies in the path of extraction. In general, lesions that extend lateral to the optic nerve should be approached with extreme caution and careful planning as crossing this vital structure could result in loss of vision.[12]

The superior approach by means of craniotomy is the preferred neurosurgical technique for cranio-orbital disease as well as orbital lesions arising in the orbital apex and/or optic canal.[13,14] Transcranial surgery in the orbit is predominantly divided into two approaches. The first utilizes a bicoronal incision to remove frontotemporal bone and preserve the supraorbital rim. Entry into the superior and anterior confines of the orbit is gained superiorly to the levator and superior rectus muscles. The more commonly used approach uses a bicoronal incision to remove the frontotemporal bones along with the supraorbital arch, providing visualization of the orbital contents with minimal retraction of the brain (Fig. 1). Exposure is best for tumors that sit in the superior/posterior orbit or orbital-cranial junction, such as the sphenoid wing meningiomas and gliomas for which intracranial and intraorbial resection is necessary.[14,15]

5. COMMON ORBITAL TUMORS

Common pediatric tumors of the orbit that can extend into the sinus or intracranial spaces consist of dermoids, lymphangiomas, gliomas, and rhabdomyosarcomas. Orbital dermoids are cystic lesions that are classically found superotemporally along the region of the zygomaticofrontal or superonasally to the orbital rim along suture lines. On imaging, lesions are smooth, well defined non-enhancing masses, with cystic, solid, or calcified regions. Orbital dermoids are commonly associated with bony changes on CT, such as irregular scalloping of neighboring bone.[16] Surgical management requires complete removal of the lesion with its capsule intact, to prevent inflammation, recurrence, or fistulization.[17]

Venolymphatic malformations are orbital lesions that form from vascular dysgenesis, containing both venous and lymphatic components. They are characteristically associated with enlargement during upper respiratory tract infections and can present with sudden proptosis from spontaneous intralesional hemorrhage or thrombosis. Purely distensible venous varices classically present with increased exophthalmos with Valsalva maneuvers, but enophthalmos may be noted in long-standing lesions due to atrophy of adjacent fat.[18] On MRI, the finding of multiple grapelike cystic lesions with fluid-fluid layering is a pathognomonic finding. In symptomatic patients, injection of intralesional sclerosing agents with cystic drainage, coil embolization, carbon dioxide laser surgery, cyanoacrylate glues, with or

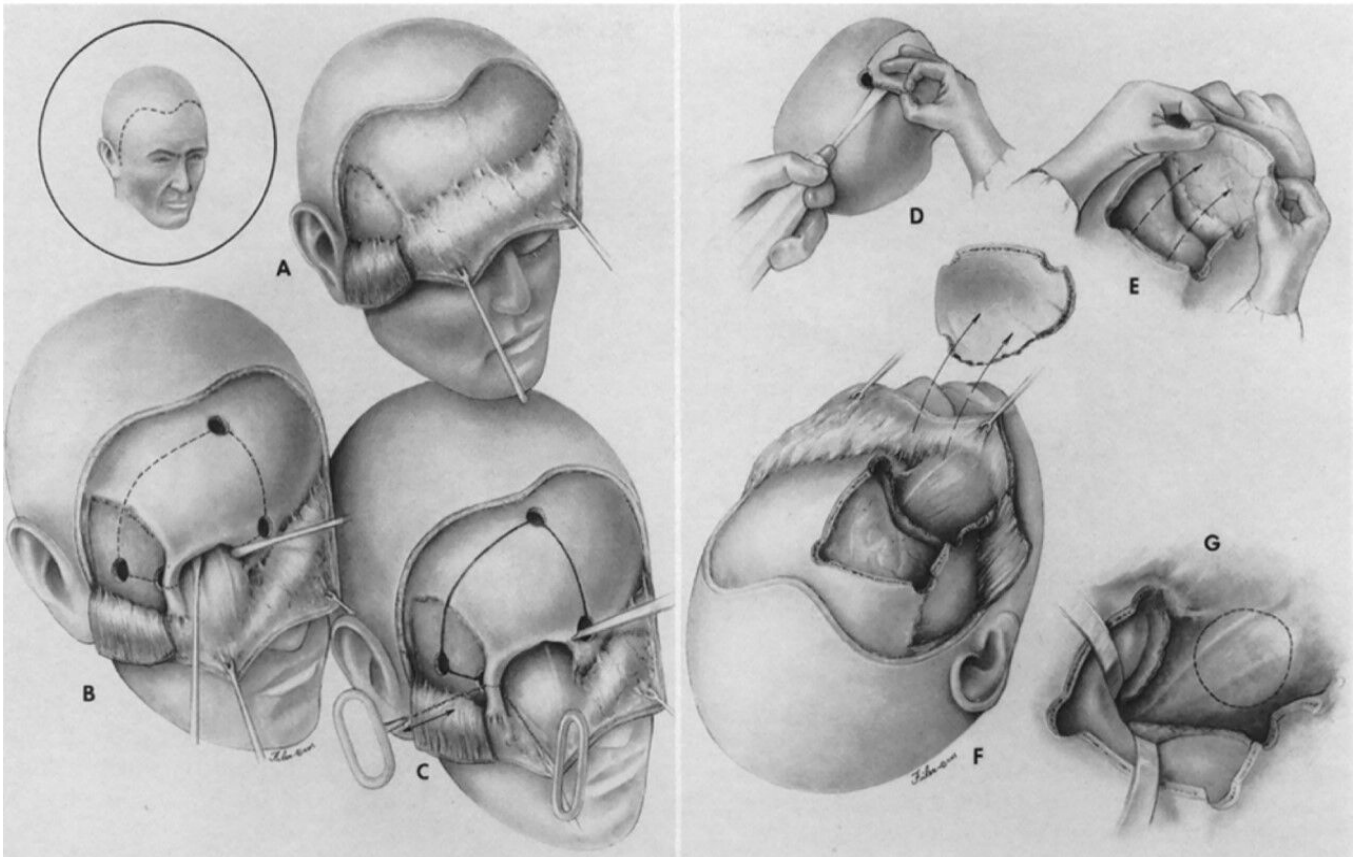


Figure 1. Transcranial approach to the superior orbit using a bicoronal flap and supraorbital arch removal. Reproduced with permission of Maroon JC, et al. JS. Surgical approaches to the orbit. Indications and techniques. J Neurosurg. 1984; 60:1226-35[14]

without surgical excision are pursued to reduce tumor bulk for subsequent subtotal resection when necessary.[18,19]

Optic nerve gliomas are commonly associated with neurofibromatosis 1, but can also be found sporadically in young adults. On CT imaging, lesions can be observed as a spindle-shaped thickening of the optic nerve on axial views and rounded, enlarged lesions on coronal views. In cases threatening chiasmal invasion, optic nerve gliomas can be resected through a transcranial approach.[13]

Rhabdomyosarcoma is the most common primary orbital maglinancy of childhood, classically presenting with sudden onset, rapidly progressing unilateral proptosis. Urgent workup with imaging would determine the extend of the lesion, but biopsy, likely through an anterior orbital approach, should be undertaken for definitive diagnosis.[20]

The most common orbital tumors found in adults consist of cavernous hemangiomas, schwannomas, osteomas, lymphomas, and metastases, all of which can extend into neighboring compartments. Cavernous hemangiomas are well-circumscribed, ovoid lesions that enhance with contrast imaging. Surgically, these lesions will typically have a clear plane of cleavage that allows for a more straightforward dissection and en-bloc resection. The exceptions are those filling the orbital apex, which may be seen to envelope neurovascular tissue making resection challenging.

Orbital schwannomas are proliferations of Schwann cells, encapsulated by perineurium. Surgical resection is directed by location and complete removal is usually possible due to the nature of the lesion.

Osteomas of the orbit are benign tumors that involve any of the periorbital sinuses. On CT imaging, lesions will appear densely hyperostotic with well-defined margins. When symptomatic, complete excision is advised via a sino-orbital approach.

The majority of lymphoproliferative lesions in the orbit are non-Hodgkin B-cell lymphomas, often located anteriorly or beneath the conjunctiva, where they may appear as a classically described salmon-patch lesion. Orbital imaging is characteristic for puttylike molding of the tumor to normal structures without bony erosion or infiltration.[21] Open biopsy is generally preferred prior to treatment of orbital lymphomas.

Metastatic lesions are mainly found in older patients and occasionally present with enophthalmos, common in scirrous breast cancer, instead of the classic picture of exophthalmos. The most common lesions that metastasize to the orbit include breast, prostate, and melanoma, but a metastatic tumor should be included in the differential diagnosis for any patient with cancer history and orbital findings.

6. MULTIDISCIPLINARY APPROACH

A great variety of tumors and mass lesions that occur in the orbit are of interest to several surgical disciplines, and coordination amongst a multidisciplinary team can be valuable when planning and implementing management. Neuroradiology colleagues are pivotal in the initial impression, characterizing precise tumor type and location to aid in surgical planning and monitoring of masses. Interventional radiology can be consulted to devascularize lesions through transarterial or transvenous embolizations, making the tumors safer for resection. Oculoplastic surgeons can clinically monitor for specific ocular signs and symptoms while surgically specializing in numerous direct orbital approaches. Neurosurgeons allow access to tumors through various transcranial and superior approaches. Otolaryngologists and Oral Maxillofacial surgeons utilize direct and endoscopic approaches through sinuses bordering the superior, medial, and inferior margins of the orbit. Neurosurgical surgeons can aid in the resection or biopsy of lesions with intracranial extension. Plastic Surgery specialists can aid in the craniofacial reconstruction of bony and soft tissue anatomy, with possible utilization of 3-D printing technology when appropriate.[22] Depending on the nature of the tumor, Radiation and Medical Oncology subspecialties are particularly useful in providing primary, adjuvant, definitive, or ongoing care for the patient. Such sequential multidisciplinary expertise ensures maximal safety and complete care for each patient with orbital pathology.

In summary, when considering complex orbital tumors, a methodical approach can be utilized to optimize diagnostic and therapeutic interventions while minimizing morbidity – proceeding from clinical exam, to imaging, to biopsy, to definitive treatment. A thorough clinical history and physical examination provide diagnostic clues and localizing signs that may still be more sensitive and precise than modern imaging modalities. Each of the various orbital imaging modalities has relative strengths, so the clinical scenario should dictate the most appropriate study. Tissue biopsies further elucidate the biologic nature of the tumor, and minimally invasive biopsy approaches can be employed in the appropriate context. The optimal surgical approach depends on lesion location, behavior, and surgical goals. In the appropriate context, such as large tumors with extension into the sinuses or cranium, multidisciplinary approaches should be considered. Common orbital tumors in adults and children have myriad clinical, radiographical, and histopathological findings that are useful from early planning stages to later treatment phases. When approached in this fashion, surgeons and patients can achieve excellent aesthetic and functional outcomes, even in the face of significant multi-compartmental orbital disease.

Ethical Disclosures

Conflicts of Interest: The authors have no financial conflicts

Corresponding Author:
Michelle M. Maeng
mmm2412@cumc.columbia.edu

REFERENCES

1. Loewenstein JI, Palmberg PF, Connett JE, Wentworth DN. Effectiveness of a pinhole method for visual acuity screening. Arch Ophthalmol. 1985; 103: 222-3.
2. Huna-Baron R, Glovinsky Y, Habot-Wilner Z. Comparison between Hardy-Rand-Rittler 4th edition and Ishihara color plate tests for detection of dyschromatopsia in optic neuropathy. Graefes Arch Clin Exp Ophthalmol. 2013; 251: 585-9.
3. Guo BJ, Yang ZL, Zhang LJ. Gadolinium deposition in brain: current scientific evidence and future perspectives. Front Mol Neurosci. 2018; 11: 335.
4. Shah AH, Olivero JJ. Gadolinium-induced nephrogenic systemic fibrosis. Methodist Debakey Cardiovasc J. 2017; 13: 172-3.
5. Hande PC, Talwar I. Multimodality imaging of the orbit. Indian J Ra-

diol Imaging. 2012; 22: 227-39.
6. Grech R, Cornish KS, Galvin PL, Grech S, Looby S, O'Hare A, et al. Imaging of adult ocular and orbital pathology--a pictorial review. J Radiol Case Rep. 2014; 8: 1-29.
7. Wiktorin ACH, Dafgård Kopp EME, Tani E, Söderén B, Allen RC. Fine-needle aspiration biopsy in orbital lesions: a retrospective study of 225 cases. Am J Ophthalmol. 2016; 166: 37-42.
8. Rubin PA, Remulla HD. Surgical methods and approaches in the treatment of orbital disease. Neuroimaging Clin N Am. 1996; 6: 239-55.
9. Kennerdell JS, Dubois PJ, Dekker A, Johnson BL. CT-guided fine needle aspiration biopsy of orbital optic nerve tumors. Ophthalmology. 1980; 87: 491-6.
10. Castelnuovo P, Turri-Zanoni M, Battaglia P, Locatelli D, Dallan I. Endoscopic endonasal management of orbital pathologies. Neurosurg Clin N Am. 2015; 26: 463-72.
11. Tsirbas A, Kazim M, Close L. Endoscopic approach to orbital apex lesions. Ophthalmic Plast Reconstr Surg. 2005; 21: 271-5.
12. Curragh DS, Halliday L, Selva D. Endonasal approach to orbital pathology. Ophthalmic Plast Reconstr Surg. 2018; 34: 422-7.
13. Carrizo AG. Transcranial Approach to Lesions of the Orbit. In: Quinones-Hinojosa A, editor. Schmidek & Sweet Operative Neurosurgical Techniques: Indications, Methos, and Results. Amsterdam: Elsevier; 2006.
14. Maroon JC, Kennerdell JS. Surgical approaches to the orbit. Indications and techniques. J Neurosurg. 1984; 60: 1226-35.
15. Kennerdell JS, Maroon JC, Malton ML. Surgical approaches to orbital tumors. Clin Plast Surg. 1988; 15: 273-82.
16. Nugent RA, Lapointe JS, Rootman J, Robertson WD, Graeb DA. Orbital dermoids: features on CT. Radiology. 1987; 165: 475-8.
17. Shields JA, Shields CL. Orbital cysts of childhood--classification, clinical features, and management. Surv Ophthalmol. 2004; 49: 281-99.
18. Islam N, Mireskandari K, Rose GE. Orbital varices and orbital wall defects. Br J Ophthalmol. 2004; 88: 1092-3.
19. Harris GJ, Sakol PJ, Bonavolontà G, De Conciliis C. An analysis of thirty cases of orbital lymphangioma. Pathophysiologic considerations and management recommendations. Ophthalmology. 1990; 97: 1583-92.
20. Shields CL, Shields JA, Honavar SG, Demirci H. Clinical spectrum of primary ophthalmic rhabdomyosarcoma. Ophthalmology. 2001; 108: 2284-92.
21. Sullivan TJ, Whitehead K, Williamson R, Grimes D, Schlect D, Brown I, et al. Lymphoproliferative disease of the ocular adnexa: a clinical and pathologic study with statistical analysis of 69 patients. Ophthalmic Plast Reconstr Surg. 2005; 21: 177-88.
22. Callahan AB, Campbell AA, Petris C, Kazim M. Low-cost 3D printing orbital implant templates in secondary orbital reconstructions. Ophthalmic Plast Reconstr Surg. 2017; 33: 376-80.

Section 3

Orbital Inflammation

8. Orbital Inflammatory Disease

OPHTHALMOLOGY
Sara Filipa Teixeira Ribeiro, MD, PhD, FEBO; Jorge Vasco Costa, MD; Marco Sales-Sanz, MD, PhD, FEBO

Summary

Orbital inflammatory disease is a benign inflammatory condition. It is usually confined to the orbit and can affect any structure. Extraorbital extension may however occur. Diagnosis is based on a detailed clinical history, a careful eye examination, and imaging findings. Biopsy is usually reserved for unusual cases. The mainstay of treatment is the administration of corticosteroids. Alternative therapies such as targeted immunotherapy with biologic medications have assumed an important role in the treatment of these diseases.

Keywords: *orbital myositis; dacryoadenitis; orbital Inflammatory diseases; orbital pseudotumor; idiopathic orbital inflammation; IgG4-related ophthalmic disease; specific orbital inflammation.*

INTRODUCTION

Orbital inflammatory disease (OID) represents a diverse spectrum of conditions unified in their association with abnormal inflammation in the periorbital region.[1-3] These pathologies can be placed into two groups, nonspecific orbital inflammatory disease and specific orbital inflammatory disease.[2] The nonspecific orbital inflammatory cases are usually divided into 5 categories: anterior, apical, lacrimal, myositic and sclerosing.[1-3] The knowledge of OID has been refined over the last few years, specially the entity of sclerosing OID, comprising both IgG4-related and IgG4-non-related sclerosing inflammation.[1,2,4] With the new advances and the description of new entities, the idiopathic orbital inflammatory syndrome group became smaller. This review is organized according to the two subgroups mentioned. Within each disease category, specific diseases and their associated therapies will be addressed.

1) IDIOPATHIC ORBITAL INFLAMMATORY SYNDROME (ORBITAL PSEUDOTUMOR)

Idiopathic orbital inflammatory syndrome (IOIS), also known as orbital pseudotumor, is a rare nonmalignant heterogeneous group of disorders that are not secondary to any identifiable local or systemic cause.[5] Although it was first described in 1905 by Birch-Hirschfeld as "orbital pseudotumor", there is still a clear lack of understanding about its etiology, aggravated by the variety of clinical and histologic presentations of the disease.[6] Viral infection and immune-mediated processes have been suggested, but its exact pathogenesis remains a mystery.[7] The incidence is greater in the 4th and 5th decades, and no gender or race predisposition has been found.[6] Since the inflammation can compromise any and every orbital structure, there is a wide spectrum in clinical presentation, clinical course, and outcome. Patients with IOIS usually present with acute unilateral onset of proptosis and eyelid swelling associated with orbital pain, chemosis, conjunctival injection, and double vision.[5] However, in a minority of patients, the clinical course can be bilateral, subacute or even chronic. Patients can also complain of decreased visual acuity, altered color perception or visual field defects, which are signs of optic nerve compromise. These symptoms emerge from an idiopathic inflammation of the orbit, characterized by a polymorphous orbital infiltration of lymphocytes and plasma cells with variable fibrosis and mass effect. Usually, this disease is classified according to the affected anatomic structures. However, it can also be stratified based on pathological findings. Since there is a wide variety of presenting symptoms and signs, other orbital and systemic conditions may mimic IOIS. Orbital cellulitis, thyroid eye disease, sarcoid lymphoma, lymphangioma, metastatic carcinoma, and ruptured dermoid cyst are amongst those who are more often considered in the differential diagnosis. Computed tomography (CT) and magnetic resonance imaging (MRI) scans (always along with clinical examination) can often distinguish each disease based on radiographic characteristics. IOIS usually have a prompt and effective improvement with systemic corticotherapy, but inflammation associated with other conditions may also improve with this treatment. We will discuss to a great extent the pathophysiology of this disease, as well as the differential diagnosis. We will also debate the most important aspects concerning imaging, treatment, and prognosis.

Etiology

Currently, the pathoetiology of IOIS is still unknown. Notwithstanding, multiple studies have tried to find an explanation to the origin, progression and great variability of this disease. Viral, allergic and autoimmune mechanisms have been theorized as potential factors involved in its pathogenesis. Some reports, such as those by Alsaikh, Kawasaki and Badilla, have linked upper respiratory tract infections and viral illness to IOIS.[8-10] However, the often-described association with certain rheumatologic disorders, such as giant cell arteritis, systemic erythematosus lupus, ankylosing spondylitis, and rheumatoid arthritis suggest that IOIS may have an autoimmune background.[11,12] Based on the nature of the cells found in biopsies, it is presumed that this is an immune-mediated condition, mediated by both B and T lymphocytes. The rapid response of inflammation to corticosteroids and other immunosuppressive agents also supports this theory,

although a direct correlation with systemic disorders cannot be made. In conclusion, whether this is an environmentally triggered immune event or a genetically predetermined autoimmune condition remains a mystery.

Pathology

Histopathology reveals a benign, nonspecific inflammatory pattern with varying degrees of granulomatous inflammation, lymphocytes, macrophages, eosinophils, fibrosis, and sclerosis.[5] Although there is a significant overlap, some authors tried to subgroup IOIS pathologically. The classification system described by Mombaerts is the most widely accepted for histologically classifying IOIS.[13] It divides IOIS into 5 distinct forms. This classification is summarized in Table 1.

Table 1 Mombaerts histopathological classification.

Histopathology	Features
Classical lymphocytic IOIS	Predominant inflammatory cells (mostly mature lymphocytes), increased amount of connective tissue with variable amounts of tissue edema and fibrosis
Sclerosing IOIS	Predominant connective tissue sclerosis and hyalinization, scarcity of inflammatory cells
Granulomatous IOIS	Histiocytic infiltration and multinuclear giant cells
Vasculitic IOIS	Vasculitis of the small blood vessels
Eosinophilic IOIS	Predominant eosinophilic inflammation

Adapted from: Mombaerts I, et al. What is orbital pseudotumor? Surv Ophthalmol. 1996;41:66-78.13

Clinical classification

Although the histological classification has a well-validated role in the differentiation and prognosis of this disease, truth is that there is a significant overlap between the different suggested subgroups.[14] Additionally, sometimes one subgroup can later evolve and develop into another subgroup.[5] A more clinical and anatomic classification is usually preferred in everyday practice.

Several classifications have been described but consensus has yet to be reached. We find that the classification of this disease into 5 different categories is the most intuitive and helpful way to differentiate this illness. The last category (sclerosing IOIS) is the most indolent one, while the other four usually have an acute onset. It separates IOIS into groups that are unique with regards to their differential diagnosis, evaluation, and treatment.

1. Anterior/Sclerotenonitis: The inflammation is focused on the sclera and surrounding tenon capsule. Patients usually experience pain, proptosis, ptosis, chemosis, and conjunctival hyperemia. Complaints of visual loss are also frequent. This is the most common form in children albeit it can occur at any age.[14] Imaging reveals anterior irregular orbital and globe inflammation associated with retinochoroidal thickening (Fig. 1). Echography can demonstrate sclerotenonitis with edema and swelling of Tenon's space. This phenomenon doubles the shadow of the optic nerve and creates a specific sign called the T-sign.[14] Fundoscopic anomalies can be present, namely choroidal folds, exudative retinal detachment, papillitis, and uveitis. Oral corticosteroids are the standard treatment and characteristically patients have an excellent response.

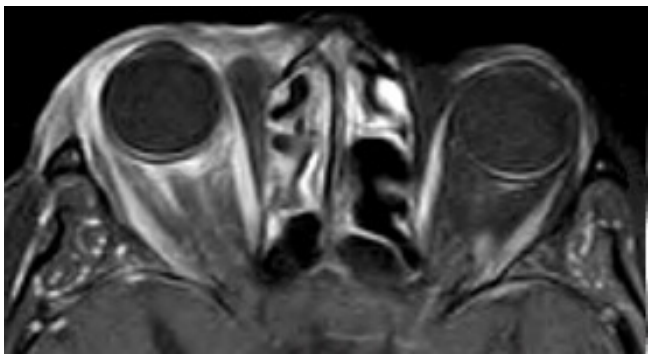


Figure 1. Right anterior irregular inflammation with tenonitis.

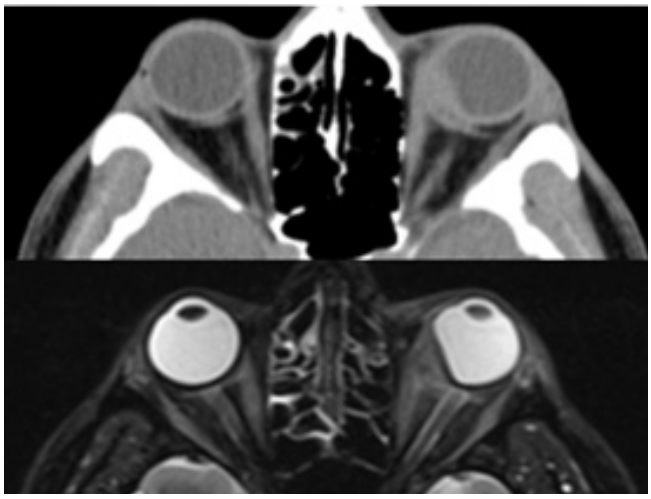


Figure 2. Left eye diffuse inflammation on CT scan (above) and STIR MRI scan (below). Besides the inflammatory mass in the medial posterior aspect of the eye globe, we can also observe mild fat and nerve sheath involvement.

2. Apical inflammation/Tolosa-Hunt syndrome (THS): This is a specific syndrome that is also considered another variant of IOIS. There is a granulomatous inflammation of the superior orbital fissure and/or cavernous sinus which usually manifests as acute, unilateral painful ophthalmoplegia (Fig. 3). The 3rd nerve is the most commonly affected cranial nerve, followed by the 6th, 5th and 4th nerves.[15] Since there are several causes of painful ophthalmoplegia, the diagnosis of THS remains one of exclusion. This condition may appear at any age and equally affects males and females.[16] CT scans are helpful to exclude bone erosion but MRI is more sensitive for cavernous sinus involvement. It typically demonstrates enhancement and enlargement of the cavernous sinus with extension to the

orbital apex. THS is very responsive to corticosteroid therapy. However, half of the patients experience recurrent episodes in the ipsilateral or contralateral orbit.[3]

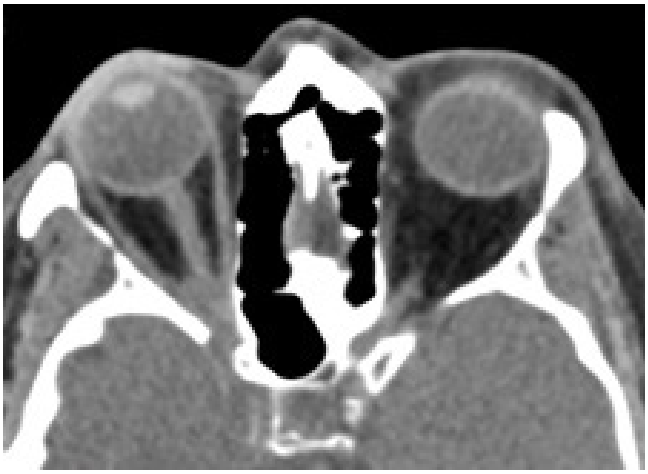


Figure 3. Tolosa-Hunt syndrome. Apical inflammation with severe painful ophthalmoplegia.

3. Myositis: Orbital myositis occurs in multiple forms and may be recurrent, unilateral or bilateral, acute or chronic, and may involve one or multiple extraocular muscles.[16,17] Rootman reported that the muscles most commonly involved were the superior and medial rectus.[18] Myositis has a female predilection. Diplopia, pain, proptosis, and external signs of inflammation are common in the acute inflammatory phase. The typical examination reveals proptosis and a motility limitation in the field of action of the inflamed muscle, with variable external signs such as chemosis.[16] This subtype is the most frequently mistaken for thyroid orbitopathy. Clinical distinction can usually be made based on the fast development of myositis and its characteristic symptoms. Imaging distinction is made by the diffuse involvement of the muscle and tendon on CT and MRI, in contrast to the swelling of only the muscle portion on thyroid orbitopathy. Corticosteroids are classically the mainstay of treatment of orbital myositis (Fig. 4).[2,3,16,19,20]

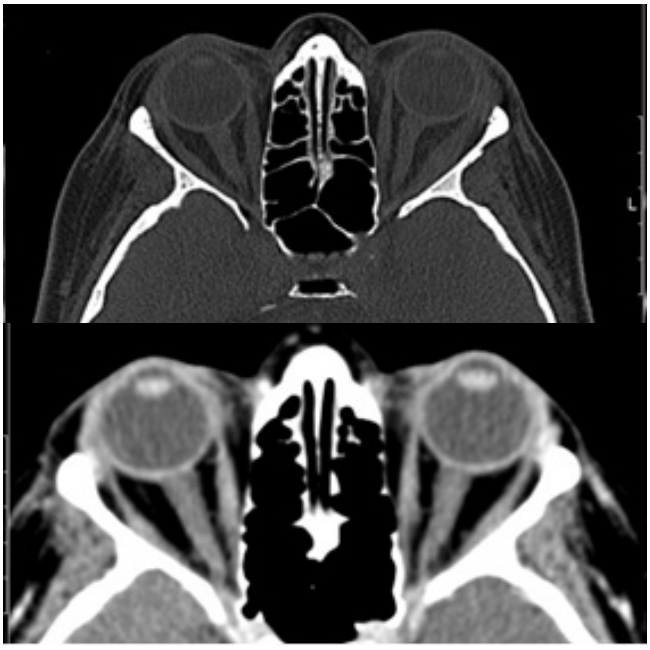


Figure 4. Lateral rectus myositis (left eye) before (left) and after (right) corticosteroids therapy.

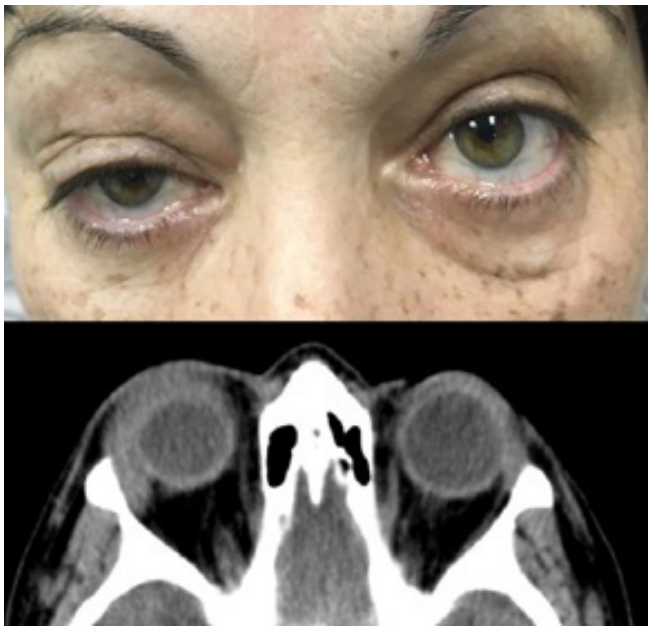


Figure 5. Right dacryoadenitis. The upper image shows the typical swelling of the upper eyelid.

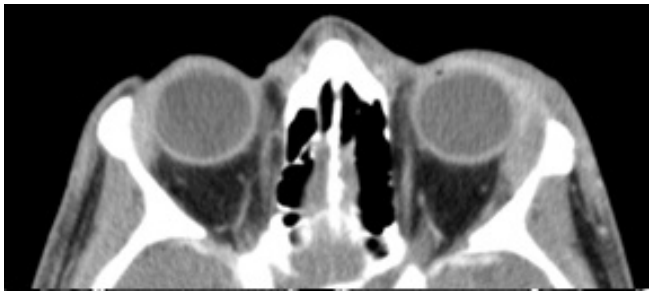


Figure 6. Exuberant dacryoadenitis of the left orbit.

4. Dacryoadenitis: It's the idiopathic inflammation of the lacrimal gland. Dacryoadenitis comprises up to 50% of IOIS.[2] It should be noted that inflammation of the lacrimal gland may have different causes, including infections, infiltration by neoplasm, sarcoidosis, and other systemic conditions. Hence, biopsy of these lesions is sometimes necessary. Patients characteristically present with pain, swelling, and flushing of the temporal half of the superior eyelid (Fig. 5). The lid acquires a typical S-shaped deformity and is exquisitely tender to palpation.[18] Patients may have bilateral affection, although it rarely occurs. Examination of the superotemporal area of the conjunctiva displays prominence of the secretory ducts and redness of the visible portion of the lacrimal gland. CT scans reveal the presence of an inflammatory mass in the superotemporal orbit which is contiguous with the globe and generally does not involve other tissues[14], as shown in Fig. 6.

5. Sclerosing orbital inflammation: Some patients with IOIS develop a chronic scarring orbitopathy with extensive fibroblastic proliferation, with formation of dense fibrous connective tissue and severe orbital dysfunction. Patients often present severe and progressive vision loss due to optic nerve dysfunction, and double vision from the involvement of the

extraocular muscles.[21] The onset is more insidious, can simulate a tumor, and proptosis is frequently present. The desmoplastic reaction around the optic nerve may mimic a primary optic nerve tumor in imaging studies. Biopsy of the lesions reveals the defining feature of this entity: the dense desmoplastic reaction with scarring and scarce inflammatory cells.[14] These cases have the worst response to oral corticosteroids of all types of IOIS.[22] Usually there is an early response; however, most have an inexorable course notwithstanding, and many require second-line immunosuppressive agents. Early and more aggressive treatment may be more successful.[7]

Sclerosing OID comprises both IgG4-related and IgG4-non-related sclerosing inflammation. IgG4-related disease is an underdiagnosed, recently recognized disorder characterized by tumefactive lesions affecting different organs such as pancreas, retroperitoneum, lymph nodes, kidneys and skin. The orbit is frequently involved, especially lacrimal glands, the infraorbital part of the trigeminal nerve, extraocular muscles and orbital fat. It seems to be responsible for 23%–40% of IOIS cases. MRI shows diffuse involvement of multiple extraocular muscles (often inferior rectus), lacrimal glands, infraorbital nerve and oculomotor nerves. Serum IgG4 and eosinophils may be elevated or normal, so that a biopsy of the involved tissue is needed to confirm the diagnosis; it shows dense lymphoplasmacytic infiltration, fibrosis and obliterative phlebitis with a high proportion of plasma cells staining positively for IgG4 expression.[4,20, 23-27]

Diagnostic criteria for IgG4-related disease have recently been suggested by Okazaki *et al*: 1) Diffuse or focal enlargement, or mass-forming lesions in one or more organs; 2) Elevated levels of serum IgG4 (more than 135 mg/dl); 3) Histopathological findings as follows: a) prominent infiltration of lymphocytes and plasmacytes with fibrosis, but no neutrophilic infiltration; b) abundant infiltration of IgG4-positive plasmacytes (more than 10/high power field) and/or a ratio of IgG4/IgG-positive cells of more than 40%; c) storiform/swirling fibrosis; d) obliterative phlebitis.[28,29]

Steroids are generally effective and, in non-responsive cases, rituximab may be used (Fig. 7).[4]

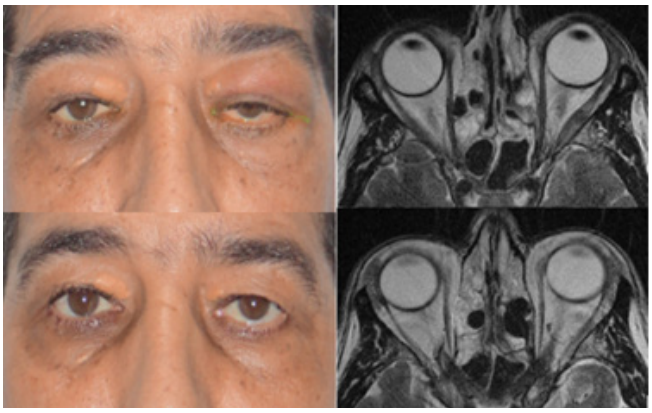


Figure 7. Patient with biopsy proven IgG4 disease before (top) and after (bottom) treatment with oral steroids and intravenous rituximab, added due to recurrence after steroid tapering.

Differential diagnosis

The diagnosis of IOIS largely remains one of exclusion. Although fast improvement following corticosteroids therapy helps confirm the diagnosis, inflammation associated with other orbital diseases (e.g. sarcoidosis, lymphoma, metastatic carcinoma, etc.) may also respond to this treatment strategy. Careful investigations to exclude orbital tumors, thyroid orbitopathy, orbital cellulitis or other systemic causes of inflammatory mass lesions should be performed. These can often be differentiated based on a meticulous clinical examination and CT and MRI characteristics. A biopsy is indicated if the etiology of an orbital lesion is still not clarified, and/or if there is a poor or refractory response to medical therapy. The risk of iatrogenic damage must be considered, especially in deep orbital lesions. [7]

Thyroid orbitopathy may be the most difficult to distinguish from IOIS. This autoimmune inflammatory disorder can also present with diffuse orbital inflammation. However, severe pain is rare, is most commonly bilateral, and most patients have extraocular muscles involvement, usually presenting with muscle enlargement confined to the muscle bellies, in contrast to IOIS, where there is an involvement of both the bellies and tendons.[7] Table 2 summaries the main differences between these two conditions.[14]

Table 2. Differences between thyroid orbitopathy and idiopathic orbital inflammatory syndrome.

	Thyroid orbitopathy	Idiopathic orbital inflammatory syndrome
Onset	Gradual, subacute	Acute (hours/days)
Laterality	Mainly bilateral Some asymmetry	Almost always unilateral
Eye movement	Restrictive dysfunction	Impaired in the field of action of the inflamed muscle
Pain	No pain/mild discomfort	More severe, exacerbated by eye movements
Eyelid	Retraction	Ptosis
Vision	Usually good (unless orbital apex compromise)	Impaired with posterior scleritis, perineuritis, and optic neuritis
Imaging	Multiple muscles enlarged; regular borders and tendon sparing, does not extend to fat	Multiple muscles enlarged with irregular borders and extension to orbital fat, enhancement around the globe
Response to steroids	Slow and moderate	Immediate and often complete

Adapted from: Liu G, et al. Liu, Volpe, and Galetta's Neuro-Ophthalmology: Diagnosis and treatment. 2nd ed. Amsterdam: Elsevier; 2010.[14]

Treatment

Treatment should be started immediately after clinical

diagnosis is suspected and imaging studies support the findings. Systemic corticosteroids remain the hallmark of IOIS treatment. Intravenous prednisolone (1 mg/kg) usually yield dramatic improvements of all symptoms and findings, especially pain. However, recurrences and refractory cases are common.[5,6] Steroids should be tapered slowly as soon as the clinical response is complete, and should be tailored to each patient's response over weeks to months. Nonsteroidal anti-inflammatory drugs may be helpful, especially when the inflammatory burden is low and in selected patients, such as those with diabetes, who tolerate steroids poorly.

The adverse effects and poor response of some patients to these therapies have led to a broadening of therapeutic agents, to include a variety of immune-modulating agents. Cyclophosphamide, cyclosporine, methotrexate, rituximab and antibodies against tumor necrosis factor α (infliximab) and IL-2 receptor (daclizumab) are some of the alternative treatments used in steroid-sparing strategies for recalcitrant IOIS.[7] In refractory inflammation, recurrence, contraindications to systemic steroids or the sclerosing variety, radiation therapy is an alternative. The dosage is between 1000 and 3000 cGy in 10 divided fractions, and complications are rare.

2) Specific orbital inflammatory diseases

Specific orbital inflammatory diseases include an etiologically diverse spectrum of conditions such as vasculitic disorders (granulomatosis with polyangiitis, polyarteritis nodosa, Churg-Strauss syndrome, Bechet´s disease, large vessel vasculitis), rheumatoid and autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis, sarcoidosis, psoriatic arthritis, inflammatory bowel disease) and orbital inflammation associated with rare disorders such as Castleman´s disease, Kimura´s disease, Melkersson-Rosenthal syndrome and Rosai-Dorfman disease.[2]

Sarcoidosis

Sarcoidosis is characterized by a systemic granulomatous inflammation involving the lungs, hilar lymph nodes, eyes and skin. Ocular involvement occurs in 25% to 50% of patients and may include infiltration of the lacrimal gland (Fig. 8), extraocular muscles, orbital fat, optic nerve and uveal tract. Conjunctival granuloma or solitary orbital granuloma may also be found. Clinical features include pain, proptosis, oculomotor dysfunction, uveitis and vision loss. Radiological findings comprise bilateral hilar adenopathy and parenchymal pulmonary involvement. Noncaseating granulomas are the classic histological finding. Serum angiotensin-converting enzyme and lysozyme levels can be useful as adjuncts to clinical, radiological and histological findings but not as primary diagnostic tools because of their limited sensitivity and specificity[6,16,30]

Granulomatosis with polyangiitis

Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) is a necrotizing, granulomatous inflammation and vasculitis that affects the respiratory and renal systems; there is ocular involvement in about 50% of cases.[6,31] Granulomatosis with polyangiitis (GPA) is a rare disease but an important differential diagnosis for IOIS because of its association with high morbidity and mortality. Bilateral eye pain, proptosis, redness and ocular motility

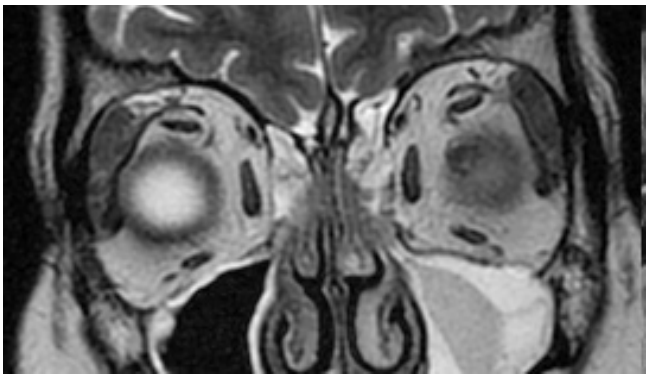


Figure 8. Bilateral lacrimal gland enlargement in sarcoidosis.

dysfunction are common clinical features. Ocular and orbital manifestations of GPA include conjunctivitis, marginal ulcerative keratitis, scleritis, uveitis, retinal vasculitis and optic neuropathy, dacryoadenitis and nasolacrimal duct obstruction. Histological findings consist of necrotizing, granulomatous inflammation and vasculitis.

Serum levels of antineutrophil cytoplasmic antibodies (ANCA) that display a cytoplasmic immunofluorescent staining pattern (cANCA) are elevated in the majority of patients with active GPA, and are very helpful in diagnosis and differential diagnosis. However, it should not replace biopsy. Despite this robust correlation with cANCA, a minority of patients presents with strong clinical and pathologic evidence of GPA but remains ANCA negative (Fig. 9). Also, the association between cANCA and GPA limited to the orbit is unclear. A percentage between 52% to 75% test positive for cANCA, mostly among patients with systemic GPA involving the orbit.[32] About 10% of patients with limited orbital involvement test positive for pANCA.[32] Orbital involvement occurs in about 15% of patients and it can be the initial presentation or it could also occur anytime during the course of the systemic illness. Sometimes it is the only presenting sign (primary orbital disease). Up to 65% of orbital GPA present with a limited, non-life-threatening form of the disease.[33]

Treatment of GPA generally requires long-term therapy with corticosteroids and immunosuppressant drugs, such as cyclophosphamide, methotrexate and rituximab. GPA-associated orbital inflammation should be approached in a similar manner to nonlife-threatening GPA, with more aggressive treatment reserved for those with optic nerve compromise.[6,16,34-36]

Churg-Strauss syndrome

Churg-Strauss syndrome, characterized by a necrotizing vasculitis, eosinophilic infiltration of the involved tissues, and extravascular granulomas, often presents with the clinical features of eosinophilia and asthma. Multiple organ system involvement is common in this disease and may include the heart, central nervous system, orbit, liver, colon, gallbladder, kidney, peripheral nerves, brain and musculoskeletal system. Laboratory evaluation may also reveal increased serum IgE and identify the presence of pANCA antibodies, which is associated with ischemia and poor visual prognosis. Relapses are common in Churg-Strauss syndrome, occurring in about

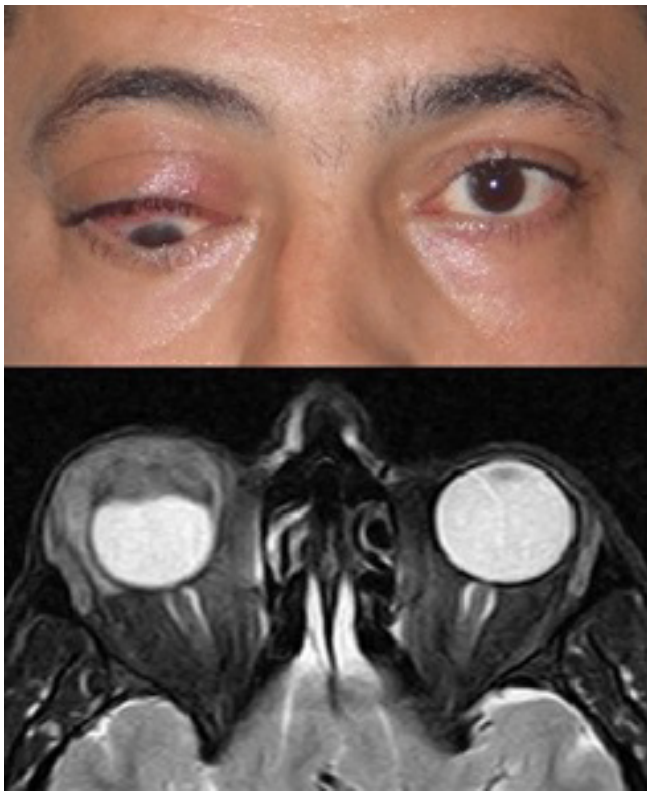


Figure 9. Large anterior right orbital inflammation. No other systemic involvement was present. C-ANCA where negative. Biopsy confirmed granulomatosis with polyangiitis.

25% of affected individuals.[16,37]

Ocular manifestations are uncommon and can usually be divided into two groups: orbital inflammatory pseudotumor-like and ischemic vasculitis. The first group includes clinical presentations like dacryoadenitis, myositis, periscleritis, perineuritis, conjunctival granuloma, and episcleritis. Usually, these patients have an insidious onset, conjunctival involvement, orbital lesions on imaging studies, negative ANCA, no other cranial nerve involvement, and good visual outcome in response to steroid treatment. The ischemic vasculitis-type patients usually experience a sudden onset of ocular symptoms, no conjunctival involvement, no abnormalities on orbital imaging studies, positive ANCA, occasional involvement of the III and IV cranial nerves, and poor visual outcomes, even with adequate treatment. However, the two groups can overlap, and the same patient might have manifestations from the two different categories.[37]

It is crucially important to distinguish the patients with Churg-Strauss syndrome from those with IOIS, because the latter does not have other systemic manifestations. Churg-Strauss syndrome, on the other hand, is occasionally life-threatening if sufficient corticosteroid therapy is not administered. Thus, this differentiation is mandatory for ophthalmologists. Once Churg-Strauss syndrome is suspected, orbital biopsy should be performed and prompt treatment must be initiated.[37]

CONCLUSION

Orbital inflammatory disease embodies a true diagnostic and sometimes therapeutic puzzle. Although it generally presents with acute ocular findings and responds well to systemic corticosteroids, it remains a diagnosis of exclusion. Notwithstanding its rarity, it is often associated with systemic inflammation, so a complete and detailed medical history, relevant blood tests, and imaging studies are important to exclude other orbital and systemic illnesses. A biopsy is indicated in refractory cases or when the clinical course is otherwise unusual. The mainstay of therapy is corticosteroids; however, other treatment options can and should be used when patients suffer from a more relapsing disease. New immunosuppressive agents may offer additional possibilities in the future.

Acknowledgments

To Marco Sales Sanz MD, PhD, FEBO for his participation in the drafting of the final document.

To Jorge Costa MD for his participation in all phases of this work.

To Andreia Soares MD for her participation in the bibliographic research.

To Cristina Freitas MD for the help in selecting the cases that illustrate the chapter.

Ethical Disclosures

Conflicts of Interest: The authors have no financial conflicts

Confidentiality of Data: Patient consent obtained.

Corresponding author:

Sara Filipa Teixeira Ribeiro

sara_ribeiro25@hotmail.com

REFERENCES

1. Young SM, Chan ASY, Jajeh IA, Shen S, Seah LL, Choo CT, et al. Clinical Features and Treatment Outcomes of Orbital Inflammatory Disease in Singapore: A 10-Year Clinicopathologic Review. Ophthalmic Plast Reconstr Surg. 2017;33:182-8.
2. Moore GH, Rootman DB, Roybal CN, Goldberg RA. Orbital relapsing polychondritis: a unique presentation, complication, and treatment. Ophthalmic Plast Reconstr Surg. 2016;32:e34-6.
3. Lutt JR, Lim LL, Phal PM, Rosenbaum JT. Orbital inflammatory disease. Semin Arthritis Rheum. 2008;37:207-22.
4. Berry-Brincat A, Rose GE. Idiopathic orbital inflammation: a new dimension with the discovery of immunoglobulin G4-related disease. Curr Opin Ophthalmol. 2012;23:415-9.
5. Swamy BN, McCluskey P, Nemet A, Crouch R, Martin P, Benger R, et al. Idiopathic orbital inflammatory syndrome: clinical features and treatment outcomes. Br J Ophthalmol. 2007;91:1667-70.
6. Yuen SJ, Rubin PA. Idiopathic orbital inflammation: distribution, clinical features, and treatment outcome. Arch Ophthalmol. 2003;121:491-9.
7. Espinoza GM. Orbital inflammatory pseudotumors: etiology, differential diagnosis, and management. Curr Rheumatol Rep. 2010;12:443-7.
8. Alshaikh M, Kakakios AM, Kemp AS. Orbital myositis following streptococcal pharyngitis. J Paediatr Child Health. 2008;44:233-4.
9. Kawasaki A, Borruat FX. An unusual presentation of herpes zoster ophthalmicus: orbital myositis preceding vesicular eruption. Am J Ophthalmol. 2003;136:574-5.
10. Badilla J, Dolman PJ. Orbital myositis involving the oblique muscles associated with herpes zoster ophthalmicus. Ophthalmic Plast Reconstr Surg. 2007;23:411-3.
11. Sobrin L, Kim EC, Christen W, Papadaki T, Letko E, Foster CS.

Infliximab therapy for the treatment of refractory ocular inflammatory disease. Arch Ophthalmol. 2007;125:895-900.
12. Garrity JA, Coleman AW, Matteson EL, Eggenberger ER, Waitzman DM. Treatment of recalcitrant idiopathic orbital inflammation (chronic orbital myositis) with infliximab. Am J Ophthalmol. 2004;138:925-30.
13. Mombaerts I, Goldschmeding R, Schlingemann RO, Koornneef L. What is orbital pseudotumor? Surv Ophthalmol. 1996;41:66-78.
14. Liu G, Volpe N, Galetta S. Liu, Volpe, and Galetta's Neuro-Ophthalmology: Diagnosis and treatment. 2nd ed. Amsterdam: Elsevier; 2010.
15. Kline LB. The Tolosa-Hunt syndrome. Surv Ophthalmol. 1982;27:79-95.
16. Gordon LK. Orbital inflammatory disease: a diagnostic and therapeutic challenge. Eye. 2006;20:1196-206.
17. Siatkowski RM, Capo H, Byrne SF, Gendron EK, Flynn JT, Munoz M, et al. Clinical and echographic findings in idiopathic orbital myositis. Am J Ophthalmol. 1994;118:343-50.
18. Rootman J RW, Lapointe JS. Diseases of the orbit: A multidisciplinary approach. Philadelphia: Lippinicott; 1988.
19. Pakdaman MN, Sepahdari AR, Elkhamary SM. Orbital inflammatory disease: Pictorial review and differential diagnosis. World J Radiol. 2014;6:106-15.
20. Montagnese F, Wenninger S, Schoser B. "Orbiting around" the orbital myositis: clinical features, differential diagnosis and therapy. J Neurol. 2016;263:631-40.
21. Hsuan JD, Selva D, McNab AA, Sullivan TJ, Saeed P, O'Donnell BA. Idiopathic sclerosing orbital inflammation. Arch Ophthalmol. 2006;124:1244-50.
22. Rootman J, McCarthy M, White V, Harris G, Kennerdell J. Idiopathic sclerosing inflammation of the orbit. A distinct clinicopathologic entity. Ophthalmology. 1994;101:570-84.
23. Andrew N, Kearney D, Selva D. IgG4-related orbital disease: a meta-analysis and review. Acta Ophthalmol. 2013;91:694-700.
24. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25:1181-92.
25. Kubota T, Moritani S. Orbital IgG4-related disease: clinical features and diagnosis. ISRN Rheumatol. 2012;2012:412896.
26. Lindfield D, Attfield K, McElvanney A. Systemic immunoglobulin G4 (IgG4) disease and idiopathic orbital inflammation; removing 'idiopathic' from the nomenclature? Eye . 2012;26:623-9.
27. Plaza JA, Garrity JA, Dogan A, Ananthamurthy A, Witzig TE, Salomao DR. Orbital inflammation with IgG4-positive plasma cells: manifestation of IgG4 systemic disease. Arch Ophthalmol. 2011;129:421-8.
28. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Takaoka M. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. J Gastroenterol. 2011;46:277-88.
29. Okazaki K, Uchida K, Miyoshi H, Ikeura T, Takaoka M, Nishio A. Recent concepts of autoimmune pancreatitis and IgG4-related disease. Clin Rev Allergy Immunol. 2011;41:126-38.
30. Costabel U, Teschler H. Biochemical changes in sarcoidosis. Clin Chest Med. 1997;18:827-42.
31. Weber AL, Jakobiec FA, Sabates NR. Pseudotumor of the orbit. Neuroimaging Clin N Am. 1996;6:73-92.
32. Woo TL, Francis IC, Wilcsek GA, Coroneo MT, McNab AA, Sullivan TJ, et al. Australasian orbital and adnexal Wegener's granulomatosis. Ophthalmology. 2001;108:1535-43.
33. Santiago YM, Fay A. Wegener's granulomatosis of the orbit: a review of clinical features and updates in diagnosis and treatment. Semin Ophthalmol. 2011;26:349-55.
34. Duna GF, Galperin C, Hoffman GS. Wegener's granulomatosis. Rheum Dis Clin North Am. 1995;21:949-86.
35. Bhatia A, Yadava U, Goyal JL, Chaturvedi KU. Limited Wegener's granulomatosis of the orbit: a case study and review of literature. Eye. 2005;19:102-4.
36. Perry SR, Rootman J, White VA. The clinical and pathologic constellation of Wegener granulomatosis of the orbit. Ophthalmology. 1997;104:683-94.
37. Takanashi T, Uchida S, Arita M, Okada M, Kashii S. Orbital inflammatory pseudotumor and ischemic vasculitis in Churg-Strauss syndrome: report of two cases and review of the literature. Ophthalmology. 2001;108:1129-33.

9. Orbital Cellulitis

OTORHINOLARYNGOLOGY
João Subtil, MD Phd FEB; Richard Voegels, MD PhD

Summary

Orbital cellulitis is an inflammatory process involving the orbital adipose tissue posterior to the orbital septum. However, the term is generally used to describe inflammation of orbital fat and extraocular muscles caused by infection. It is a severe condition, manifesting with erythema and edema of the eyelids, as well as vision loss, fever, headache, proptosis, chemosis, and diplopia. It is usually a complication of sinus infection, it is uncommon, and more prevalent in the pediatric population. Prompt diagnosis and treatment remain crucial as it can lead to potentially fatal intracranial complications. Aggressive medical treatment is needed, and, sometimes, surgical intervention can prevent vision loss and more severe complications. Most often, the endonasal approach is preferred when surgery is indicated, for it is regarded as safe and effective and simultaneously solves sinusitis, allowing a draining route to the nose, with no scar, and with faster recovery.

Keywords: *Orbital Cellulitis; Orbital Diseases; Sinusitis/complications*

INTRODUCTION

Orbital cellulitis is, by definition, the inflammation of adipose tissue inside the orbit. Therefore, inflammation of other tissues (muscle or globe) is not cellulitis, although myositis frequently co-occurs. The same is true for pre-septal (facial) cellulitis, as it is not inside the orbit. Also, pre-septal cellulitis has external causes (trauma, skin problems, insect bites) and different treatments, and the majority of cases have a very favorable prognosis. Orbital cellulitis is more prevalent in children and is frequently a complication of paranasal sinus infection. It is a severe situation, and if unrecognized and left untreated, may lead to vision loss or fatal complications.

PATHOPHYSIOLOGY

Almost all orbital infections occur as a complication of sinus infections.[1] The lamina papyracea is a very thin bone that composes the medial orbital wall. It has numerous, natural dehiscences and is perforated by multiple vessels and nerves that allow a wide communication between the ethmoid air cells and the subperiosteal space. This makes the medial area the most common location for orbital abscess formation.[1]
The subperiosteal space is a virtual space where collection can develop. Within orbital fat, fibrous septations form small compartments that can also develop localized abscesses.
The orbital septum is a rather dense membrane extending from the periosteum of the orbital rim to the eyelids, and since it has no lymphatic vessels, it effectively separates the orbital fat from the periorbital skin fat, protecting the orbit from pre-septal sources of infection.[1]
Within the orbit, valveless veins allow intracranial, retrograde spread of infection to the cavernous sinus,[1] the most feared complication.
When orbital cellulitis occurs as a complication of sinusitis, the most frequently involved sinus is the ethmoid. Other possible causes are ophthalmic surgery, dacryocystitis, and trauma.

MICROBIOLOGY

Microbiology is difficult to obtain, as it is only possible when surgical drainage is performed, and, even then, cultures are frequently negative.[2] Nevertheless, the most commonly identified pathogens are *Streptococcus anginosus* group (*Str. millieri*), *Staphylococcus aureus*, group A beta-hemolytic streptococci (*Streptococcus pyogenes*), and *Streptococcus pneumoniae*.
Other agents that may be found include *Haemophilus* (on unvaccinated children), *Pseudomonas*, and *Anaerobes*. Multiorganism infection is rare in young children,[3] but it is the rule amongst older children and adults.[4] Fungi (*Mucorales* or *Aspergillus* spp.) and mycobacteria infections are almost exclusive to immunocompromised patients and often very invasive and fatal.

SYMPTOMS AND CLINICAL MANIFESTATIONS

Orbital cellulitis is usually diagnosed on a child with nasal symptoms (nasal obstruction, rhinorrhea) who suddenly becomes more irritable, feverish and shows eyelid swelling (Fig. 1). Major characteristics of orbital cellulitis are organized in Table 1.[1] It is essential to distinguish orbital cellulitis from preseptal cellulitis, and promptly treat it to avoid complications. Both share eyelid edema and redness, and both are common in children. Unlike pre-septal cellulitis, orbital cellulitis is painful, and the child is irritable, which is rarely seen on pre-septal cellulitis.

Proptosis may not be evident due to eyelid edema, and an irritable child will make proper observation very difficult. The same applies to other manifestations, such as vision loss or ophthalmoplegia. Here, the ophthalmologist has a critical role, and both experience and patience are relevant – a crying baby with a swollen eyelid will only offer fractions of seconds to observe the eye movements, pupillary reactions and proptosis. Therefore, whenever it is suspected, orbital cellulitis must be investigated and even treated as such when confirmation is not fully possible.

Orbital fat and extra-ocular muscles inflammation cause pain with eye movements early in the course of cellulitis, even before

Table 1 Orbital and preseptal cellulitis clinical manifestations, adapted from Botting's paper[1]

MANIFESTATION/ SYMPTOM	ORBITAL CELLULITIS	PRESEPTAL CELLULITIS
Proptosis	Usually, but may be subtle	No
Pain with eye movements	Yes	No
Vision impairment	May be present	No
Ophthalmoplegia or diplopiav	Yes	No
Eyelid swelling	Yes	Yes
Eye pain	Yes	May be present
Chemosis	May be present	Rarely present
Fever	Usually present	May be present
Leukocytosis	May be present	May be present

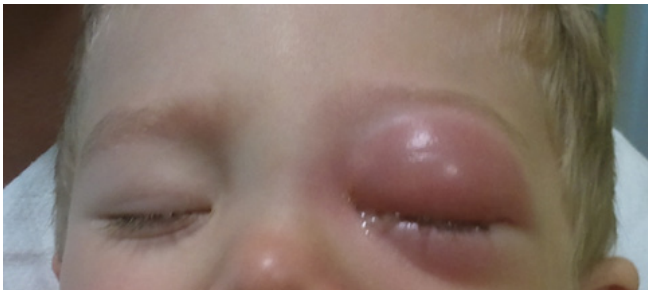


Figure 1. Orbital cellulitis.

it is evident on the eyelids. Also early is ophthalmoplegia and diplopia, induced by muscle inflammation. Proptosis becomes obvious due to inflammation and edema. Chemosis manifests later, secondary to a compromised venous and lymphatic drainage. Vision loss emerges as inflammation and ischemia affects the optic nerve.[5]

COMPLICATIONS

Complications from cellulitis are local (in the orbit), regional or systemic. Local complications are subperiosteal and orbital abscesses, which can both develop rapidly and cause a rapid expansion of orbital contents. These abscesses are common (up to 34%[1]) and should be anticipated by a regular checking for clinical and tomographic signs. Vision loss occurs in 3% to 11% of patients due to optic nerve inflammation or ischemia, or from central retinal artery occlusion.[6]

Regional complications come from the extension of infection (meningitis, brain abscess) or from retrograde venous thrombosis that cause cavernous sinus thrombophlebitis. These are feared and fatal complications. Cavernous sinus thrombosis will manifest with cranial nerve palsy (VI before the III and IV, because it is less protected inside the sinus), severe dermatome pain and hypoesthesia (unilateral V1 and V2), visual loss, and chemosis.[7] After several hours, contralateral symptoms can ensue due to the extension of thrombosis and infection through the sella venous plexus. Severe headache, protracted vomiting, and mental status changes come late and are ominous, late-stage symptoms that are fatal if left untreated.

Systemic complications are not common, but orbital cellulitis is fatal in 1% to 2% of patients.[6]

DIAGNOSIS

Clinical suspicion elicits prompt treatment, but confirmation requires computerized tomography (CT) scan. Imaging will support the diagnosis, differentiate pre-septal from orbital cellulitis, exclude complications, and document the probable source of infection, like sinusitis (Fig. 2). Howe's guidelines suggest that imaging is indicated when 1) it is impossible to assess visual acuity; 2) proptosis, ophthalmoplegia, bilateral edema, or deteriorating visual acuity occur; 3) lack of improvement after 24 hours of administration of intravenous antibiotics; 4) "swinging" fevers not resolving within 36 hours; 5) signs or symptoms of central nervous system involvement.[8] Magnetic resonance (MR) is superior in imaging orbital soft tissues and diagnosing,[9] but frequently is not readily available, it is more time consuming, and children must often be sedated. Therefore, CT scan is mostly preferred, in general. When cavernous sinus thrombosis is suspected an angiogram (MR or CT) is needed.

If CT scan is not readily available, the ophthalmologist's evaluation is critical: regular checking of eye movements, pupillary reactions and proptosis will help the diagnosis. Also, after diagnosis, regular observation may replace sequential CT scans, and therefore avoid radiation exposure, especially relevant in small children. Fundoscopy is also crucial to detect papillary edema, a sign of optic nerve compromise and possible cavernous sinus thrombosis.

Because complications may develop rapidly, close monitoring of visual acuity and pupillary light reflex is indicated, at least daily. A sluggish or absent pupillary light reflex or a relative afferent pupillary defect indicates optic nerve involvement. Upon any worsening of the patient's symptoms or signs, a contrast-enhanced computed tomography (CT) scan of the orbits and sinuses (or repeat CT if previously performed) should be performed to detect an abscess.

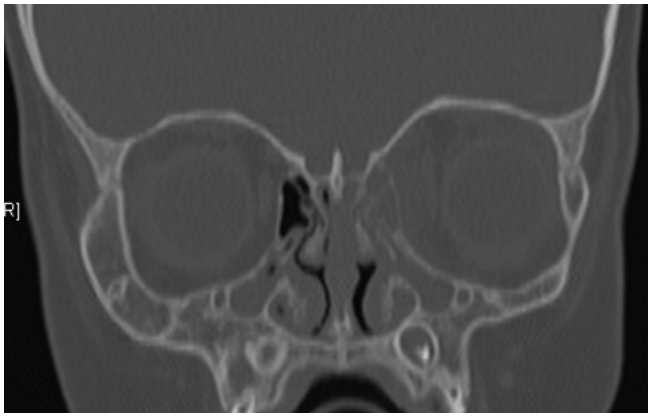


Figure 2. Orbital subperiosteal abscess

Laboratory tests should also be ordered. An absolute neutrophil count (ANC) >10,000 cell/microL was found to be an independent risk factor for orbital abscesses.[10] Although frequently negative, blood cultures should be obtained before starting antibiotic treatment, to allow for an eventual correction. If surgery is done, purulent material should also be cultivated, and if the patient is immunodeficient, the presence of fungi and mycobacterium should be investigated.

TREATMENT

The majority[11,12] of cases are manageable with antibiotics only[11,12]: in young children, where single organism infections are the rule, antibiotic treatment is usually efficient most of the times[3]; however, in older children and adults, surgery is frequently needed to drain abscesses.[4]

When selecting antibiotic treatment, common choices are broad-spectrum parenteral regimen covering *S. aureus* (including methicillin-resistant *S. aureus* - MRSA), S. pneumoniae and other streptococci, as well as Gram-negative bacilli. If intracranial extension is suspected, anaerobes should be included. Prompt treatment is important because delayed intervention can lead to vision loss or other serious complications. An appropriate regimen should include vancomycin plus one of the following: ceftriaxone, cefotaxime, ampicillin-sulbactam or piperacillin-tazobactam.[13] If intracranial extension is suspected on a patient being treated with ceftriaxone or cefotaxime, metronidazole should be added to include coverage for anaerobes.[13] Adults and children with a serious allergy to penicillins and/or cephalosporins can be treated with a combination of vancomycin and either ciprofloxacin or levofloxacin.[13] The first choice can be modified in accordance to response and cultures.

Improvement usually begins after 24-48 hours, and the switch to oral therapy should start after fever relief and significant improvement of periorbital edema (usually about day 3-5). If no culture is positive, empiric oral treatment should include either clindamycin or trimethoprim-sulfamethoxazole plus one of the following: amoxicillin, amoxicillin-clavulanic, cefpodoxime or cefdinir.[13] In adults and children who have serious allergies to penicillins and cephalosporins, appropriate alternatives to the agents listed above are ciprofloxacin or levofloxacin.[13] When a fluoroquinolone is used, it should be combined with clindamycin or trimethoprim-sulfamethoxazole to cover MRSA.[13] Prolong oral therapy for seven days after relevant symptoms have resolved.

To control sinusitis, topical nasal therapy is necessary. Other important treatments may include nasal steroids, decongestants, and saline nasal douches.[14,15]

Patients unresponsive to therapy after 24-48 hours, with severe manifestations, or with large abscesses (>10 mm in diameter) should be submitted to surgical drainage.[13] Surgery relieves pressure from collected abscesses and inflamed tissues, provides material for culture, and establishes a drainage route. As most often sinusitis is the source of infection, and orbital collections are frequently medial or inferior, a transnasal route for orbital drainage also addresses the need for surgical management of unresponsive complicated acute sinusitis.[16] Lateral abscesses may be addressed with external routes.

Surgical steps in endonasal orbital drainage are the following:

1. Acute inflamed sinusitis is very bloody and easily impairs the operating field. Therefore, all efforts should be made to decongest nasal mucosa (vasoconstriction, proclive position, warm douching, general anesthesia with opioid analgesia)
2. The second step is middle meatus swab for culture (in the event of not having enough purulent material from an abscess).
3. Gently medialize the middle turbinate to expose the uncinate process and bulla ethmoidalis.
4. Retrograde uncinectomy and supraturbinal antrostomy to drain the maxillary sinus and expose the orbital floor.
5. Bullectomy and exposure of the lamina papyracea.
6. Fracture and removal of a fragment of the lamina papiracea with Cottle elevator to expose subperiosteal space and allow drainage.
7. If an abscess is intra-orbital, use a sickle knife to perform a periosteum incision.
8. Collect pus for culture
9. Extend to posterior ethmoid or sphenoid sinus as needed.
10. Irrigate the nasal fossa with saline. Review hemostasis as needed. Do not pack.

The acutely inflamed mucosa has high potential to bleed and seriously compromise visualization, especially on a pediatric nose. The surgeon must recognize when the safety and completeness of a procedure may be compromised, and be prepared to convert to an external approach.

Ethical Disclosures

Confidentiality of Data: Patient consent obtained.

Conflicts of Interest: The authors have no financial interest in the products or procedures mentioned in this chapter

Corresponding author

João Subtil

joaosubtil@gmail.com

REFERENCES

1. Botting AM, McIntosh D, Mahadevan M. Paediatric pre- and post-septal peri-orbital infections are different diseases. A retrospective review of 262 cases. Int J Pediatr Otorhinolaryngol. 2008;72:377-83.
2. Seltz LB, Smith J, Durairaj VD, Enzenauer R, Todd J. Microbiology and antibiotic management of orbital cellulitis. Pediatrics. 2011;127:e566-72.
3. Harris GJ. Subperiosteal abscess of the orbit. Age as a factor in the bacteriology and response to treatment. Ophthalmology. 1994;101:585-95.
4. Brook I, Frazier EH. Microbiology of subperiosteal orbital abscess and associated maxillary sinusitis. Laryngoscope. 1996;106:1010-3.
5. Patt BS, Manning SC. Blindness resulting from orbital complications of sinusitis. Otolaryngol Head Neck Surg. 1991;104:789-95.
6. Osguthorpe JD, Hochman M. Inflammatory sinus diseases affecting the orbit. Otolaryngol Clin North Am. 1993;26:657-71.
7. Southwick FS, Richardson EP, Swartz MN. Septic thrombosis of the dural venous sinuses. Medicine. 1986;65:82-106.8.
8 Howe L, Jones NS. Guidelines for the management of periorbital cellulitis/abscess. Clin Otolaryngol Allied Sci. 2004;29:725-8.
9. Eustis HS, Mafee MF, Walton C, Mondonca J. MR imaging and CT of orbital infections and complications in acute rhinosinusitis. Radiol Clin North Am. 1998;36:1165-83, xi.
10. Rudloe TF, Harper MB, Prabhu SP, Rahbar R, Vanderveen D, Kimia AA. Acute periorbital infections: who needs emergent imaging? Pediatrics. 2010;125:e719-26.
11. Mahalingam-Dhingra A, Lander L, Preciado DA, Taylormoore J, Shah RK. Orbital and periorbital infections: a national perspective. Arch Otolaryngol Head Neck Surg. 2011;137:769-73.
12. Nageswaran S, Woods CR, Benjamin DK, Givner LB, Shetty AK. Orbital cellulitis in children. Pediatr Infect Dis J. 2006;25:695-9.
13. Gappy C, Archer S, Barza M. Orbital cellulitis. UpToDate. Waltham: UpToDate Inc; 2018. [Accessed 24/08/2018] Available from http://www.uptodate.com..
14. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice

10. Thyroid Eye Disease: Therapeutic Challenges

OPHTHALMOLOGY, MAXILLOFACIAL SURGERY
Ana Duarte, MD; Pedro Gomes Oliveira, MD; Michael Kazim, MD

Summary

The management of thyroid eye disease (TED) offers multiple challenges. It may become a long and demanding process that includes the treatment of thyroid dysfunction, the control of known risk factors, medical and surgical management of orbital features and the recognition of the psychological impact of the disease on patients. A multidisciplinary team including Endocrinology, Ophthalmology, Head and Neck Surgery, Neurosurgery, Internal Medicine, Radiotherapy and Psychiatry should be involved. In this chapter, we will address some of the challenges and difficulties frequently found when handling these cases.

Keywords: *Eye Diseases/therapy; Thyroid Diseases/therapy; Graves Ophthalmopathy/surgery; Graves Ophthalmopathy/therapy*

INTRODUCTION

Thyroid Eye Disease (TED), also known as Graves' ophthalmopathy or thyroid-associated orbitopathy, results from an immune-mediated inflammation, whose pathophysiology is not yet fully understood. TED affects up to 50% of patients with autoimmune thyroid disease,[1,2] however the relationship between the orbitopathy and the thyroid still needs to be clarified. It is believed that a reaction against antigens shared by the thyroid and orbital tissues may lead to a lymphocytes influx to the orbit, unleashing a cascade of events that culminate in adipogenesis, inflammation, edema, and fibrosis. Orbital signs usually occur after or at the same time as the thyroid disease, however they may precede it, making an accurate diagnosis challenging.

TED is more prevalent in females, and ophthalmic involvement manifests with variable degrees of inflammatory signs such as redness and congestion of the eyes and eyelids, lid retraction, proptosis, ocular motility disturbance, and rarely vision loss due to optic nerve compression. Disease activity (inflammatory symptoms and signs) and severity are usually evaluated and categorized using grading systems such as the clinical activity score (CAS) and the vision, inflammation, strabismus, and appearance (VISA) classification.[3]

The majority of cases are mild and managed with conservative measures. Only 3-7% of patients progress to the most severe, sight-threatening forms of the disease. [4]

Rundle´s curve describes the natural history of untreated TED.[5,6] This biphasic self-limited disease has an initial active, progressive, inflammatory phase (usually 12-18 months long) that reaches a peak of severity, followed by an inactive, stable, plateau stage, where sequelae may persist. It is important to be aware of this intrinsic evolution when interpreting the results of uncontrolled studies on treatment efficacy for TED.

One of the main questions that needs to be answered, to better diagnose and treat these cases, is how to predict which of the Graves´s patients will develop TED.[7] Also, why clinical presentations may become so distinct, and some patients deviate from the more "typical" presentations, why asymmetric presentations occur, muscle or fat are variably involved, and some muscles (medial and inferior rectus) are more often affected. There is still a long way to go in understanding the pathophysiology and risk factors of TED, and in finding more specific diagnostic and prognostic markers. The review of pathophysiology, clinical manifestations and diagnostic tools in TED is beyond the scope of this chapter. Our purpose is to shortly review where we stand in the treatment of this condition.

Four topics will be discussed and in the end of the chapter two clinical cases will be presented.

1. Advances in pharmacological treatment
2. Radiotherapy
3. Surgical timing
4. Pediatric TED

1. ADVANCES IN PHARMACOLOGICAL TREATMENT

There are several non-surgical options in TED´s treatment algorithm. The control of thyroid function becomes a key point for the success of other therapies since hyper or hypothyroidism are important factors for the exacerbation of orbital signs.[8] In the early, active stage, nonsurgical measures should be the first option, leaving surgery to the quiescent phase if any functional and aesthetic sequela persist.[9]

1.1 OCULAR LUBRICANTS – Traditional measures for mild disease should include artificial tears for ocular surface symptoms. Fifty percent of patients with mild signs spontaneously improve, 30% stay stable and 16% progress.[10] Smoking avoidance is particularly important in all stages of the disease, as it increases the risk of severe disease and limits treatment efficacy.[11]

1.2 SELENIUM – This trace mineral is incorporated into selenoproteins involved in the cell reduction-oxidation status and thyroid hormones metabolism. Selenium supplementation (200 µm daily) has been shown to reduce antithyroperoxidase antibodies (TPOAb) levels in chronic autoimmune thyroiditis.[12] The potential utility of selenium in patients with mild TED was suggested in a multicenter randomized, double-blind, controlled trial.[13] The study, however, was conducted in regions with marginal selenium deficiency in the general population, raising the question of whether the same benefit could be extrapolated to selenium-sufficient areas.[14]

1.3 SYSTEMIC GLUCOCORTICOSTEROIDS (GS) - It is still the first-line treatment in active (clinical activity score - CAS ≥ 3/7 or CAS ≥ 4/10) moderate-to-severe TED patients, with possible adjunctive orbital irradiation.[15] The intravenous pulse administration has been shown to be more effective than oral taking, being also associated with a lower risk of side effects[16,17]. The protocol from the European Group on Graves´orbitopathy (EUGOGO) statement using weekly pulses of methylprednisolone (500 mg for 6 weeks, followed by 250 mg for 6 weeks) is a popular treatment schedule[15], and can be adjusted depending on the clinical response. In cases of compressive optic neuropathy (CON) a daily dose of 0.5-1 g of methylprednisolone for three consecutive days, repeated in the following week if needed, has proven to be effective. A maximum cumulative dose of 8 g should be respected due to the risk of liver toxicity and cardiovascular damage, and systemic conditions such as uncontrolled diabetes, uncontrolled hypertension, uncontrolled glaucoma, severe cardiovascular comorbidities, active infection, and liver dysfunction should be ruled out prior to therapy.[15] Even though GS have demonstrated their beneficial effect on the inflammatory signs of TED, recent studies have suggested that the risk of progressing to optic neuropathy and ocular movement restriction persist.[18] These last cases, as well as those non-responsive or with an incomplete response to treatment, or who develop serious secondary effects or flare-ups after GS discontinuation, have always been the most challenging ones, constituting strong arguments for the development of alternative therapies.

1.4 BIOLOGICAL AGENTS - Considering recent discoveries regarding the pathophysiology of the disease, with better characterization of the roles of lymphocytes B and T and cytokines, new biological therapies have emerged.[19] Etanercept, adalimumab, rituximab, infliximab, and more recently tocilizumab and teprotumumab have arisen as logical new options. Even though the results are promising, further studies are needed to demonstrate with a high level of evidence their advantage over intravenous (IV) GS, the current standard therapy. Besides, larger follow-ups will be required to better clarify the medium and long-term side effects of these therapies, and which patients have a greater chance of response. It will also be crucial to know if and how these therapies prevent more severe complications of the disease, such as optic neuropathy and restrictive strabismus, and if they actually reduce the need for more surgical procedures. For now, their use should be limited to steroid-resistant, steroid-dependent or steroid-intolerant patients. The next few years will undoubtedly bring more solid information about their role in TED's therapeutic algorithm.

Rituximab (RTX) – This anti-CD 20 monoclonal antibody induces transient B-cell depletion and blocks early B-cell and T-cell activation.[20] Two recent randomized controlled studies presented conflicting results in cases of moderate-to-severe active TED. In one report, RTX was shown to be more effective than IV GS,[21] in the second, no additional benefit was found when compared to saline.[20] Conflicting data also exist concerning the use of RTX in CON. While some studies describe its successful use in these cases, in others it fails to prevent or improve visual loss.[22]
Nonetheless, discrepancies in patients´ enrollment between these reports, namely in the severity and stage of the orbital disease, make it difficult to reach unequivocal conclusions, and more studies are needed to better clarify the potential of RTX in TED´s treatment.

Tocilizumab – This is a recombinant humanized monoclonal antibody which blocks Interleukin-6 receptor. It was shown that IL-6 has an important role in the pathogenesis of TED.[23] A recent randomized controlled trial of 32 patients with moderate to severe corticosteroid-resistant TED compared monthly infusions of IV tocilizumab with a placebo drug over 3 infusions.[24] The authors found a 93.3% response rate (improvement of clinical activity score) at week 16 versus 58.8% in patients receiving placebo. An exophthalmos size change was also described in the tocilizumab group, however not statistically meaningful, the same occurring with diplopia. A few case reports have also suggested the benefit of tocilizumab in severe TED cases refractory to IV GC and orbital decompression[25,26] and even as a first treatment option in CON secondary to TED.[6]

Teprotumumab – The insulin-like growth factor-1 (IGF-1) receptor seems to be involved in the pathophysiology of TED´s orbital autoimmunity. Teprotumumab is an IGF-I receptor inhibitory monoclonal antibody which has recently shown optimistic results when compared to placebo. In a multicenter, double-masked, randomized, placebo-controlled trial published in the New England Journal of Medicine, a 69% response rate was found after eight infusions, with a 2 mm reduction in proptosis.[27] Even though this response rate is lower than that described with IV CS, it is, to date, the medical therapy that demonstrates the most significant reduction in exophthalmometry values.

2. ORBITAL RADIOTHERAPY (RT)

RT has been used for more than 6 decades; however, the exact mechanism of its therapeutic effect on TED has not been clearly understood. A standard dose of 20Gy is delivered over 10 days to the retroocular area, presumably acting through a direct effect on orbital lymphocytes and fibroblasts.[28] Few side-effects have been reported, nonetheless, due to the risk of radiation-induced retinopathy, uncontrolled hypertension and diabetes mellitus (particularly those with diabetic retinopathy) are relative contraindications. RT is now a second-line therapy, and ideal candidates should be in the early, active phase of the disease and present moderate to severe orbital manifestations, including strabismus and optic neuropathy.[29] It may become a valid first option in cases where GS are contraindicated or poorly tolerated.[30] Literature suggests a higher efficacy of RT in the reduction of soft tissue inflammation, motility disturbance[31] and optic neuropathy, being proptosis improvement less likely.[18,31-34] RT benefit is not immediate, being first observed after approximately one month, with the maximum effect taking up to 3 months. It should therefore not be adopted alone when the goal is a rapid decrease of inflammatory signs. Recent studies have shown that steroids combined with RT are superior to each used separately.[18,32-34] This association prevents not only the development of optic neuropathy in high-risk progressive TED[18] but also the need for emergent surgical decompression in patients with established CON[32,35] and the recurrence of vision loss after orbital decompression.[36] When used as adjuvant therapy, oral steroids should be added to prevent the risk of increased inflammation that occurs after its start.[26]
Importantly, most of the literature comparing RT associated with GS versus GS alone have used oral dosing and not intravenous pulses. A prospective study is now being conducted by the International Thyroid Eye Disease Society comparing RT associated with IV GS versus IV GS alone (CRISEPTED study). This investigation will try to answer previous controversies regarding the benefit of RT in reducing the risk of developing optic neuropathy or restrictive

strabismus in patients with early progressive TED.

3. SURGICAL TIMING

This is still one of most debated and least clarified topics in TED. Two major indications for surgery may be considered.

3.1 ACTIVE PHASE:

3.1.1 **Surgical decompression** should always be considered in cases of optic neuropathy (caused by nerve compression or rarely by stretching) with an absent or incomplete response to the initial therapy with IV GS.[37] Surgery allows an immediate mechanical relief of nerve compression by the enlarged extraocular muscles through bone, and eventually fat, removal. No guidelines exist about the exact timing for the procedure, and reinterventions may be needed due to CON recurrence.[38,39] Therefore, it becomes essential to maintain surveillance for signs of neuropathy in these patients even in the absence of a pronounced inflammation. Although the chance of visual recovery is inversely correlated to the duration of optic neuropathy,[40] even longstanding and severe visual loss may improve after orbital decompression.[9] See chapter 11 on orbital decompression in TED.

3.1.2 **Lid narrowing procedures** may be needed in cases of exposure with corneal breakdown secondary to proptosis and/or lid retraction. This includes tarsorrhaphy, botulinum toxin[41] or corticosteroids[42] injections in the upper eyelid.

3.2 INACTIVE PHASE:

After several months of stability and controlled thyroid status, aesthetic rehabilitation of TED can be programmed.[43] Patient expectations should be discussed and confronted with what is surgically achievable. Since orbital decompression influences the motility, and the position of the globe and muscles affects the position of the eyelids, surgical rehabilitation in TED usually follows a logical order, adjustable to each case. This may be a long journey, sometimes of 2 or even more years, a scenario that the patient should be aware of.

The surgical sequence should be:

1º. Orbital decompression for disfiguring proptosis, longstanding soft tissue congestion[15] or globe prolapse
2º. Strabismus surgery
3º. Eyelid surgery (for eyelid retraction and blepharoplasty)

Concerning strabismus surgery, it should be offered after deviation measurements are stable for at least 6 months.[9] Recessions are preferred over resections.

Recently, a single–stage procedure consisting of combined orbital decompression and aesthetic eyelid surgery (including upper and lower blepharoplasty, upper and lower eyelid retraction repair and closed lateral canthopexy) has been proposed as a valid alternative to the staged approach, with good patient satisfaction and significant cost reduction. None of the 40 patients needed further eyelid surgery.[44] Considering what is known about the influence of orbital decompression and strabismus surgery on upper and lower eyelid position,[9,18,45] as well as the fact that under general anesthesia the adjustment of the eyelid position becomes more difficult, this option should be individualized, and patients well informed and involved in the decision-making process.

4. PEDIATRIC THYROID EYE DISEASE

Graves disease is rare in the pediatric population. The reported incidence of TED in children is 1.7–3.5 cases per 100,000 people per year.[46] Considering pediatric Graves disease, rates of TED vary from 17%[47] to 63%[48] of cases, also occurring associated with chronic lymphocytic thyroiditis.[49] It is more common in girls and between 11 and 18 years old (68.2% of cases).[46] It is believed that the pathophysiology of the disease in this age group is similar to adults, however more studies are lacking.[50] Passive smoking and, in adolescence, active smoking seems to be a risk factor for TED.[46]

Pediatric TED is usually milder than in adult ages,[51] and most commonly manifested through proptosis, eyelid retraction, and lid lag[47,51]. For reasons not clearly understood, volume increase occurs at the expense of the orbital fat and not of the extraocular muscles as in adults.[52] Some studies have shown an increased risk of developing or aggravating myopia in this patients,[50] probably due to the enlargement of orbital contents conditioning a change in the globe´s shape with elongation of the optical axis.[53] Complications such as restrictive strabismus and CON are rarely seen in pediatric patients.[52]

Medical treatment

TED treatment in childhood presents several age-specific challenges. First, close interaction with the endocrinologist is essential for the treatment of thyroid disease. In children, as TED manifestations are usually mild, conservative management (eye lubricants, selenium supplementation) with euthyroidism restoration generally allow the regression of the orbital signs.[53] When these measures are not sufficient it becomes necessary the use of immunosuppressants:

- Steroids: An initial dose of 20 mg of prednisone daily for 4-6 weeks with subsequent tapering may be used.[54] Intravenous administration may be considered taking into account the benefits demonstrated in the adult population. Prolonged use of corticosteroids in children may have serious side effects (delayed growth, immunosuppression, weight gain) that should be considered.
- Biologic agents: although there is not yet much data on the use of immunomodulatory therapies (tocilizumab, rituximab, infliximab, adalimumab) in pediatric TED, they may become a valid option in this age group, similar to what has been demonstrated in adulthood. Further studies are needed to confirm this hypothesis.

Radiotherapy

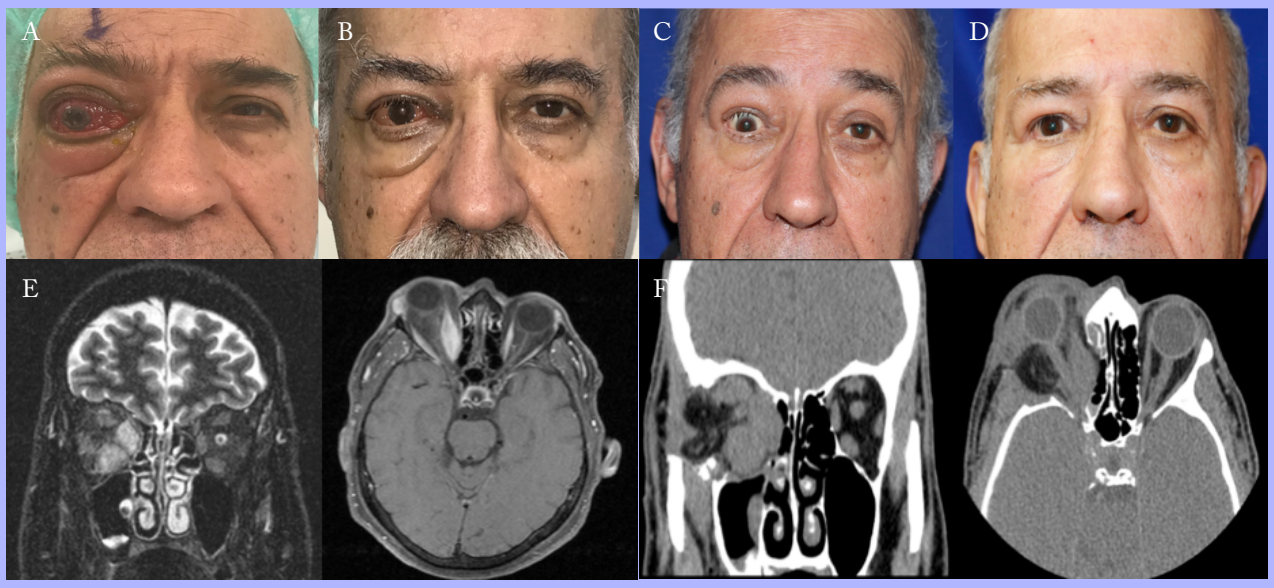
It is not recommended in pediatric TED due to its long-term theoretical risks of secondary tumors.[55]

Surgical treatment

As CON is rarely seen in these ages, emergence orbital decompression is not usually needed. So far, there is only one article reporting sight-threatening TED in children requiring orbital decompression.[56] Orbital or eyelid surgery are most frequently indicated in cases with disfiguring proptosis and/or eyelid retraction when signs of activity are absent, and the endocrinological picture is stable, being delayed until adolescence if possible. In a recent retrospective case series of 67 children with ages between 0 to 18 years, proptosis (100%) and eyelid retraction (69%) were the most common clinical signs at presentation. Differences between prepubertal and postpubertal TED were not statistically significant. Orbital decompression was performed in five cases for exposure keratopathy and severe proptosis with good outcomes.[51]

CASE 1

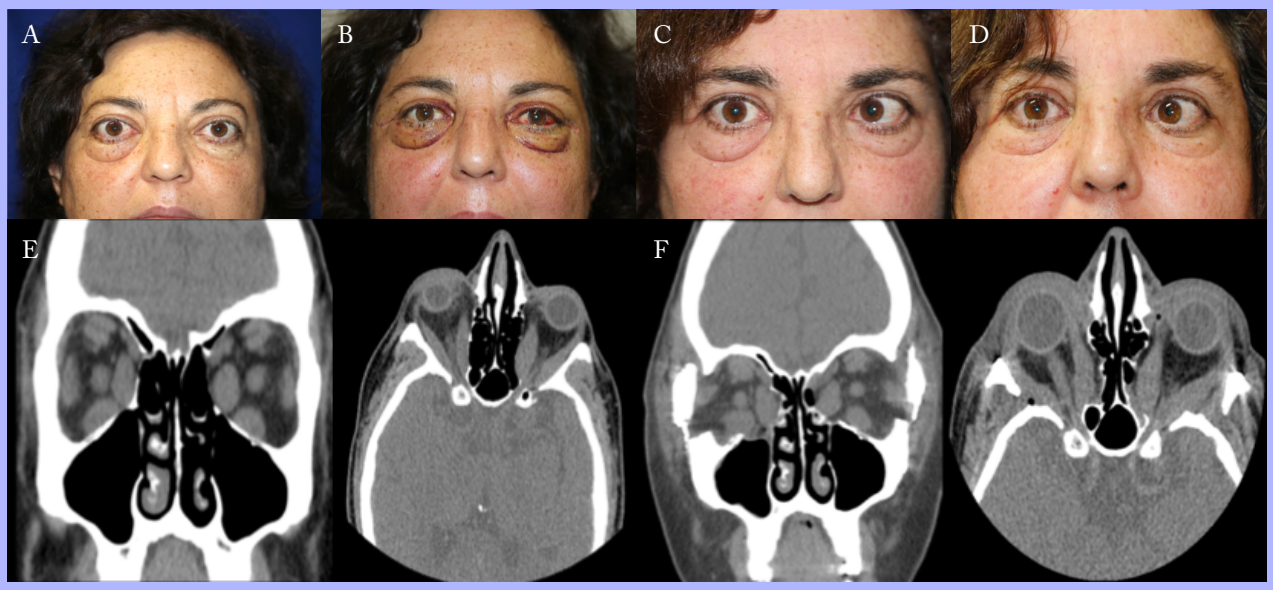
A 67-year-old male, non-smoker, presented with an 11-month progressive, sight-threatening TED, despite previous high-dose IV steroid therapy. At presentation (A) a right relative afferent pupillary defect was visible, and visual acuity was counting fingers OD and 10/10 OS. A severe right proptosis , ocular motility restriction in all gaze positions and exposure keratopathy were also disclosed. Magnetic resonance imaging (MRI) showed a bilateral enlargement of the extraocular muscles, more markedly of the right inferior and medial rectus, with an ipsilateral apical crowding (E).
The patient underwent surgical three-wall decompression of the right orbit (F) with an immediate postoperative reduction of proptosis and visual acuity improvement (B). Due to persistent signs of activity orbital radiotherapy (20Gy over 10 sessions) was indicated with a good response. One year after completion of treatment and 8 months of inflammatory control and motility stability (C) the patient underwent strabismus surgery of the right eye. Twenty-four months after orbital decompression visual acuity was 6/10 OD and 10/10 OS. Proptosis reduction was observed, together with a general improvement of extraocular movements and diplopia remission in the primary gaze and infraversion (D).



Case 1

CASE 2

A 52-year-old female, non-smoker, presented with an 8-month history of sight-threatening thyroid eye disease (TED) on the left side, with limited response to high-dose IV corticosteroids (which resulted in a psychotic episode and hepatotoxicity), and a more recent progression of the disease on the right side (A). Ophthalmic examination revealed a best corrected visual acuity (BCVA) of 1/10 on the right eye and counting fingers on the left eye, and a left relative afferent pupil defect. Ophthalmometry (Hertel's) reading was 30 mm on the right eye and 29 mm on the left eye, and a bilateral upper eyelid retraction was visible, together with a moderate bilateral motility restriction at elevation. Clinical Activity Score (CAS) was 5 points out of 7. Computed tomography showed bilateral extraocular muscle swelling (mainly the inferior and medial rectus) resulting in an apical crowding and optic nerve compression. (E)
The patient underwent surgical bilateral three-wall decompression (F), combined with a perioperative regimen of IV methylprednisolone. In the early postoperative period, immediate improvement of visual acuity and exophthalmos was noted (B). A few weeks later orbital irradiation (20Gy total over 10 sessions) was indicated, however, due to the persistence of signs of activity and limited visual improvement in the following months (C), medical treatment with tocilizumab was initiated with good response and tolerance. Eight months after surgery, five months after radiotherapy and 2 months treatment with tocilizumab (D), visual acuity was 8/10 OD, 6/10 OS and a significant improvement of inflammatory signs was visible. A post-surgical left esotropia is under surveillance, and future surgery will be indicated after total remision of inflammation and adequate clinical stabilization.



Case 2

CONCLUSIONS

TED is challenging for both physicians and patients. A thorough clinical evaluation with an accurate characterization of the activity and severity of the disease is fundamental for treatment selection and follow up. TED management should be individualized and involves a multidisciplinary team including Ophthalmologists, Endocrinologists, Head and Neck Surgeons, Neurosurgeons, Radiotherapy specialists. To date, standard therapy has included corticosteroids, radiotherapy, and surgery, however, as new doors open in the knowledge of the disease pathophysiology, unanswered questions will hopefully be addressed. Biological agents have shown to be promising in the treatment of TED, nevertheless, more randomized, controlled and scientifically robust trials will be needed to draw any conclusions. Several pathways exist to track, whether in diagnosis, through a better understanding of the pathogenesis of the disease and determination of new biomarkers, whether in treatment, with a better characterization of drugs' efficacy and safety, as well as the costs involved. Finally, in children with thyroid dysfunction a close follow up by an ophthalmologist becomes essential to promptly identify and manage orbital complications. Both adults, children and adolescents may experience a significant reduction in their quality of life and self-confidence secondary to the ocular manifestations of TED. Recovery may be a long process, and the importance of adequate psychological monitoring cannot be underestimated. We believe that the future of TED treatment will be based on a targeted treatment strategy, and look forward to the insights that the coming years will bring.

Ethical Disclosures

Conflicts of Interest: The authors have no financial conflicts
Confidentiality of Data: Patient consent obtained.

Corresponding author

Ana Filipa Duarte
anaf.duarte@hotmail.com

REFERENCES

1. Perros P, Zarkovic M, Azzolini C, Ayvaz G, Baldeschi L, Bartalena L, et al. PREGO (presentation of Graves' orbitopathy) study: changes in referral patterns to European Group On Graves' Orbitopathy (EUGOGO) centres over the period from 2000 to 2012. Br J Ophthalmol. 2015;99:1531-5.
2. Bahn RS. Current Insights into the pathogenesis of Graves' ophthalmopathy. Horm Metab Res. 2015;47:773-8.
3. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velazquez-Villoria A, Galofre JC. Graves' ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. J Ophthalmol. 2015;2015:249125.
4. Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010;362:726-38.
5. Bartley GB. Rundle and his curve. Arch Ophthalmol. 2011;129:356-8.
6. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to the effect of thyroidectomy. Clin Sci. 1945;5:177-94.
7. Wiersinga W, Zarkovic M, Bartalena L, Donati S, Perros P, Okosieme O, et al. Predictive score for the development or progression of Graves' orbitopathy in patients with newly diagnosed Graves' hyperthyroidism. Eur J Endocrinol. 2018;178:635-43.
8. Bartalena L, Macchia PE, Marcocci C, Salvi M, Vermiglio F. Effects of treatment modalities for Graves' hyperthyroidism on Graves' orbitopathy: a 2015 Italian Society of Endocrinology Consensus Statement. J Endocrinol Invest. 2015;38:481-7.
9. Morin J, Dolman PJ. Challenges and developments in both surgical and non-surgical treatments for thyroid eye disease. Expert Rev Ophthalmol. 2018;13:105-12.
10. Menconi F, Profilo MA, Leo M, Sisti E, Altea MA, Rocchi R, et al. Spontaneous improvement of untreated mild Graves' ophthalmopathy: Rundle's curve revisited. Thyroid. 2014;24:60-6.
11. Czarnywojtek A, Komar-Rychlicka K, Zgorzalewicz-Stachowiak M, Sawicka-Gutaj N, Woliński K, Gut P, et al. Efficacy and safety of radioiodine therapy for mild Graves ophthalmopathy depending on cigarette consumption: a 6month followup. Pol Arch Med Wewn. 2016;126:746-53.
12. Duntas LH, Mantzou E, Koutras DA. Effects of a six month treatment with selenomethionine in patients with autoimmune thyroiditis. Eur J Endocrinol. 2003;148:389-93.
13. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, et al. Selenium and the course of mild Graves' orbitopathy. N Engl J Med. 2011;364:1920-31.
14. Ruchala M, Sawicka-Gutaj N. Advances in the pharmacological treatment of Graves' orbitopathy. Expert Rev Clin Pharmacol. 2016;9:981-9.
15. Bartalena L, Baldeschi L, Dickinson AJ, Eckstein A, Kendall-Taylor P, Marcocci C, et al. Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid. 2008;18:333-46.
16. Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab. 2005;90:5234-40.
17. Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L. Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. J Clin Endocrinol Metab. 2009;94:2708-16.
18. Shams PN, Ma R, Pickles T, Rootman J, Dolman PJ. Reduced risk of compressive optic neuropathy using orbital radiotherapy in patients with active thyroid eye disease. Am J Ophthalmol. 2014;157:1299-305.
19. Douglas RS, Gianoukakis AG, Goldberg RA, Kamat S, Smith TJ. Circulating mononuclear cells from euthyroid patients with thyroid-associated ophthalmopathy exhibit characteristic phenotypes. Clin Exp Immunol. 2007;148:64-71.
20. Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. J Clin Endocrinol Metab. 2015;100:432-41.
21. Salvi M, Vannucchi G, Curro N, Campi I, Covelli D, Dazzi D, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab. 2015;100:422-31.
22. Stan MN, Salvi M. Management of endocrine disease: Rituximab therapy for Graves' orbitopathy - lessons from randomized control trials. Eur J Endocrinol. 2017;176:R101-9.
23. Mesquida M, Leszczynska A, Llorenc V, Adan A. Interleukin-6 blockade in ocular inflammatory diseases. Clin Exp Immunol. 2014;176:301-9.
24. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez FM, et al. Efficacy of Tocilizumab in patients with moderate-to-severe corticosteroid-resistant graves orbitopathy: a randomized clinical trial. Am J Ophthalmol. 2018;195:181-90.
25. Sy A, Eliasieh K, Silkiss RZ. Clinical response to tocilizumab in severe thyroid eye disease. Ophthalmic Plast Reconstr Surg. 2017;33:e55-7.
26. Strianese D. Update on Graves disease: advances in treatment of mild, moderate and severe thyroid eye disease. Curr Opin Ophthalmol. 2017;28:505-13.
27. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for Thyroid-associated ophthalmopathy. N Engl J Med. 2017;376:1748-61.
28. Trott KR, Kamprad F. Radiobiological mechanisms of anti-inflammatory radiotherapy. Radiother Oncol. 1999;51:197-203.
29. Godfrey KJ, Kazim M. Radiotherapy for active thyroid eye disease. Ophthalmic Plast Reconstr Surg. 2018;34:S98-S104.
30. Schaefer U, Hesselmann S, Micke O, Schueller P, Bruns F, Palma C, et

al. A long-term follow-up study after retro-orbital irradiation for Graves' ophthalmopathy. Int J Radiat Oncol Biol Phys. 2002;52:192-7.
31. Grassi P, Strianese D, Piscopo R, Pacelli R, Bonavolonta G. Radiotherapy for the treatment of thyroid eye disease-a prospective comparison: Is orbital radiotherapy a suitable alternative to steroids? Ir J Med Sci. 2017;186:647-52.
32. Kazim M, Trokel S, Moore S. Treatment of acute Graves orbitopathy. Ophthalmology. 1991;98:1443-8.
33. Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G, Lepri A, Pinchera A. Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. J Endocrinol Invest. 1991;14:853-60.
34. Ng CM, Yuen HK, Choi KL, Chan MK, Yuen KT, Ng YW, et al. Combined orbital irradiation and systemic steroids compared with systemic steroids alone in the management of moderate-to-severe Graves' ophthalmopathy: a preliminary study. Hong Kong Med J. 2005;11:322-30.
35. Gold KG, Scofield S, Isaacson SR, Stewart MW, Kazim M. Orbital radiotherapy combined with corticosteroid treatment for thyroid eye disease-compressive optic neuropathy. Ophthalmic Plast Reconstr Surg. 2018;34:172-7.
36. Chundury RV, Weber AC, Perry JD. Orbital radiation therapy in thyroid eye disease. Ophthalmic Plast Reconstr Surg. 2016;32:83-9.
37. Boboridis KG, Uddin J, Mikropoulos DG, et al. Critical appraisal on orbital decompression for thyroid eye disease: a systematic review and literature search. Adv Ther. 2015;32:595-611.
38. Kauh CY, Gupta S, Douglas RS, Bunce C, Mangouritsas G, Voudouragkaki IC, et al. Compressive optic neuropathy and repeat orbital decompression: a case series. Ophthalmic Plast Reconstr Surg. 2015;31:385-90.
39. Zhang-Nunes SX, Dang S, Garneau HC, Hwang C, Isaacs D, Chang SH, et al. Characterization and outcomes of repeat orbital decompression for thyroid-associated orbitopathy. Orbit. 2015;34:57-65.
40. Devoto MH, Golnik K, Bernardini FP, Alencar VM. Improvement from no light perception after orbital decompression for graves' optic neuropathy. Ophthalmology. 2014;121:431-2 e431.
41. Costa PG, Saraiva FP, Pereira IC, Monteiro ML, Matayoshi S. Comparative study of botox injection treatment for upper eyelid retraction with 6-month follow-up in patients with thyroid eye disease in the congestive or fibrotic stage. Eye. 2009;23:767-73.
42. Xu D, Liu Y, Xu H, Li H. Repeated triamcinolone acetonide injection in the treatment of upper-lid retraction in patients with thyroid-associated ophthalmopathy. Can J Ophthalmol. 2012;47:34-41.
43. Dolman PJ. Evaluating Graves' orbitopathy. Best Pract Res Clin Endocrinol Metab. 2012;26:229-48.
44. Bernardini FP, Skippen B, Zambelli A, Riesco B, Devoto MH. Simultaneous aesthetic eyelid surgery and orbital decompression for rehabilitation of thyroid eye disease: the one-stage approach. Aesthet Surg J. 2018;38:1052-61.
45. Rootman DB, Golan S, Pavlovich P, Rootman J. Postoperative changes in strabismus, ductions, exophthalmometry, and eyelid retraction after orbital decompression for thyroid orbitopathy. Ophthalmic Plast Reconstr Surg. 2017;33:289-93.
46. Krassas GE, Segni M, Wiersinga WM. Childhood Graves' ophthalmopathy: results of a European questionnaire study. Eur J Endocrinol. 2005;153:515-21.
47. Goldstein SM, Katowitz WR, Moshang T, Katowitz JA. Pediatric thyroid-associated orbitopathy: the Children's Hospital of Philadelphia experience and literature review. Thyroid. 2008;18:997-9.
48. Chan W, Wong GW, Fan DS, Cheng AC, Lam DS, Ng JS. Ophthalmopathy in childhood Graves' disease. Br J Ophthalmol. 2002;86:740-2.
49. Kirmizibekmez H, Yesiltepe Mutlu RG. Atypical presentation of Hashimoto's disease in an adolescent: thyroid-associated ophthalmopathy. J Clin Res Pediatr Endocrinol. 2014;6:262-5.
50. Novaes P, Diniz Grisolia AB, Smith TJ. Update on thyroid-associated Ophthalmopathy with a special emphasis on the ocular surface. Clin Diabetes Endocrinol. 2016;2:19.
51. Chua MR, Tomlinson LA, Binenbaum G, Katowitz WR. Pediatric thyroid eye disease: clinical characteristics and orbital decompression outcomes. Ophthalmic Plast Reconstr Surg. 2018;34:S52-5.
52. Holt H, Hunter DG, Smith J, Dagi LR. Pediatric Graves' ophthalmopathy: the pre- and postpubertal experience. J AAPOS. 2008;12:357-60.
53. Szczapa-Jagustyn J, Gotz-Wieckowska A, Kociecki J. An update on thyroid-associated ophthalmopathy in children and adolescents. J Pediatr Endocrinol Metab. 2016;29:1115-22.
54. Krassas GA. Thyroid-associated ophthalmopathy in juvenile graves'disease: clinical, endocrine and therapeutic aspects; thyroid in childhood and adolescence. Pediatr Adolesc Med Basel. 2007; 11:192–209.
55. Wiersinga WM. Thyroid associated ophthalmopathy: pediatric and endocrine aspects. Pediatr Endocrinol Rev. 2004;1 Suppl 3:513-7.
56. Wu CY, Elner VM, Kahana A. Severe pediatric thyroid eye disease: surgical case series. Ophthalmic Plast Reconstr Surg. 2017;33:S186-8.

11. Orbital Decompression for Thyroid Eye Disease

OPHTHALMOLOGY, OTORHINOLARYNGOLOGY
Marco Sales-Sanz MD, Ph.D.; Hae-Ryung Won Kim, MD.; João Subtil, MD Phd FEB;

Summary

Thyroid eye disease can cause vision impairment and unaesthetic exophthalmos, being decompression surgery indicated when these are no longer medically manageable. Each bony wall has its unique anatomy and relationships with other key structures, and several techniques have been described to address each one of them.
In this chapter, we describe from a multidisciplinary perspective (Ophthalmology and Otorhinolaryngology) the approach to each wall, detailing the surgical routes, results, tips and pitfalls.

Keywords: *Thyroid Eye Disease; orbit; surgery; decompression; osteotomy; dysthyroid optic neuropathy;*

INTRODUCTION

The indications for an orbital decompression in thyroid eye disease (TED) are dysthyroid optic neuropathy resistant to high dose intravenous steroids or disfiguring exophthalmos.
TED creates a space conflict within the orbit. There is an increase in the orbital contents in a non-distensible continent. Therefore, there are two possible approaches for treating the exophthalmos: to decrease the contents, with a fat decompression, or to enlarge the continent, performing a bony decompression.

1. BONY DECOMPRESSION

Bony decompression of the orbit can include the following walls: the medial wall, the orbital floor and the lateral wall. Nowadays the roof is no longer decompressed as this procedure has a high risk of complications and renders very little decrease in the exophthalmometry.

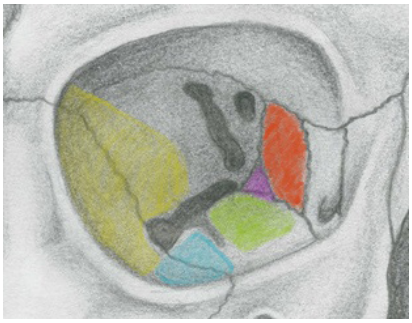


Figure 1. Anterior view of the orbital bones

1.1 MEDIAL WALL

Doing a medial wall decompression entails performing a complete ethmoidectomy. (Fig.1 red)
The limits of medial wall decompression are:

- Anterior: posterior lacrimal crest.
- Posterior: sphenoid anterior to the optic foramen.
- Superior: anterior and posterior ethmoidal vessels, which mark the fronto-ethmoidal suture. If this limit is surpassed, the risk of perforation into the cranial cavity is high. Thence the importance of identifying and keeping clear of this border during surgery. Coagulation of these vessels is not required.
- Inferior: Infero-medial strut, formed by the maxillo-ethmoidal suture. We should try to keep it intact during surgery to decrease the risk of postoperative diplopia. If the patient has an optic neuropathy, we can remove the posterior third of the strut (Fig.1 purple) to reduce the pressure on the optic nerve.

The available surgical approaches for medial wall decompression are:

- Transcaruncular: It is the surgical approach of choice. It provides a direct, fast and safe access to the medial wall, avoiding any visible scar. The advantages of this approach over the endoscopic approach are that it allows a better visualization and preservation of the strut and the fact that it enables us to work from the orbit outwards so that we can continuously protect the orbital contents with a malleable retractor. On the other hand, the surgeon must avoid the ethmoid roof, located frequently below the frontal-ethmoidal suture in the orbit.
- Endoscopic: It is a safe approach, and it provides a complete visualization of the ethmoid bone. One of its advantages is that it allows a more complete ethmoidectomy because of its direct access. With this approach, the ethmoid cell complex is completely removed, leaving more room for orbital content expansion, while it remains untouched in the transcaruncular approach. Also, the ethmoidal roof is more safely protected, avoiding a potential fistula. Decompressing the posterior third is also easier and less disturbing to the orbital contents. Finally, this approach becomes necessary if an optic canal decompression is planned. On the other hand, one of its disadvantages is that we work towards the orbit, with no protection of its contents. However, ethmoid dissection is done in a stepwise approach, and so, removing the ethmoid cells first, with clear identification of the lamina papiracea, and only then dissecting the bony wall and preserving the periosteum, the safety of this approach is increased.
- Superior eyelid crease: It is an alternative to the transcaruncular approach. The incision is hidden in the

palpebral crease.
- Inferior transconjunctival: This approach provides a partial access to the medial wall, but with poor visualization of the ethmoidal vessels, and therefore it carries a higher risk of complications.
- Coronal: To perform a complete medial decompression through a coronal approach, the ethmoidal vessels must be coagulated and cut.
- Lynch: It has become obsolete because it leaves a visible scar and has no advantage over the transcaruncular approach.

1.2 ORBITAL FLOOR

When planning an orbital decompression, we divide the orbital floor into two parts: medial and lateral to the infraorbital nerve.

The limits of the decompression of the floor medial to the infraorbital nerve are: (Fig.1 green)
- Medial: Inferomedial strut.
- Lateral: Infraorbital nerve.
- Anterior: 1 cm of the floor measured from the orbital rim. This is the section of the orbital floor that supports the globe. Removing it during floor decompression can induce a hipoglobus and also increases the risk of post-surgical diplopia.
- Posterior: Posterior wall of the maxillary sinus. A helpful surgical maneuver is to insert the tip of a freer elevator into the maxillary sinus until the posterior wall is touched. Then the tip is brought again to the orbit keeping in touch with the posterior wall until the remaining edge of the floor is reached.

Surgical approaches to the orbital floor are:
- Transconjunctival: It is the surgical approach of choice. It can be preseptal or retroseptal. We prefer the preseptal entry, in which the orbital fat does not interfere with the procedure. No associated canthotomy or cantholysis are required.
- Transcutaneous: The subciliary approach has a higher risk of inferior eyelid retraction, and it does not provide a better surgical field that the transconjunctival approach, so we always prefer the latter. The subtarsal approach has less risk of inferior eyelid retraction than the subciliary approach but has a high risk of unaesthetic, visible scar.
- Endoscopic: The main disadvantage of the endoscopic approach for decompressing the orbital floor is that the most anterior portion of the orbital floor is out of reach for a comfortable dissection. Also, the inferomedial strut is usually removed for better exposure. As its removal implies a higher risk of diplopia, the endoscopic approach has fewer indications for decompressing the floor than the medial wall.
- Transantral: It used to be one of the main approaches for orbital floor decompression, but nowadays it has been entirely replaced by the transconjunctival approach.

Decompression of the orbital floor lateral to the infraorbital nerve is usually performed together with lateral wall decompression. It can be associated or not with medial orbital floor decompression.

The limits of the decompression of the floor lateral to the infraorbital nerve are: (Fig.1 blue)
- Anterior: The orbital rim. It is not necessary to leave 1 cm of floor in this section because this portion of the orbital floor does not support the eyeball.
- Posterior: Inferior orbital fissure.
- Medial: It depends on whether we are planning only a lateral decompression or a three wall decompression. If the floor is not decompressed (i.e., we are performing only a lateral decompression), the medial limit is the lateral wall of the maxillary sinus, so the sinus is not entered during surgery. If a floor decompression is associated, then the lateral decompression can be prolonged medially up to the infraorbital nerve.
- Lateral: The lateral decompression, as this part of the floor is almost always decompressed associated with the lateral wall.

Surgical approaches for the lateral orbital floor are the same as for the lateral wall or the orbital floor. In fact, the lateral orbital floor can be considered as a prolongation of the lateral wall, which is described independently only for teaching purposes.

1.3 LATERAL WALL

The lateral orbital wall can be divided into two parts when considering orbital decompression. The superficial lateral wall is the anterior part which is in contact with the temporalis muscle (Fig.2 green), and the deep orbital wall is the part that corresponds to the cancelous bone of the greater wing of the sphenoid, anterior to the middle brain fossa (Fig.2 red).

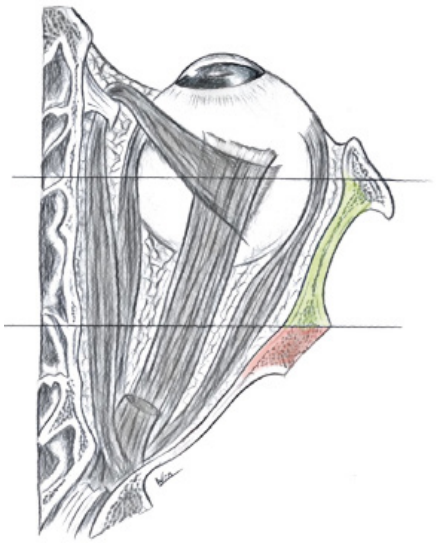


Figure 2 Superior view of the orbit

The anatomical limits of the lateral decompression are: (Fig.1 yellow)
- Anterior: The lateral orbital rim. There are even some authors that completely remove it without repositioning it at the end of surgery. We believe that the lateral rim and the lateral part of the ascendant process of the malar bone are important to provide an adequate morphology to the external canthus.
- Medial: Superior and inferior orbital fissures. Anterior

to the inferior orbital suture, the decompression can be extended to the infraorbital nerve.
- Posterior: Usually the posterior limit is the inner cortical bone of the sphenoid. Some authors extend the burring until complete exposure of the dura mater.

Surgical approaches for the lateral wall are:
- Upper eyelid crease: It provides a complete exposure of the lateral wall. Its main advantages compared to the lateral canthotomy approach are that it does not disturb the lateral canthus and it decreases the degree of corneal exposure during surgery.
- Canthotomy: It also provides a complete exposure of the lateral wall. Its main disadvantages are corneal exposure during surgery, and that the lateral canthus must be reconstructed. Nevertheless, they are two minor disadvantages. Whether the eyelid crease or the canthotomy approach is chosen depends mainly on the surgeon's preference.
- Coronal approach: It provides a wide field and allows burring from the outside of the orbit (*ab-externum*) without manipulation of the orbital rim. Its only indication nowadays is the extremely rare cases in which a bony advancement of the orbit is performed.

Surgical techniques for lateral decompression:
Lateral wall decompression can be performed using three different techniques. They can be classified depending on whether they remove or not the orbital rim, and depending on the approach (from the inside or the outside of the orbit).
- Lateral decompression without bony marginotomy
  - *Ab interno*
  - *Ab externum*
- Lateral decompression with bony marginotomy

Ab interno Lateral Decompression:
After exposing the lateral orbital rim, the periosteum of the inner side of the lateral wall is elevated. From the inside of the orbit, with an electric burr, the bone of the lateral wall beyond the orbital rim is removed until the temporalis muscle is exposed. The window is enlarged to the limits previously described using burrs and rongeurs.
- Advantages:
  - It does not affect the lateral orbital rim.
- Disadvantages:
  - Surgical exposure is scarce, especially for burring the deep lateral wall.
  - It requires applying high pressure on the orbital contents to allow proper exposure.
  - Control of bleeding from the temporalis muscle is more difficult.

Ab Externum Lateral Decompression:
After exposing the lateral orbital rim, the periosteum of the inner and the outer side of the lateral wall is elevated. With a chisel or electric saw, the lateral portion of the ascending process of the malar bone is removed. After completing the subperiosteal dissection of the external side of the lateral wall, the bone of the lateral wall is removed with an inverse Kerrison rongeur or an electric burr from the outside of the orbit. The orbital content is protected with a malleable retractor. The window is enlarged to the limits previously described.

Advantages:
- Little pressure is applied to the contents of the orbit, as work with the surgical instruments is performed from outside the orbit

Disadvantages:
- It removes the lateral part of the ascending process of the malar bone. It can lead to a depression of the external part of the lateral canthus.
- Surgical exposure of the deep lateral wall is also scarce, unless a complete primary exposure of the dura mater is performed.

Lateral decompression with bony marginotomy
After exposing the lateral orbital rim, the periosteum of the inner and the outer side of the lateral wall is elevated. With an electric saw, two perpendicular cuts are performed on the lateral wall, one just superior to the zygomatic arch, and the other superior to the fronto-zygomatic fissure. The marginotomy is completed with a chisel over the spheno-zygomatic fissure and the lateral rim is removed. The orbital content is always protected with a malleable retractor. The superficial lateral wall is removed with rongeurs, and the deep lateral wall with an electric burr. The window is enlarged to the limits previously described. The lateral rim is prepared by removing the remaining lateral wall with an electric saw leaving in place only the rim and the lateral aspect of the ascendant process of the malar bone that is not included in the lateral wall. The rim is secured in place with a 1.2 mm rim microplate and 3 mm screws.

Advantages:
- It provides complete and comfortable exposure of the deep lateral wall.
- When associated with a medial wall decompression (balanced orbital decompression) it also provides better exposure of the medial wall as it allows the orbital content to be displaced laterally through the marginotomy.
- It allows for better management of temporal muscle bleeding.
- It produces little pressure on the contents of the orbit, as work with the surgical instruments is also performed from the outside. Disadvantages
- It requires fixation material. Although it could also be performed with wire or even non-absorbable sutures, we prefer the titanium microplate as it provides a much more stable fixation.
- Some authors argue that it takes longer to perform the marginotomy. We believe that the time employed performing the marginotomy is compensated with the ease in burring the deep lateral wall due to the bigger surgical field exposed, leading to an overall faster surgery.

The amount of exophthalmos reduction achieved is more significant with the lateral wall decompression, if the deep portion is included, followed by medial wall decompression, and lastly with the orbital floor. The reduction obtained with

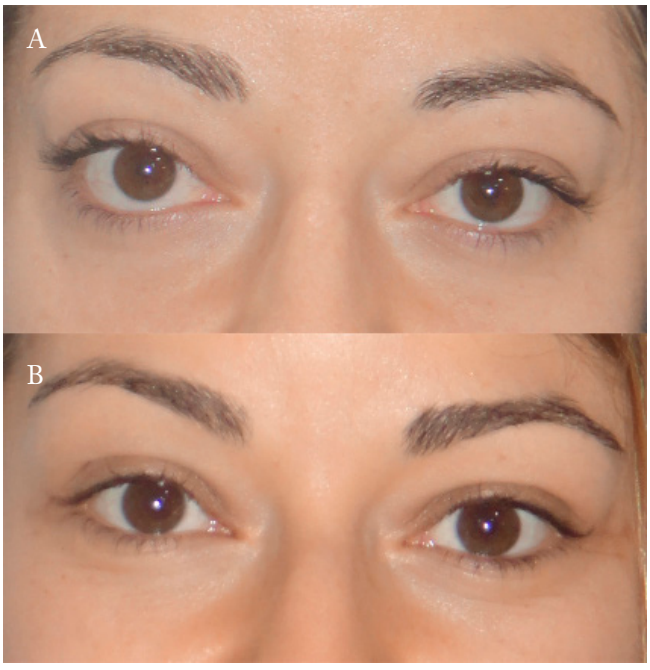
balanced decompression ranges between 3.2 and 4.8 mm, and for three wall decompression between 5.6-6.5 mm.[1] Nevertheless, there is a significant variation depending on the anatomical characteristics of each's orbital walls.

Complications:

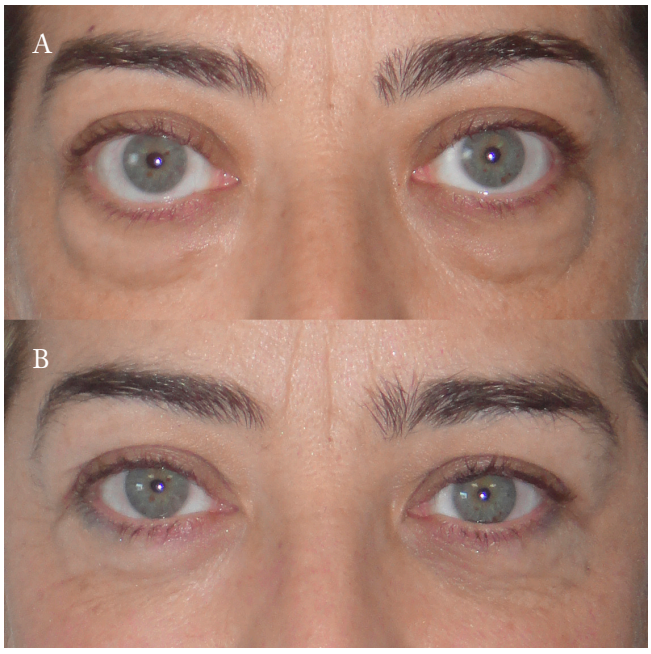
- Vision loss: It can be due to intraoperative surgical compression or most frequently due to retrobulbar hemorrhage. Fortunately, it is very uncommon. Meticulous dissection and hemostasis decrease its incidence.
- Cerebrospinal fistula and meningitis: It is mainly a complication of medial wall decompression. It is essential to keep the ethmoidal vessels as the superior limit of the decompression. Dura mater tears during lateral wall decompression have less risk of complications as there is no communication with the paranasal sinuses and have the whole orbit acting as a muscle-fat flap to block them.
- Hypoesthesia: Orbital floor decompression can produce infraorbital nerve hypoesthesia, especially if the bone roof of the infraorbital canal is damaged. Deep lateral wall decompression can also produce infraorbital hypoesthesia if burring is carried deep over the superior aspect of the inferior orbital fissure. It is important to irrigate abundantly during this step to avoid heating of adjacent tissues (especially in this case, the infraorbital nerve). Also, lateral wall decompression can produce hypoesthesia in the zygomatic-facial nerve territory. Hypoesthesias are usually transient.
- Diplopia: It is not an uncommon complication of orbital decompression. It has been reported in 20% - 30% of cases, depending on the different walls decompressed and techniques employed, reaching in some series up to 80%.[2-6] Lateral wall decompression seems to produce less diplopia. The origin of postoperative diplopia is multiple. Transient diplopia is usually due to intraoperative muscle trauma, direct or indirect, with secondary muscle inflammation.[7] Spontaneous recovery usually occurs between the second week and the third postoperative month. There have been cases reported in which the diplopia recovered up to one year after surgery.[7] Permanent diplopia is due in most cases to an infero-medial displacement of the orbital contents, including the globe and the muscular cone. In unilateral cases, postoperative strabismus develops as hypotropia, and in bilateral cases as endotropia. The development of postoperative diplopia does not depend on the orbital approach employed, although endoscopic and transantral decompression seems to have a higher risk.[1,7-10]

In summary, orbital decompression entails the increase of the orbital continent, which may be achieved through several approaches. We have the possibility of decompressing three different walls, two of them to a higher or lesser degree, and they can be combined in a customized way depending on each patient's situation.

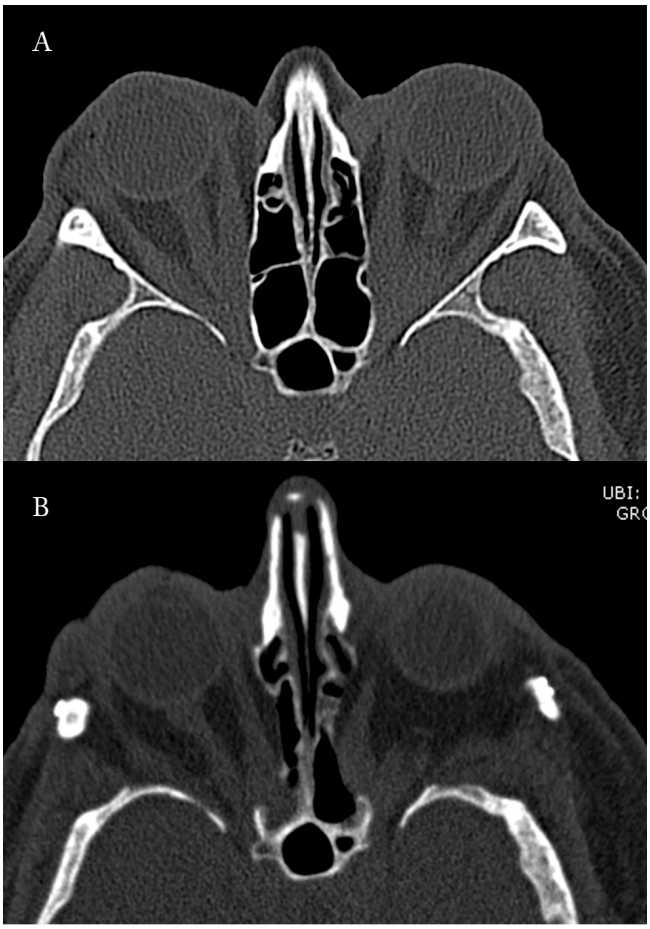
CLINICAL CASES



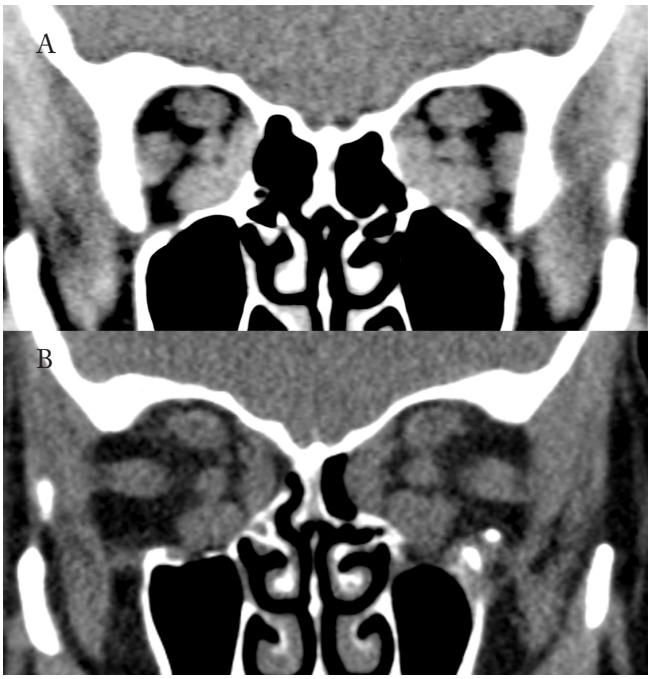
Case 1. Patient before (A) and after (B) medial and lateral wall orbital decompression.



Case 2. Patient before (A) and after (B) medial and lateral wall orbital decompression with inferior lipectomy.



Case 3. Axial computed tomography (CT) scan before (A) and after (B) three wall decompression.



Case 4. Coronal CT scan before (A) and after (B) three three wall decompression

Ethical Disclosures
Confidentiality of Data: Patient consent obtained.
Conflicts of Interest: The authors have no financial interest in the products or procedures mentioned in this chapter

Corresponding author
Marco Sales-Sanz
marco@sales-sanz.com

REFERENCES

1. Paridaens D, Lie A, Grootendorst RJ, van den Bosch WA. Efficacy and side effects of 'swinging eyelid' orbital decompression in Graves' orbitopathy: a proposal for standardized evaluation of diplopia. Eye. 2006;20:154-62.
2. Shorr N, Neuhaus RW, Baylis HI. Ocular motility problems after orbital decompression for dysthyroid ophthalmopathy. Ophthalmology. 1982;89:323-6.
3. Warren D, Spector JG, Burde R. Long-term follow-up and recent observations on 305 cases of orbital decompression for dysthyroid orbitopathy. Laryngoscope. 1989;99:35-40.
4. Morax S, Bok C, Hurbli T. Troubles oculomoteurs dans l'ophtalmopathie thyroïdienne. Ophtalmologie. 1996;10:487-94.
5. Lyons CJ, Rootman J. Orbital decompression for disfiguring exophthalmos in thyroïd orbitopathy. Ophthalmology. 1994;101:223-30.
6. Kalmann R, Mourits MP, Vanderpol JP, Koornneef L. Coronal approach for rehabilitative orbital decompression in Graves'ophthalmopathy. Br J Ophthalmol. 1997; 81:41-5.
7. George JL, Tercero ME, Maalouf T, Angioï-Duprez K. Evolution et pronostic des diplopies compliquant les decompressions osseuses des orbitopathies thyroidiennes J Fr Ophtalmol. 2001, 24:245–52.
8. Mourits MP, Koornneef L, Wiersinga WM. Orbital decompression for Graves' ophthalmopathy by infero-medial, by infero-medial plus lateral, and by coronal approach. Ophthalmology. 1990, 97:636–41.
9. Paridaens D, Hans K, van Buitenen S, Mourits MP. The incidence of diplopia following coronal and translid orbital decompression in Graves' orbitopathy. Eye. 1998;12:800-5.
10. Siracuse-Lee DE, Kazim M. Orbital decompression: current concepts. Curr Opin Ophthalmol. 2002;13:310-6.

Section 4

Orbital tumors

12. Tumors of the Lacrimal Gland and Lymphoproliferative Disease

OPHTHALMOLOGY

Mara Ferreira, MD; João Cabral, MD

Summary

The major causes of lacrimal gland enlargement are neoplastic, inflammatory, and structural. Together, they constitute 4% to 10% of all orbital masses. This chapter covers primary benign and malignant tumors derived from the epithelial structures of the lacrimal gland and lymphoproliferative disease. They are characterized by a noninflammatory mass effect with proptosis and inferior and nasal displacement of the globe. Benign epithelial tumors and lymphomas generally are painless, whereas malignant epithelial tumors and inflammations are more likely to cause pain. On imaging studies, benign lesions show normal adjacent bone and, malignancies may show infiltration of soft tissue and bone destruction.

Keywords: *Orbital Neoplasms; Lacrimal Gland Tumors; Lymphoproliferative Disorders;*

TUMORS OF THE LACRIMAL GLAND

1. PRIMARY EPITHELIAL TUMORS OF THE LACRIMAL GLAND

About 20% of the solid lacrimal gland masses are of epithelial origin whereas 80% are of nonepithelial origin.[1] Of the reported epithelial tumors, 55% are benign and 45% are malignant.[1] The most important primary benign epithelial neoplasm is pleomorphic adenoma (PA). Primary epithelial malignancies of the lacrimal gland are 60% adenoid cystic carcinoma (ACC), 20% pleomorphic adenocarcinoma, 10% primary (*de novo*) adenocarcinoma, 5% mucoepidermoid carcinoma, and 5% miscellaneous malignant epithelial neoplasms.[1]

They occur mostly in middle-aged adults, however, ACC has a biphasic age distribution, with some occurring in children in the first or second decade and another group occurring in young to middle-aged adults.[1] There is no known predilection for race or gender.

1.1 LACRIMAL GLAND PLEOMORPHIC ADENOMA (BENIGN MIXED TUMOR)

Pleomorphic adenoma (PA) is the most common neoplasm of the lacrimal gland. It usually arises from the orbital lobe and primarily occurs in young to middle-aged adults, even though it may also occur in children.

The typical presentation of PA is a unilateral progressive nonpainful fullness in the lateral upper lid (Fig.1A), with proptosis and inferonasal displacement of the globe occuring as the tumor enlarges.

Computerized tomography (CT) (Fig. 1 B,C) or magnetic resonance imaging (MRI) scans show a round-to-ovoid, well-circumscribed mass with a smooth or slightly irregular surface in the lacrimal gland fossa. The anterior portion appears to terminate at the orbital rim or posterior to it, suggesting that the lesion affects the orbital lobe and spares the palpebral one. Frank bone destruction, as in malignancies, is usually not evident, but there may be bone remodeling. Like malignant epithelial tumors, MRI shows low to isointense signal on T1-weighted and hyperintense signal on T2-weighted images.

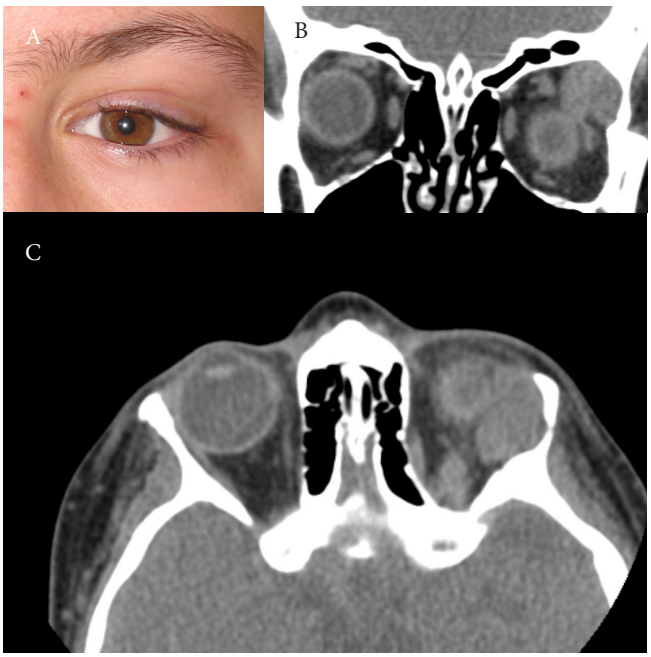


Figure 1. Young patient with left lacrimal gland pleomorphic adenoma (A). Coronal (B) and axial (C) CT scans from the same patient.

The histopathology shows a combination of benign epithelial and mesenchymal elements.

If a PA is suspected, it should be removed by performing a superolateral orbitotomy. An eyelid crease incision may be used, with an extraperiosteal approach, with or without an osteotomy. In general, it is mandatory to completely excise the mass in its capsule without a prior biopsy. For an incompletely excised PA, the risk of recurrence or malignant transformation is 10% within 20 years and 20% within 30 years.[2]

1.2 LACRIMAL GLAND ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma (ACC) is the most common

(60%[1]) malignant epithelial tumor of the lacrimal gland. It represents 12% - 18%[1,2] of all lacrimal gland lesions and 1% - 2%[1,2] of all orbital lesions. It is highly malignant. The mean age at presentation is 40 years, with a bimodal occurrence in the second and fourth decades, however it can occur as early as at the age of 10 years.
ACC causes progressive proptosis, faster than benign tumors, with inferior and nasal deviation of the eye (Fig.2). Because of its tendency to invade nerves, patients typically present within a few months complaining of pain. Hypoesthesia in the periocular area suggests posterior neural invasion and should be tested in patients with suspected ACC. Distant metastasis usually occur in the lung.

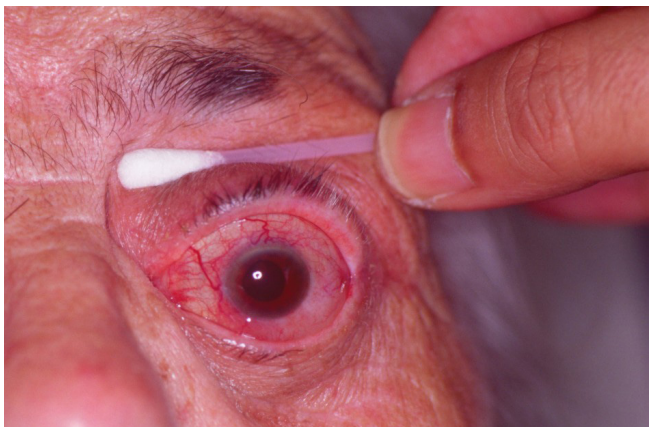


Figure 2. Elderly female patient with a left lacrimal gland adenoid cystic carcinoma

Typical CT demonstrates a round or elongated soft tissue mass, sometimes with irregular outlines (Fig. 3). Infiltration of the adjacent tissue and bone erosion is seen with larger, more aggressive lesions. Foci of calcification are suggestive of malignancy but that can also be observed with epibulbar choristomas and dermoid cysts. On MRI, the ACC shows low to isointense signal on T1-weight images, hyperintense signal on T2-weight images, and moderate contrast enhancement.
Five histologic patterns have been described: cribriform (glandular, Swiss cheese), solid (basaloid), tubular (ductal), sclerosing, and comedocarcinomatous. More than one pattern may be present on a single tumor. Perineural (or intraneural) or perivascular spread is very characteristic. The most common morphologic pattern is cribriform.[3] The least common is the dominant basaloid pattern, felt to be associated with a more aggressive behaviour, and most patients die within five years of recurrence.
Small and circumscribed tumors are treated by local excision followed either by brachytherapy or radical external beam therapy. If the tumor extends into the bone or soft tissues the treatment is orbital exenteration with removal of the affected bone supplemented by radical external beam therapy. The role of local regional or systemic chemotherapy remains unclear.

1.3 LACRIMAL GLAND PLEOMORPHIC ADENOCARCINOMA (CARCINOMA EX PLEOMORPHIC ADENOMA)

Pleomorphic adenocarcinoma is the second most important primary epithelial malignancy of the lacrimal gland.[1] It is

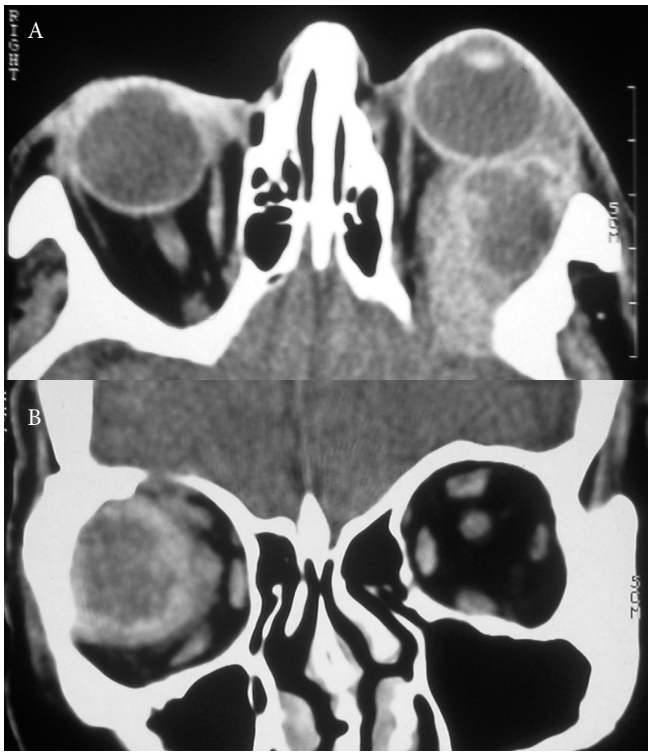


Figure 3. Axial and coronal CT scans of a left (A) and a right (B) lacrimal gland adenoid cystic carcinoma

a malignant transformation of pleomorphic adenoma, and it can develop from an incompletely excised pleomorphic adenoma. Therefore, patients are usually 10 to 20 years older than patients with the benign lesion.
The clinical features of pleomorphic adenocarcinoma are similar to ACC: proptosis, inferonasal displacement of the globe, motility disturbance, and sometimes pain. It originates distant metastasis to the bone.
CT and MRI imaging are similar to that of ACC. Histologically, it contains fewer glandular structures and the cells have more anaplastic features than pleomorphic adenoma. The tumor can infiltrate orbital bone and nerves.
The management of pleomorphic adenocarcinoma is identical to that of ACC. However, the prognosis of pleomorphic adenocarcinoma appears to be somewhat better than that of ACC.[1]

Rose and Wright suggest that the major clinical characteristics that differentiate the risk of malignant versus benign lesions are based on clinical features such as the duration of symptoms (less than ten months), persistence of pain and the evidence of sensory loss. CT signs of malignancy are ill-defined round or oval mass, molding of the mass to the globe or along the lateral orbital wall, tumor calcification, and bone invasion.[3]

2. LYMPHOPROLIFERATIVE DISEASE OF THE ORBIT

Ocular adnexal lymphoproliferative disorders represent 10% of all extranodal disease,[2] 8% of all orbital tumors in general population and 28% in older adults.[4] Lymphoproliferative disorders comprise a wide spectrum of diseases, ranging from benign (low-grade lymphoid hyperplasias) to malignant lymphoma, and should be

differentiated from idiopathic orbit inflammation, which is an entity characterized histopathologically by polymorphic cellularity from different cell lineages.
The diagnosis and classification of lymphoid proliferations are one of the most difficult and challenging problems encountered by the pathologists. The classification currently used is the updated version of the World Health Organization of the Revised European American Lymphoma (REAL).

2.1 REACTIVE LYMPHOID HYPERPLASIA

Reactive lymphoid hyperplasia represents approximately 16%[4] of all lymphoproliferative lesions of the orbit. It consists of histologically identifiable focal lymphoid collections, including secondary lymphoid follicles with germinal centers, and intact mantle zones that are widely separated by orbital fat and fibrous tissue. Its hallmark is the presence of polyclonal infiltrates.
Clinically, reactive lymphoid hyperplasia may simulate lymphoma, have an indolent course, featuring painless lesions that appear as firm or rubbery, slightly nodular, anterior orbital infiltrations (Fig. 4). Usually, it does not lead to any functional deficits. It can be a multisystem polyclonal disease.

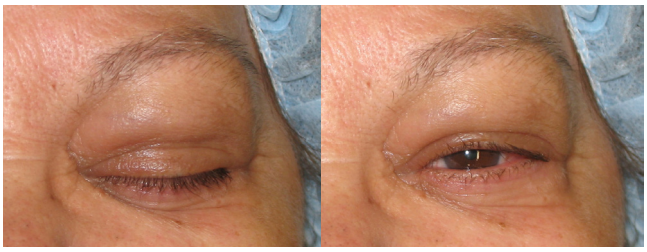


Figure 4. Patient with a left orbital reactive lymphoid hyperplasia

On imaging, reactive lymphoid hyperlasia mimics other lymphoproliferative disorders of the orbit, with perhaps slightly more infiltrative margins and less smooth nodularity (Fig. 5).
The reactive lesions improve with medium to moderate doses of prednisone. Failure to respond can be treated with relatively low-dose radiotherapy (2000cGy).
Clinical follow-up is recommended in all cases.

2.2 NON-HODGKIN LYMPHOMA (NHL)

NHL of B-cell is the most common malignant orbital tumor,[1] accounting for 24%[1,5] of all orbital malignancies in patients >59 years old. The most common categories of NHL are extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) (the dominant orbital and adnexal subtype), small lymphocyte lymphoma (SLL), lymphoplasmacytoid lymphoma (a less common small B-cell lymphoma) and mantle cell lymphoma.
Orbital lymphoma occurs mainly in the sixth or seventh decade of life, and it may be a local orbital disease or a systemic condition. The incidence of systemic lymphoma among patients with orbital involvement is 50%[1], and it is more common in immunosuppressed patients.
NHL presentes as a painless, slowly progressive, uni- or bilateral (in one third of the patients[2]) anterior orbital mass (confined to the lacrimal gland, superotemporal and extraconal within the orbit). It can often be palpable through the eyelid as a mobile rubbery lesion with nodular borders and slightly rounded

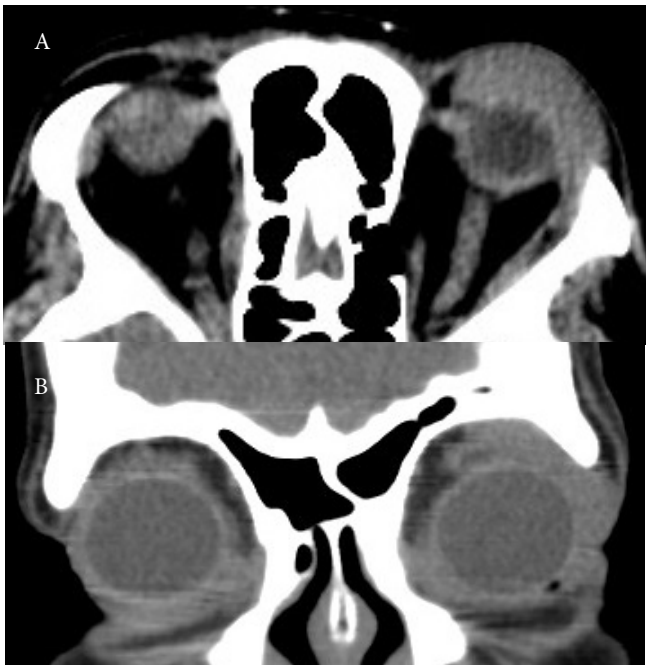


Figure 5. Axial (A) and coronal (B) CT scans of the same patient as in Figure 4

margins (pancake-like). Typically, there are no overlying skin changes as induration, yellowing, or lichenification (as in dermatotropic T-cell lymphomas) (Figs. 6,7). On the conjunctiva, it typically appears as a pink, fleshy (salmon patch) subconjunctival infiltration (Fig. 8). Usually, it does not affect vision or optic nerve function. There may be mild-to-moderate nonaxial proptosis and ptosis. It is important to evaluate the uveal tract for iris or choroidal infiltration, which strongly suggests that the orbital lesion is lymphoma.

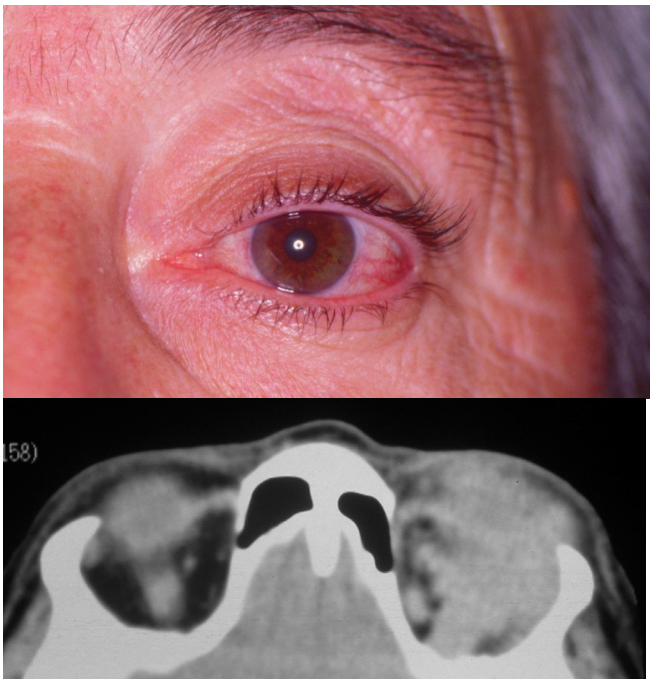


Figure 6. Superior left orbit with non-Hodgkin lymphoma.

On CT and MRI, it presents as an ovoid or elongated mass with lobulated or nodular well-defined edges, homogeneous, that tends to mold to adjacent orbital structures (Figs. 6,7). It shows

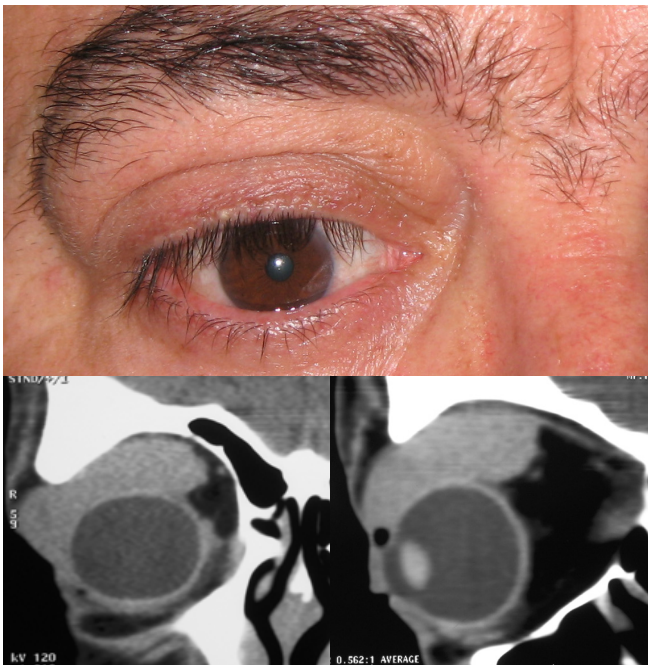


Figure 7. Superior right orbit with non-Hodgkin lymphoma

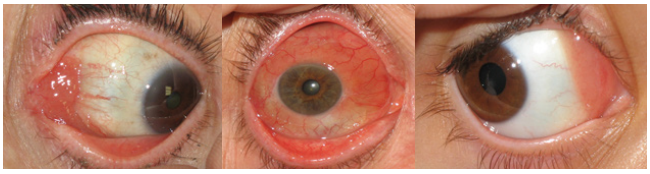


Figure 8. Non-Hodgkin lymphoma subconjunctival salmon patch infiltrations

moderate enhancement with contrast. It is usually extraconal, predominantly located in one quadrant, and confined to soft tissue. Five percent of the lesions have a multifocal presentation in the orbit, and one quarter is bilateral[3]. Calcification occurs in only 4% of NHL cases.[3] Bone and adjacent sinus involvement is rare. Fat-suppressed and gadolinium-enhanced T1-weighted MR scans are the most helpful techniques for delineating the extent of the tumor.

On ultrasound, lymphomas are acoustically homogeneous and of low reflectivity. They are poorly compressible.

Underlying systemic disorders, including Sjögren's syndrome, collagen vascular disease, hematologic and nonhematologic malignancies are common in patients with lymphoid lesions of the ocular adnexa. Patients should be evaluated systemically, both physically and with ancillary tests, to rule out associated systemic diseases.

Histopathologically, most lymphomas are classified as monoclonal B-cell extranodal marginal-zone, featuring anaplastic cells with large cleaved nuclei, nuclear pleomorphism, and prominent nucleoli.

The diagnosis is made by excisional or incisional orbital biopsy (lesions usually have a slightly friable texture on surgery), removing as much of the orbital tumor as possible while avoiding damage to the surrounding structures. If the patient has a known lymphoma that has already been diagnosed and staged, a fine-needle aspiration biopsy can be performed to confirm the orbital diagnosis. Prior communication with a pathologist is mandatory so that the specimen can be processed appropriately with immunohistochemistry and flow cytometry.

A multidisciplinary team provides the best management. If a systemic lymphoma is present and chemotherapy is advised, then the orbital lesion can be followed, with no further treatment[1], or be irradiated. If the disease is local, then it can be treated with orbital radiotherapy (3,500-4,000cGy).

Currently, there is some interest in treating MALT lymphoma of the conjunctiva with antibiotics, considering the relationship between gastric MALT lymphoma and *Helicobacter pylori* and *Chlamydia species*.

If systemic disease is not present, patients should have a yearly or biyearly follow-up for the risk of developing systemic lymphoma.

Overall, prognosis is excellent for these patients. The exception is mantle cell lymphoma, which tends to behave aggressively.

2.3 ORBITAL PLASMACYTOMA AND LYMPHOPLASMACYTOID TUMORS

Plasmacytomas are tumors predominantly composed of plasma cells, while lymphoplasmacytoid tumors are composed of B lymphocytes and plasma cells. The plasma cell is a B lymphocyte that produces large amounts of immunoglobulin.

Clinically, lymphoplasmacytoid tumors are similar to lymphoma. Plasmacytoma can occur as a solitary form of extramedullary plasma cell tumor or as part of multiple myeloma, a plasma cell neoplasm characterized by plasma cell infiltration of bone marrow and monoclonal immunoglobulin (Bence-Jones protein) in the serum.

The diagnostic approach and management are similar to non-Hodgkin lymphoma.

2.4 ORBITAL BURKITT LYMPHOMA

Burkitt lymphoma is a non-Hodgkin B-cell lymphoma. It has three distinct forms: the African type, non-African (American) type, and an acquired immunodeficiency syndrome (AIDS) type.

In the African type, orbital involvement is commonly secondary to invasion from the maxillary bone, with proptosis and upward displacement of the globe unilaterally (Fig. 9) or bilaterally, and an abdominal mass. The American type typically involves lymph nodes, bone marrow, and viscera. The AIDS type is more aggressive and mainly affects the central nervous system.

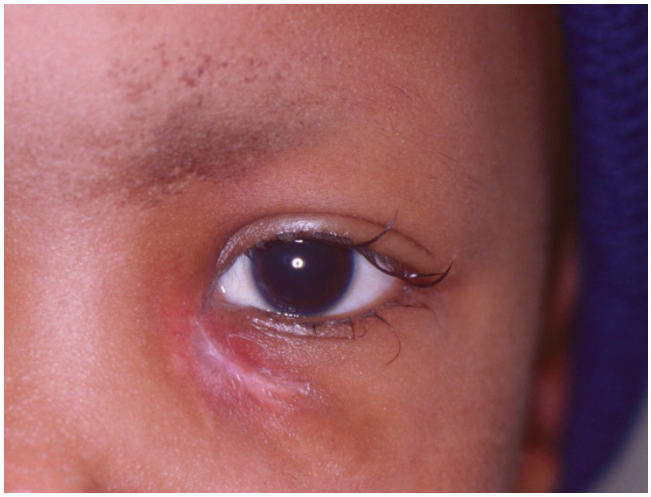


Figure 9. Left orbital Burkitt lymphoma

In the African type, imaging reveals a maxillary mass with secondary orbital involvement, in the American type an irregular mass in the paranasal sinuses with secondary orbital invasion, and the AIDS form can involve both soft tissue and bone. Suspected Burkitt lymphoma should call for a systemic evaluation for lymphoma and HIV infection.
The tumor is very sensitive to chemotherapeutic agents.

2.5 CUTANEOUS T-CELL LYMPHOMA (MYCOSIS FUNGOIDES)

Cutaneous T-cell lymphoma, or mycosis fungoides, is more aggressive than B-cell lymphoma: it grows faster and can destroy the eye. Most patients feature a systemic disease. The treatment is the same as for the B-cell lymphoma and the prognosis is guarded.

2.6 ORBITAL INVOLVEMENT BY LEUKEMIA

Leukemia is a neoplastic proliferation of abnormal leukocytes. Any form of leukemia can occasionally affect the orbit. Sometimes, the orbital involvement is the first sign of systemic disease. The most frequent form of orbital leukemia is soft tissue invasion by myeloid sarcoma, which is a rare childhood disease occurring in the first decade of life. The affected child presents with unilateral or bilateral eyelid edema, proptosis, or displacement of the globe. A firm rubbery mass can sometimes be palpated or visualized in the conjunctiva as a red-pink fleshy mass.
MRI shows an orbital soft tissue mass that enhances with contrast agents. Occasionally, it involves bone and extends into the temporal fossa.
The differential diagnosis includes lymphoma, metastatic neuroblastoma and idiopathic orbital inflammation.
Any child with an orbital mass should have an initial complete blood count to exclude leukemia.
Treatment of the orbital disease is with chemotherapeutic agents as in systemic leukemia.

Ethical Disclosures
Conflicts of Interest: The authors have no financial conflicts
Confidentiality of Data: Patient consent obtained.

Corresponding author
Mara Ferreira
maracoferreira@gmail.com

REFERENCES

1. Shields JA, Shields CL MD. Eyelid, conjunctival, and orbital tumors, an atlas and textbook.2nd ed. Philadelphia: Wolters Kluwer, Lippincott Williams & Wilkins; 2008.
2. Dolman PJ, Fay A. Diseases and disorders of the orbit and ocular adnexa. Amsterdam: Elsevier; 2017.
3. Rootman J.. Diseases of the Orbit. A multidisciplinary approach.2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003.
4. Font RL, Croxatto JO, Rao NA. Tumors of the eye and ocular adnexa: AFIP atlas of tumor pathology, series 4, fascicle 5. Washington: Armed Forces Institute of Pathology; 2006.
5. Pérez Moreiras JV, Prada MC. Orbit examination, diagnosis, microsurgery and pathology.New Delhi: Jaypee Medical; 2018.

13. Neuronal and Mesenchymal Tumors of the Orbit

NEUROSURGERY, OPHTHALMOLOGY
Christian Matula, MD PhD; Julius Lukas, MD PhD

Summary

In comparison to the incidence of other tumors, mass lesions of the orbit develop rarely. Nevertheless, a tumor in the orbit demands special attention due to the possibility of acuteness and malignancy, as well as the fact of being a significant burden for the patients themselves. The present chapter focuses on characteristics, epidemiology, diagnosis and treatment options of neuronal and mesenchymal tumors, and gives an overview about those lesions from a cooperative neurosurgical and ophthalmological standpoint, slightly different in selective clinical pictures. Based on several publications, the average incidence of these lesions is around 0.8/1 million. Interestingly, in the Afro-American population it seems clearly lower, around 0.2/1 million. Neoplasms of the orbit represent approximately 18% of all orbital pathologies in a neurosurgeon's practice, and around two-thirds of them are benign. Neuronal and mesenchymal tumors represent the major classes, around 2/3 depending on the different working groups. The most common are meningiomas and neurinomas, followed by epidermoids. Tumors of the orbit, in particular neuronal and mesenchymal tumors, represent a wide variety of lesions and requires special attention from different working groups for diagnosis, treatment, and aftercare.

Keywords:
Chondrosarcoma, Mesenchymal; Orbital Neoplasms/diagnosis; Orbital Neoplasms/therapy

INTRODUCTION

In comparison to the incidence of other tumors, mass enlargements of the orbit develop rarely. Nevertheless, a tumor in the orbit demands special attention due to the possibility of acuteness and malignancy, as well as the fact of being a significant burden for the patients, who are in many cases children. A patient with a diagnosis of orbital tumor requires a close cooperation between specialists from different disciplines – Ophthalmologists, Neuroradiologists, Oncologists and Neurosurgeons. Complex anatomic relationships combined with the position, constitution and magnitude of the tumor may constitute a big challenge for the surgeon, and requires many years of experience and practice. One of the oldest descriptions can be found in the papyrus Edwin Smith ("Wundenbuch"), an ancient Egyptian medical text written in Papyrus, 16th-17th Dynasty, Middle Kingdom ~ 1500 BC, one of the oldest written documents on medical treatment, and where the orbit deserves a very special attention and description.[1] In the present, as well as in the past and definitely in the future, the care of patients with orbital lesions is probably one of the biggest challenges in interdisciplinary work. In skull base surgery, in particular, the treatment of orbital tumors has made a rapid progress in recent years. The history of orbital surgery is a very long and exciting one and - as it has seldom been described in any other region– has been characterized by successes and failures.[2] From a neurosurgical point of view, it was, above all, the access routes that have always been of great interest in terms of their complexity and variability.[3] The incredible anatomical complexity of the orbital area is a particular attraction for neurosurgeons. The daily look in the mirror, often associated with the fear of suffering from a malignant disease or with the handicap of functional impairment, almost always represents a considerable burden for those affected. Unfortunately, in many cases children are involved, from newborns to older ones, which becomes also a very high emotional burden for the whole family. As already mentioned, a patient diagnosed with an orbital lesion requires a close collaboration between specialists from various disciplines - Ophthalmologists, Radiologists, Neurosurgeons, Oral surgeons, ENT surgeons, and Oncologists. Not only the complex anatomical conditions of the orbit per se, but also the variety and high number of possible lesions require many years of experience and practice in diagnosis, therapy, and aftercare. In reality, all age groups might be affected, from infants to the erderly. However, the differential diagnosis of orbital diseases covers a wide range of pathologies and has to consider different diagnostic and therapeutic facilities (Table 1).[4]

Table 1: Differential diagnosis of orbital disease

Endocrine orbitopathy	52 %
Neoplasms	18 %
Structural lesions	13 %
Infectious diseases	9 %
Vascular lesions	5 %
Functional diseases	3 %
Atrophy and degeneration	2 %

EPIDEMIOLOGY

The website of the U.S. National Institute of Health[5], which provides well-founded information on cancer statistics, estimates an incidence of 0.8 per 100 000 men and women (1998-2002). This number integrates orbital tumors as well

as tumors of the eyeball itself, and represents data from the U.S. only. No further statistics of the global incidence of orbital mass enlargements has been made available so far. Thus, the incidence of orbital tumors is estimated below this number in men and women (0.9 in men and 0.6 in woman). Multicenter, long-term data is required to obtain meaningful statistics. Published studies that rank the relative incidences of orbital tumors are either not complete or ongoing.[6] There is strong evidence that tumors of the orbit occur more frequently in whites than in patients with other ethnical origins. It is not known if the slight increase of orbital tumors is a real increase caused by environmental factors or a consequence of better diagnostic resources making it a relative increase (genuine or spurious). A large increase in orbital lymphomas was documented by Margo *et al* in the Florida cancer registry from 1931 through 1981[7], and could be proven nowadays by Julius Lukas and his group investigating immunohistochemical expression of cereblon and MUM1 as potential predictive markers of response to lenalidomide in extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma).[8]

The analysis of the incidence according to coarse age groups shows that, especially in the first two decades of life, an unexpectedly high probability of occurrence exists. However, the average mean age of patients diagnosed with an orbital tumor is approximately 60 years.[9]

TUMOR RANKING

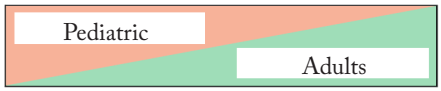
The incidence of distinct orbital tumors in patients presenting with an unilateral proptosis was described by Youman *et al* as: "Approximately one third of the patients (seen in the Columbia-Presbyterian Medical Center) proved to have hemangioma, another third had pseudotumor, thyrotoxic myositis, granuloma or other mass lesions that are not primarily neurosurgical problems; and the remaining third of these patients who presented with unilateral exophthalmos proved to have optic glioma, neurofibroma, meningioma, osteoma, encephalocele, or carotid-cavernous fistula.".[10]

Keeping in mind that not every mass enlargement in the orbit causes proptosis, and ignoring the relevance of different disciplines, Adam J Cohen *et al.* described the frequency of orbital tumors as: "Top 3 pediatric tumors are dermoid cysts, capillary hemangioma, and rhabdomyosarcoma. Top 3 adult tumors are lymphoid tumors, cavernous hemangiomas, and meningiomas" (Table 2).[11] The American Society of Ophthalmic, Plastic and Reconstructive Surgery confirmed this frequency on their website.[12] Shields et al. determined the incidence of specific orbital tumors between patients referred to an ocular oncology center. The most common diagnoses were lymphoid tumor (11%), idiopathic orbital inflammation (11%) and cavernous hemangioma (6%).[13]

Of substantial interest is another study conducted in an older adult population, published by Demirci H *et al.* In this article the sequence of frequency was similar but the overall percentage changed: the most common diagnosis was malignant lymphoma in 24% of cases, orbital inflammation in 10% and cavernous haemangioma in 8%.[14]

Neuronal and mesenchymal tumors together will represent approximately 50% of cases, and will remain as the most significant group seen by Neurosurgeons (Table 3).[15]

Table 2: The "Top Three" orbital tumors in pediatrics and adults



"Top 3" Pediatric orbital tumors	"Top 3" Adult orbital tumors
Dermoid cysts	Lymphoid tumors
Capillary hemangioma	Cavernous hemangioma
Rhabdomyosarcoma	Meningioma

Table 3: Percentage frequency of intraorbital tumors in a group of neurosurgical patients

Group of Tumor	Percentage of Frequency
Adenoid cystic Ca	1.5
AV-fistula	5.3
Cavernous Hemangioma	11.0
(Epi-)Dermoid	27.2
Infectious Pseudo TU	4.9
Capillary/Juvenile Hemangioma	10.6
Lipofibroma	0.4
Lymphangioma	3.5
Lymphoma	11.0
Metastasis	3.5
Muco-(pyo.)cele	3.3
Neurinoma	0.2
Neurofibroma	1.5
Optic glioma	0.2
Optic nerve sheet meningioma	4.9
Epithelloid cell Ca	1.1
Pleomorphic adenoma	1.5
Rhabdomyosarkoma	1.1
Orbital varix	1.5
Others	5.5
Total	100.0

ORBITAL TUMORS – AN OVERVIEW

Based on an analysis of patients at the University of British Columbia's Orbital Clinic in the period between 1976 and1999, Rootman gives the following frequency distribution of distinct neoplasia types[16]: neurogenic origin 4.9%, lymphoproliferative 4.1%, vascular 2.4%, secondary neoplasm 2.3%, mesenchymal origin 1.6%, metastasis 1.5%, lacrimal gland tumors1,2%.

Shields *et al*[13] determined in a retrospective case series the incidence of various orbital neoplasms from 1264 patients assigned to an ophthalmologic-oncological center. The most frequent diagnoses were lymphoma 11%, pseudotumor 11% and cavernous hemangioma 6%. Demirci *et al.*,[14] in another retrospective study involving only a group of patients over the age of 60 years, found that malignant lymphoma incidence was 24%, pseudotumor 10% and cavernous hemangioma 8%; Although the order of the three most common orbital neoplasms does not change, their frequency differs significantly. It has also been shown that secondary tumors and metastases increase in frequency in patients over the age of 60, resulting

in a ratio of 4: 1 compared to primary tumors.[17]
In contrast, Michael Mercandetti *et al*[18] (Members of the American Academy of Ophthalmology and American Society of Ophthalmic Plastic and Reconstructive Surgery) described lymphomas, cavernous hemangiomas and meningiomas as the three most commonly seen orbital tumors in adults; and dermoid cyst, capillary hemangioma, and rhabdomyosarcoma as the three most common childhood tumors (Table 4).

Table 4: Frequency distribution of different types of neoplasia

Neuronal Tumors	4,9 %
Lymphoproliferative TU	4,1 %
Vascular Tumors	2,4 %
Secondary Neoplasm	2,3 %
Mesenchymal Tumors	1,6 %
Metastasis	1,5 %
Lacrimal Tumors	1,2 %

1.NEURONAL TUMORS

1.1 OPTIC NERVE GLIOMA (FIG. 1)

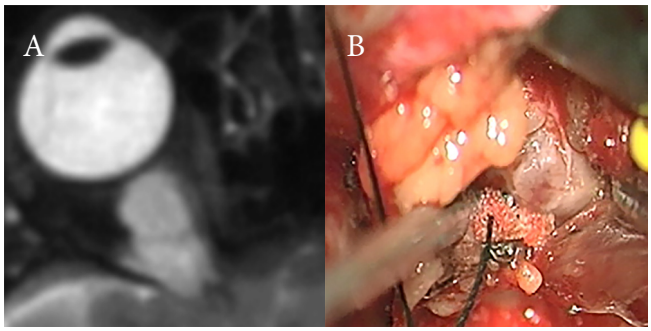


Figure 1. Optic nerve glioma

Median age: Primarily children with a mean age of 8.8 years are affected by optic nerve gliomas. Occurrence in adults might suggest a worse prognosis.[19]
Incidence: Optic nerve gliomas occur in 0.1% - 1% of adults and 3% - 6% of children presenting with unilateral proptosis.[10]
Location: The optic nerves including the chiasm and optic tract can be affected by optic nerve gliomas.
Etiopathology: The origin of optic nerve glioma remains unknown. However, mutation of p53 TSG is observed in patients with this tumor.
Clinical presentation: Visual loss, proptosis, optic disc pallor or atrophy, shunt vessels, tortuous vessels, choroidal striae, endocrine dysfunction and signs of hydrocephalus are commonly seen in patients with optic nerve glioma.
Radiological features: Enlarged and rounded optic canal. Possible deformation of the anterior third ventricle.
Histological appearance: Predominant cell type: pilocytic astrocytes, oligodendroglia-like cells, Rosenthal fibers, possible fibromatosis of the optic nerve sheath.
Treatment: Surgical resection of the optic nerve by transcranial route is one option, rising however some controversy as a treatment option,[20] Other authors suggest a period of observation.[21] In cases of chiasmal involvement surgery is associated with a severe impairment of vision, thus radiotherapy is recommended (45 to 50 gray over five weeks).[10] Also, combined chemotherapy may also be used to treat optic nerve glioma.
Prognosis: Complete resection yields 100% recurrence-free survival.[20] Prognosis in adults is very poor with an overall mortality of 97% and a mean survival of 8.7 months.[19]
Comment: Juvenile optic nerve glioma has been described as equivalent to grade 1 astrocytoma and equivalent to grade 4 astrocytoma in adults.[21] Gliomas are contingently associated with NF (especially in patients without chiasmal involvement) and to glioblastoma.

1.2 ORBITAL MENINGIOMA (FIG. 2)

Median Age: Commonly orbital meningiomas occur in the fourth and fifth decade of life. Children with neurofibromatosis can also be affected. Male to female ratio is 1:2.
Incidence: Orbital meningiomas constitute 5% to 17% of all primary orbital tumors.[22]
Location: In most cases, the origin of orbital meningioma is the dura of the optic nerve. Also, orbital meningioma may arise from the periorbita or arachnoid rests of the superior orbital fissure.
Etiopathology: Etiology of orbital meningioma is unknown. Fractures of the skull, radiotherapy and oncogenic viruses have been discussed as a trigger.[19] Orbital meningiomas are described to originate from arachnoid cap cells.
Clinical Presentation: Significant visual impairment, minor painless proptosis, progressive optic neuropathy over months and years, opticociliary shunt vessels, possible optic disc pallor, scotomas, enlarged blind spot and afferent papillary defects may be present in patients with orbital meningioma.
Radiological Features: Calcifications on computed tomography (CT) scan, thickened optic nerve, contrast enhancement, hyperostotic changes.
Histological Appearance: Meningothelial cells psammoma bodies, atrophy of the optic nerve.
Treatment: Usually surgical resection of the orbital meningioma by a transcranial route is performed. Impairment of vision frequently occurs after surgery cause by the interruption of the

Figure 2. Orbital meningioma

central retinal artery or complete removal of the optic nerve with the tumor. In case of involvement of the periorbita or growth into the superior orbital fissure, complete resection is rarely possible. This situation leads to recurrence and thus radiotherapy should be performed. *Outcome:* In general is good with a recurrence rate of approximately 10%. Orbital meningiomas behave much more aggressively in children than in adults.[15]

1.3 PERIPHERAL NERVE TUMORS

The incidence of peripheral nerve tumors is estimated by Youmans *et al.* as 5% to 15%[10], and by Gündüz *et al.* [2] as 1.4% to 5.3%[23] of all orbital tumors.

1.3.1 Neurofibroma

Neurofibromas are classified by their histological appearance in simple, diffuse and plexiform.

Median Age: Plexiform and diffuse neurofibromas occur mostly in the first decade of life. Simple neurofibromas affect middle-aged adults.

Incidence: Neurofibromas are the most frequent peripheral nerve tumors with an estimated incidence of 0.8% to 3.0%.[3]

Location: Plexiform neurofibroma is frequently located in the upper lid. Common location of simple neurofibroma is the superior lateral orbital quadrant.

Etiopathology: Neurofibromas are described to originate from neural crest cells. This tumor is frequently associated with neurofibromatosis; however they may present as isolated orbital lesions.

Clinical Presentation: Painless proptosis is typically seen in patients with neurofibroma.

- *Plexiform neurofibroma* is commonly associated with neurofibromatosis and bony hypoplasia. Clinical features might be pulsatile proptosis, S-shaped lid deformity, associated congenital glaucoma, hyperplasia of the soft tissue and proptosis.
- *Diffuse neurofibroma* is variably associated with neurofibromatosis. Patients present proptosis with or without the involvement of the eyelids.
- *Simple neurofibroma* is not usually associated with neurofibromatosis. Downward displacement of the globe, proptosis, bone destruction and invasion to the sinus are clinical findings in these patients.

Radiological Features: Moderate contrast enhancement, isointense.

Histological Appearance: Capsulated bundles of enlarged nerves in a connective tumor mass. Immunoreactivity with S-100 protein is possible.

Treatment: Surgical resection (usually using a lateral transorbital approach or a transcranial route)[15] depends on the histological type of tumor as well as its extension. Diffuse neurofibromas are extremely difficult to remove completely by surgery, while simple neurofibromas are encapsulated and thus easy to remove en-bloc. Commonly a sensory skin deficit occurs after the surgical procedure. No radiotherapy is performed in the treatment of neurofibroma.

Outcome: Excellent prognosis after complete excision. Recurrence is observed in patients with diffuse and simple neurofibroma or when residual tumor has been left in place. Malignant transformation is rare, however it may occur especially in patients with neurofibromatosis.[19]

1.3.2 Schwannoma (Neurilemmoma) (Fig. 3)

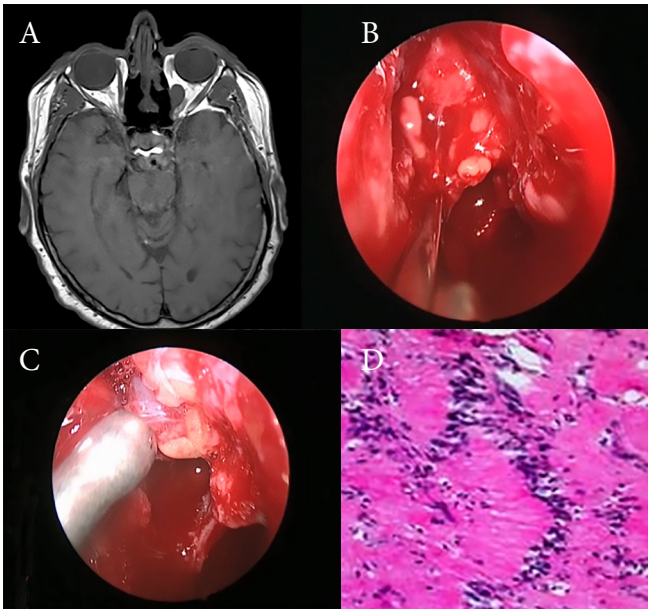


Figure 3. Schwannoma (Neurilemmoma)

Median Age: Schwannomas occur mostly in young to middle-aged adults.

Incidence: Orbital schwannomas account for less than 2% of all orbital tumors.[24]

Location: Schwannomas are intraconal or extraconal, usually positioned in the superior orbit. Invasion to the cavernous sinus through the superior orbital fissure have been described.[19] Schwannomas rarely occur at an intramuscular or epibulbar level.

Etiopathology: Schwannomas are known to develop from Schwann cells, mostly in the ophthalmic division of the trigeminal nerve. However, this tumor may originate from motor nerves.[25]

Clinical Presentation: Enormous, usually painless proptosis, downward displacement of the globe and accordingly disturbances of ocular movement.

Radiological Features: Well-circumscribed mass. Potential enlargement of the superior orbital fissure. Moderate enhancement after contrast injection in magnetic resonance imaging (MRI).

Histological Appearance: Encapsulated Antoni A pattern is cellular while compact regions Antoni B pattern are myxoid, loosely regions. Verocay (palisading) bodies, possible necrosis formation, and cystic areas. Immunoreactivity with S-100 protein.

Treatment: Usually orbital schwannomas can be easily removed; thus total excision is recommended by an anterior or superolateral orbitotomy. No radiotherapy is performed in the treatment of neurofibroma.

Outcome: Excellent prognosis in patients who underwent complete excision. Generally, no recurrence is observed, except in patients with neurofibromatosis. Malignant transformation is less likely than in neurofibromas.[19]

1.3.3 Malignant peripheral nerve sheath tumor

(Formerly known at neurofibrosarcoma or malignant schwannoma)

Median Age: This tumor occurs primarily in adults. In children is rare, usually associated with neurofibromatosis.[19]
Incidence: Malignant peripheral nerve sheath tumors are exceedingly rare.
Location: In most cases, the tumor occurs in the superior orbit.
Etiopathology: Malignant peripheral nerve sheath tumors develop mostly from the supraorbital and supratrochlear nerve.
Clinical Presentation: Rapidly progressive proptosis, displacement of the globe, pain and ptosis are seen in patients with malignant peripheral nerve sheath tumor.
Radiological Features: Well-defined, irregular borders.
Histological Appearance: Ill-defined, non capsulated, spindle cells, hyperchromatism, rich in mitotic figures. Immunoreactivity with S-100 protein.[26]
Treatment: An aggressive approach is required to treat malignant peripheral nerve sheath tumors: Total excision inclusively bony parts and radiotherapy is usually necessary.
Outcome: The prognosis of the tumor is poor. Recurrence, intracranial invasion and metastasis to lymph nodes are frequently described.[26]

1.3.4 Granular Cell Tumor

Median Age: This tumor occurs more frequently in adults than in children.[19,26] Most patients with a granular cell tumor are between 40 to 60 years.
Incidence: Rare. Skin, tongue and chest wall is more commonly affected by this tumor than the orbit. Granular cell tumors usually occur as a solitary lesion around orbicularis or rectus muscle.
Etiopathology: Still obscure. Myoblasts, histiocytes, astrocytes, Schwann-cells are discussed as the origin of these tumors.[19]
Clinical Presentation: Slowly growing proptosis, eyelid tumor, diplopia and ptosis occur in patients with granular cell tumor.
Radiological Features: Well-circumscribed orbital mass, commonly attached to muscle tissue.
Histological Appearance: Encapsulated clusters of tumor cells, collagenous tissue and skeletal muscle cells. Immunoreactivity with NSE (neuroenolase), various myelin proteins and sometimes with S-100 protein. Cytoplasmatic inclusions are observed in transmission electron microscopy.[26]
Treatment: Surgical excision is the method of choice but might be very difficult. No radiotherapy is performed in the treatment of granular cell tumor due to its intrinsic resistance.
Outcome: Malignant transformation is described; however, the prognosis is good if excision en bloc is possible.[19]

2. MESENCHYMAL TUMORS

2.1 RHABDOMYOSARCOMA (FIG. 4)

Median Age: Rhabdomyosarcomas are the most common primary malignant tumors in children. Males are more frequently affected than females.[26]
Incidence: Estimated as 7% of all orbital biopsies.[10]
Location: Rhabdomyosarcoma occurs in the muscles of the head and neck, as well as in the urogenital system and extremities.
Etiopathology: Rhabdomyosarcomas develop from remnants of embryonic mesenchyme and not, as formerly thought, from striated muscle.
Clinical Presentation: Symptoms include rapidly progressive proptosis, which can reach extreme proportions, lid edema, conjunctival hemorrhage, and lid discoloration. A mass is usually palpable.
Radiological Features: Signs of bone destruction. Enhancement after contrast injection Rhabdomyosarcomas occur close to muscles.
Histological Appearance: Hyperchromatic spindle cells of embryonic type.
Treatment: Radiotherapy and chemotherapy assisted by surgical reduction of the tumor.
Outcome: Nowadays cure is estimated as possible in 95% of cases [19], versus a cure rate of 45% observed 40 years ago. Older patients usually have better prognosis due to a higher differentiation of the tumor. Central nervous invasion worsens the prognosis dramatically and often leads to death within two years.
Comment: Three types of rhabdomyosarcomas are classified:

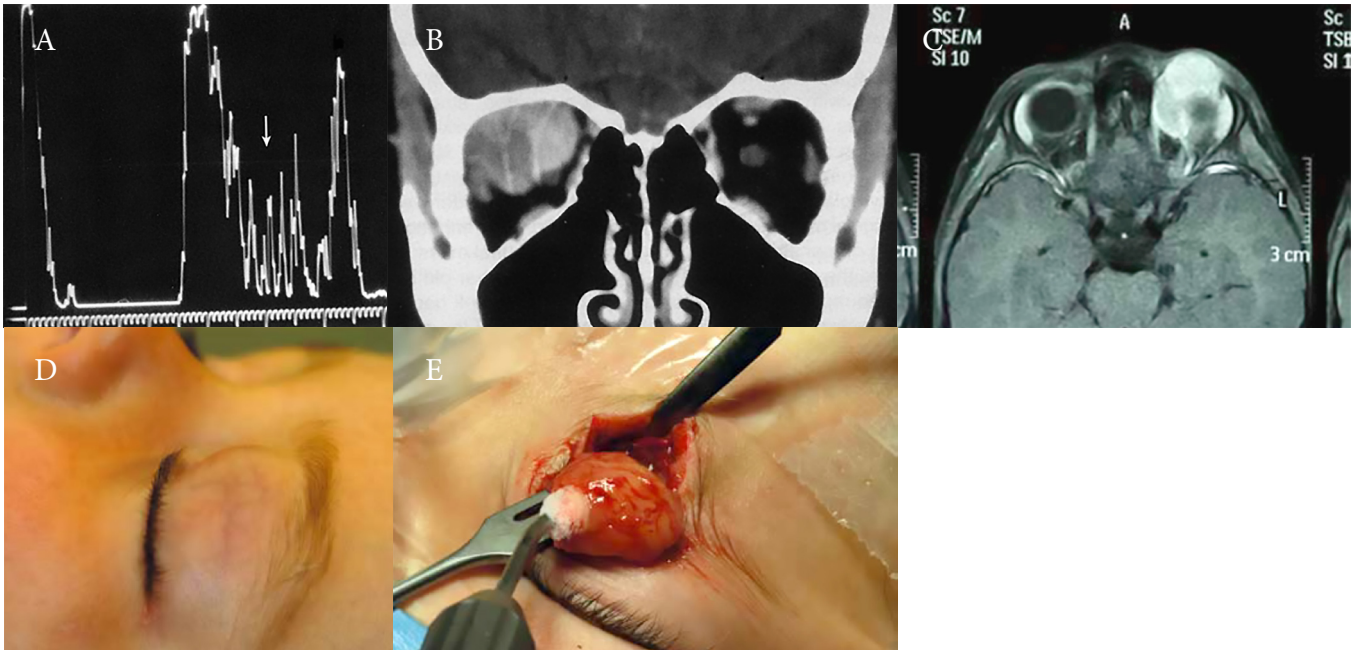


Figure 4. Rhabdomyosarcoma

embryonale differentiated, alveolar differentiated and pleomorphic differentiated.[26]

2.2 FIBROUS HISTIOCYTOMA

Represents a very heterogeneous group of mesenchymal tumors, not very frequent.[19,26]

- Fibromatosis: desmoid-type fibromatosis, juvenile fibromatosis, nodular fasciitis (=pseudosarcoma), giant cell fibroblastoma, fibroma, fibromyxoma, solitary fibrous tumor, fibrosarcoma (after radiation of retinoblastoma), dermatofibrosarcoma protuberans
- Histiocytosis:
  1. Langerhans-cell (epidermal immune cells) histiocytosis (formerly histiocytosis X)
  2. Xanthogranuloma, juvenile xanthogranuloma, cutaneous xanthomas: necrobiotic xanthogranuloma and xanthelasma which are yellow placoid skin lesions on or around the eyelids and usually occur bilaterally. Xanthelasma is associated with hyperlipidemia. Surgical excision, corticosteroids and radiation therapy may be necessary. Recurrence is observed frequently in patients with xanthelasma.

Median Age: Fibromatosis occurs commonly in adults; histiocytosis affects children between 1-15 years.
Incidence: Fibromatosis and histiocytosis are very rare orbital mass enlargements.[26]
Location: These tumors are frequently seen in the superior and anterior areas of the orbit.
Etiopathology: Is unclear; however, it is entirely possible that these tumors originate from pluripotent mesenchymal cell precursors.
Clinical Presentation: Symptoms are proptosis, decreased visual acuity and a lid mass usually palpable.
Radiological Features: Homogenous mass enhancement
Histological Appearance: Not encapsulated, infiltrative growth, spindle cells, vascular component
Treatment: Complete surgical excision is desirable; otherwise the neoplasm will recur in about one-third of patients.[15] Malignant transformation with aggressive and invasive behavior is also possible.[26] Histiocytosis is commonly treated with corticosteroids.
Outcome: Good if radically removed and no recurrence occurs.
Comment: Fibrosarcomas may occur after radiation due to retinoblastoma.[19,26] Xanthogranulomas are associated with Hand-Schüller-Christian disease, Letter –Siwe disease and Erdheim Chester disease.

Other mesenchymal tumors are fibroma and fibrosarcoma, leiomyoma and leiosarcoma, lipoma and liposarcoma but are exceedingly rare.

CONCLUSION

Dealing with neuronal and mesenchymal tumors is a challenging area. In general, orbital masses represent an unusually large heterogeneous group of lesions of various entities. Thus, a patient with a diagnosis of orbital tumor requires a close cooperation between specialists of different disciplines – Ophthalmologists, Radiologists, ENT, Oral and Maxillofacial surgeons, Oncologists and Neurosurgeons. An actively practiced interdisciplinary management appears to be the best, most effective, and most efficient way to treat orbital masses, with a special focus on functionality and aesthetics. The clinical signs of orbital masses, with a special emphasis on neuronal and mesenchymal tumors, are pain, proptosis, impaired vision and disturbance of motility. Based on our experience within the last 35 years, including more than 2000 patients seen with orbital tumors, it is not possible to distinguish a certain orbital tumor from another by its clinical signs only. The specific diagnosis needs high-level radiological evaluation by CT scan, MRI and ultrasonography (US), and confirmation by histological investigation. Ultrasound investigation in general and standardized echography in particular offer great advantages: no radiation exposure, real-time results, fast and extremely cost-effective, and can also be used in children without anesthesia, being close to histopathology. Out of several studies done by our ophthalmologists' group[27] a correct diagnosis could be proven in 94.3% of cases. Although the microsurgical management of orbital tumors denotes a severe intervention, the outcome of the affected patients is better than previously. The new techniques of cryosurgery and piezo surgery can be highly recommended as valuable strategies in certain orbital tumors, in particular of neuronal and mesenchymal origins, as well as neuronavigational techniques based on multimodal fused data sets (CCT, CTA, MRI).[28] Patients who underwent exenteration or enucleation, as well as patients who must adapt to new disability, should receive the possibility of rehabilitation and psychosocial support. Based on proven histology, additional radiation therapy, radiosurgery (LINAC, Gamma Knife, Cyberknife, Proton Bean, Carbon ion) must be considered. Thus, the establishment of an "Interdisciplinary Orbital Center" will offer the chance to bring all involved disciplines together with the possibility for personalized therapy, being highly recommended! Furthermore, no international or European guidelines exist regarding the clinical management of patients with orbital tumors, including neuronal and mesenchymal tumors. To better standardize the management of orbital mass enlargements further investigations are necessary, and the implementation of guidelines is absolutely recommended and should be done in a near future.

Acknowledgment:
The authors would like to thank Katharina Erb and Kathrin Ziegler for the excellent work with their master thesis to get the doctors degree, which builds the basis for this manuscript. We are also very grateful to our friend and colleague Wolfgang Hauff for his tireless input and inspiration in the field.
We further like to dedicate this work to our friend and colleague Franz Josef Steinkogler who unfortunately passed away much too early, we will never forget him!

Ethical Disclosures
Confidentiality of Data: Patient consents obtained.
Conflicts of Interest: The authors have no financial interest

Corresponding author
Christian Matula
christian.matula@meduniwien.ac.at

REFERENCES:

1. The Edwin Smith Papyrus from ancient Egypt. The world's first surgical treatise. Minn Med. 1985; 68:277, 279–80.
2. Cophignon J. History of orbital surgery. Neurochirurgie 2010; 56(2–3):77–80
3. Maroon JC, Kennerdell JS. Surgical approaches to the orbit. Indications and techniques. J Neurosurg. 1984; 60:1226–35.
4. Rootman J. Diseases of the Orbit: A Multidisciplinary Approach. New York: Lippincott Williams&Wilkins; 2003.;
5. National Cancer Institute. Surveillance, Epidemiology, and End Results Program [accessed Dez 2018]. Available at: http://seer.cancer.gov
6. DS Caspar, TL Chi, SL Trokel Orbital Disease: Imaging and Analyses. Stuttgart: Thieme Medical Publishers; 1993.
7. Margo CE, Mulla ZD. Malignant tumors of the orbit. Analysis of the Florida Cancer Registry. Ophthalmology. 1998; 105: 185-90.
8. Kiesewetter B, Simonitsch-Klupp I, Kornauth C, Dolak W, Lukas J, Mayerhoefer ME, et al. Immunohistochemical expression of cereblon and MUM1 as potential predictive markers of response to lenalidomide in extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma). Hematol Oncol. 2018; 36:62-7.
9. Dissertation Erb Katharina. Master thesis for obtaining the academic degree Doctor of Medicine (MD) at the Medical University of Vienna, Mat. Nr .: 0200357, submitted and accepted 2008
10. H. Richard Winn (eds). Youmans and Winn Neurological Surgery. Elsevier; 7th edition, 2016
11. [accessed Dez 2018]. Available at: http://www.emedicine.com/oph/topic758.htm 15.03.2006
12. American Society of Ophthalmic Plastic & Reconstructive Surgery. [accessed Dez 2018]. Available at: http://www.asoprs.org/tumors.htm 16.03.2006
13. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: The 2002 Montgomery Lecture, part 1. Ophthalmology. 2004; 111: 997-1008.
14. Demirci H, Shields CL, Shields JA, ̣ Honavar SG, Mercado GJ, Tovilla JC. Orbital tumors in the older adult population. Ophthalmology. 2002;109:243-8.
15. Matula C. Surgical therapy of orbital tumors from a Neurosurgeons perspective. Neurologisch. 2015:22-30.
16. Rootman J. Diseases of the Orbit: A Multidisciplinary Approach. Berlin: Lippincott Williams&Wilkins; 2003.
17. Erb Katharina. Master thesis for obtaining the academic degree Doctor of Medicine (MD) at the Medical University of Vienna, Mat. Nr .: 0200357, submitted and accepted 2011
18. Mercandetti M [accessed Dez 2018]. Available at: http://www.emedicine.com/oph/topic758.htm
19. Karcioglu ZA, editor. Orbital Tumors: Diagnosis and Treatment. Berlin: Springer; 2014.
20. Rengachary S, Ellenbogen R. Principles of Neurosurgery. Amsterdam: Elsevier; 1995.
21. Wulc A, Bergin D, Barnes D, Scaravilli F, Wright JE, McDonald WI. Orbital optic nerve glioma in adult life. Arch Ophthalmol. 1989; 107:10131016.
22. Reese A. Expanding lesions of the orbit. Trans Ophthalmol Soc. 1971; 91:85-104.
23. Gündüz K, Shields CL, Günalp I, et al. Orbital schwannoma: correlation of magnetic resonance imaging and pathologic findings. Graefes Arch Clin Exp Ophthalmol 2003;241(7):593-597
24. Jacobiecek F, Jones I. Neurogenic tumors. In: Duane T, Jaeger E, editors. Clinical Ophthalmology. Hagerstown: Harper & Row:1983. p.41:1-16
25. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. IARC. WHO Classification of Tumours of the Central Nervous System, Revised. 6th ed. Geneva: WHO; 2016.
26. El-Naggar AK, Chan JC, Grandis JR, editors. WHO Classification of Head and Neck Tumours (World Health Organization Classification of Tumours). 4th ed. Geneva: WHO; 2017.
27. Lukas J. Clinical diagnostic and standardized ultrasound of orbital mass lesions. Neurologisch. 2015:17-20.
28. Matula C, Lukas J, Hauff W, editors. Color Atlas of Microneurosurgery of Orbital Tumors. Thieme: Stuttgart; 2019.

14. Orbital Bone Tumors and Metastatic Tumors

OTORHINOLARYNGOLOGY
João Subtil, MD Phd FEB; Richard Voegels, MD PhD

Summary

Orbital tumors may grow from the neighboring paranasal sinuses. They are frequently benign, but can cause symptoms from displacing the orbital content (exophthalmia, diplopia) or from encasing and compressing nerves or vessels (visual loss, diplopia). We discuss the common benign tumors (bone tumors), and the rare malignant bone tumors and metastatic tumors.

Keywords: *Osteoma, Fibrous Dysplasia, Ossifying Fibroma, Osteogenic Sarcoma, Metastatic tumors;*

1. BONE TUMORS

INTRODUCTION

Orbital bone tumors most often grow from the neighboring paranasal sinuses; Primary lesions are very rare[1]. They are frequently benign, but cause symptoms from displacing the orbital content (exophthalmia, diplopia) or from encasing and compressing nerves or vessels (visual loss, diplopia)[1]. The most common are osteoma, fibrous dysplasia, ossifying fibroma, and cystic lesions[1]. Malignant bone tumors are rare and include osteosarcoma and Ewing's sarcoma, and usually symptoms develop rapidly and include proptosis, pain and diplopia[1].

1.1 OSTEOMA

Osteoma is the most common bony tumor in the orbit (Fig. 1). It´s a benign neoplasm composed of compact bone[2]. Its origins are not known, but theories include trauma, infection and development as possible factors[2]. Growth is slow, and most are assymptomatic[2]. The exception is the osteoma located on the optic canal, compressing the optic nerve (Fig. 2).

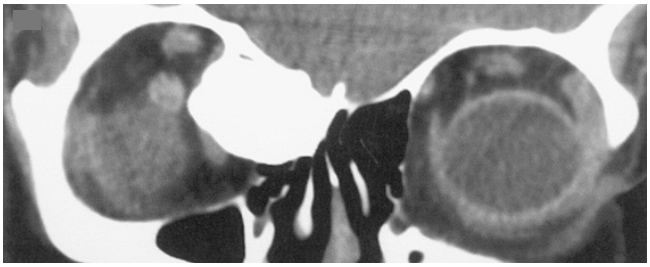


Figure 1. Ethmoidal eburnated osteoma displacing orbital content

Osteomas are almost always solitary lesions. However, in Gardner's syndrome (an autosomal dominant condition) they can be multiple and associated with intestinal polyposis and carcinomatosis[3].

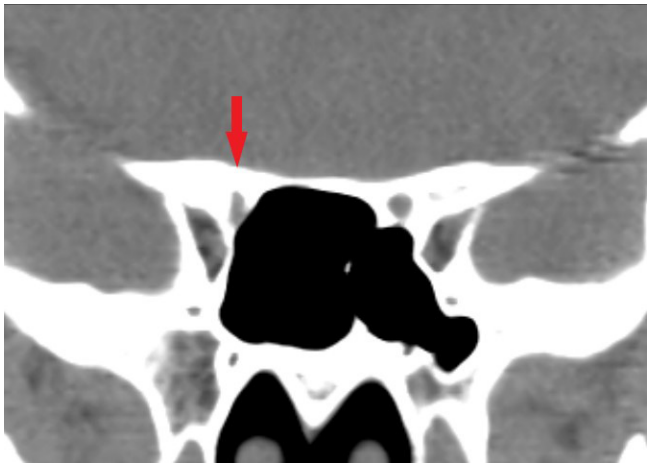


Figure 2. Osteoma of the right optic canal, compressing the optic nerve

They are classified into three types according to histology: eburnated (compact bone), fibrous (spongy bone), or mature (trabeculous bone)[2]. The eburnated osteoma is primarily composed of thick bony trabeculae with little fibrous tissue. The fibrous type contains highly vascularized fibroadipose tissue between the bony elements, which may lead to a misdiagnosis of ossifying fibroma or osteogenic sarcoma. This classification probably has little relevance, as most lesions contain all three tissue types and there seems to be no correlation with clinical behavior.

Diagnosis is made with computerized tomography and is most often incidental. It presents as highly circumscribed osteoblastic masses that can be either sessile or pedunculated. Bone window settings often reveal a trabecular central area with a dense periphery. It may present also as a complication – it may block sinus drainage (with sinusitis), cause a mucocele, or compress orbital or neurological structures. Complete observation should include fundoscopy and gastroenterology consultation (to exclude Gardner's syndrome).

Treatment is conservative – if it's not causing compression, we should "wait and scan" (repeat tomography after approximately one year) to exclude rapid growth (which is a rare presentation). Sphenoid sinus lesions that threaten the optic canal or orbital apex may be treated surgically before they become symptomatic, namely if growth is apparent.

Anterior lesions can be removed via an anterior orbitotomy, while more posterior tumors require a combined orbitocranial procedure[4]. Medial lesions are easily approached endonasally, and through this rout, sinus disease is synchronously managed.

1.2 FIBROUS DYSPLASIA

Fibrous dysplasia is a proliferation of immature woven bone, considered as an arrest in the developmental process from

lamellar bone[1]. In 75% of cases it involves a single focus on the cranial base (Fig. 3), and less comonnly (25%) multiple foci emerge. Polyostotic fibrous dysplasia develops at an earlier age and may be found as a part of McCune–Albright syndrome, a rare endocrine dysfunction consisting of precocious puberty, hyperthyroidism, and cutaneous hyperpigmentation.

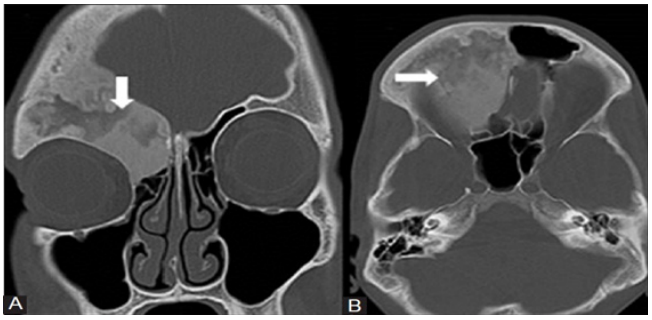


Figure 3. Fibrous dysplasia of the frontal and sphenoidal orbit.

Like osteomas, its diagnosis is usually incidental on a tomography, as it is seldom symptomatic. When symptomatic, also like osteomas, symptoms derive from displacement (proptosis, diplopia), nerve encroachment or secondary sinus involvement.
Initial diagnosis is obtained with tomography, but usually magnetic resonance is needed for differential diagnosis. Biopsy should be done to confirm the diagnosis and exclude the rare malignant transformation, but on an asymptomatic patient with typical radiologic features, a "wait and scan" approach is acceptable.
The natural history is usually of slow growth, which may continue into adult life[5]. Malignant transformation to osteosarcoma, fibrosarcoma, chondrosarcoma, and giant cell sarcoma rarely occurs, often heralded by rapid progression and increasing pain.
When indicated, treatment is surgical in order to spare important structures, bearing in mind that a complete excision is only rarely possible. Therefore, indication for surgery comes from the need to obtain tissue for diagnosis, for decompression purposes (optic nerve), or for cosmetic reasons (relieve proptosis). Optic nerve decompression can be done through an endonasal transsphenoidal approach, avoiding the transcranial approach when possible[6].

1.3 OSSIFYING FIBROMA

Ossifying fibroma only rarely affects the orbit[1]. It is rarer than the previous bone tumours, and is also known as juvenile ossifying fibroma or psammomatoid ossifying fibroma[2].
It is usually a well-defined, ovoid fibro-osseous lesion that commonly involves the cranial bones and in almost all cases presents as a monostotic disease. It has an indolent evolution, and symptoms arise from compression.
Diagnosis is radiological, and treatment is surgical, being a complete excision commonly possible.

1.4 OSTEOGENIC SARCOMA (OSTEOSARCOMA)

Osteogenic sarcoma is the most common primary malignant tumor of bone, and is more common in men and after the age of 40[2]. Presentation depends on the location and growth rate, but usually involve proptosis, diplopia, orbital pain and visual loss, all evolving rapidly. It may also present with nasal symptoms (nasal obstruction or epistaxis) or as a palpable or evident facial mass.
Diagnosis is suspected from radiology and clinical presentation but require biopsy for differential diagnosis. These tumors are more often seen in Paget's disease, fibrous dysplasia, or after radiation treatment and chemotherapy[2].
Treatment is preferentially surgical, but complete excision is rarely possible, needing chemoradiation therapy. Unlike for peripheral sites, prognosis remains poor in craniofacial tumors due to delay of diagnosis and difficulties in obtaining a complete resection[1].

2. METASTATIC TUMORS

Metastasis to the orbit is certainly an uncommon occurrence, accounting for about 6% of orbital neoplasms[7]. The distribution of its origin derives from the general incidence of tumors: the most frequent primary organs are breast in women, and lung and prostate in men. However, various types of primary tumors have been reported (Table 1).

Table 1. Origins of metastatic disease, by primary site (adapted from Karcioglu[2])

Site	*Cell type*
Breast	Lobular carcinoma, ductal carcinoma
Lung	Broncogenic carcinoma, adenocarcinoma, small-cell carcinoma, carcinoid tumor, malignant bronchial adenomas
Prostate	Carcinoma
Skin	Melanoma, squamous cell carcinoma
Kidney	Renal cell carcinoma, Wilms' tumor
Urinary bladder	Transicional carcinoma, urothelial carcinoma
Gastrointestinal tract	Adenocarcinoma, carcinoid tumor, gastric carcinoma, gastrointestinal stromal tumor
Liver	Hepatocellular carcinoma
Pancreas	Adenocarcinoma, islet cell carcinoma
Parotid gland	Malignant mixed tumor, adenoid cystic carcinoma
Thyroid	Follicular carcinoma, papillary carcinoma
Adrenal gland	Sympathoblastoma, neuroblastoma, adrenocortical carcinoma
Testis	Seminoma
Choroid	Melanoma
Soft tissue	Ewing' sarcoma, fibrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, uterine leiomyosarcoma, liposarcoma, angiosarcoma, osteosarcoma, malignant schwannoma, solitary fibrous tumor
Miscellanea	Bile ducts, gall bladder, ovary, cervix, vagina, larynx, peritoneum (mesothelioma), chordoma, pheochromocytoma

Forming metastasis is part of the undifferentiation process of tumors, where tumor cells eventually detach from the primary tumor and form a secondary tumor in lymph nodes or other organs. The process of forming this metastasis is beyond the scope of this chapter. However, metastatic tumors are usually more aggressive (as they are more undifferentiated) than primary tumors, growing and invading faster – about 90% of cancer deaths are caused by metastatic disease[2]. Paradoxically, for some tumors, like adenocarcinomas, this metastasis may take several years to reveal themselves.

Metastatic disease is therefore an ominous sign, making prognosis poorer. It means that disease is no longer local, confined to the primary site, but rather systemic and this means that treatment is not local, even for the metastasis themselves. Usually, metastatic disease must be treated in this context, presuming that cancer cells may have spread to anywhere else too, and so, treatment must also be systemic besides any local treatment one may offer to the metastasis site.

Malignant tumors may disseminate by different routes, namely blood vessels, lymphatic vessels, cerebrospinal fluid, serous cavities, or virtual spaces, and seed on preferential locations for each type of tumor. The mechanisms for these specific tropisms are still poorly understood - some preferred locations can be justified by blood flow, while others involve selective binding to endothelial cells or basement membranes from certain tissues.

Blood supply to the orbit is redundant and derives from both the internal and external carotid systems[8]. Hematogenous metastasis therefore pass through pulmonary circulation before seeding in the orbit. The venous system in the cranial base is also described as avalvular and so retrograde venous seeding may also happen[2]. There are no lymph nodes or lymphatic drainage to the orbit (only from the orbit) and other routes are likewise unlikely[2].

Orbital metastasis homing may also be explained by specific expression of cell surface molecules in orbital tissues – some variants of CD44, a transmembrane glycoprotein, are overexpressed in some cancers, and CD44 receptors are observed in the orbit in certain patients, like in thyroid eye disease[9]. Other molecular poorly understood mechanisms are certainly involved on orbital homing.

The orbit is composed of diverse tissue types (bony walls, muscle, fat) and tumor metastasis occur preferentially in specific tissues according to the primary lesions. Melanoma tends to metastasize to soft tissues and muscle, thyroid and prostate carcinomas to bone, and breast carcinoma to fat and muscle[2]. The most affected regions in the orbit appear to be the lateral and the superior orbit[10].

Since the orbit is encased in a bony walled compartment, expansion caused by metastatic disease is very soon obvious, sooner than in other sites[7]. It manifests with proptosis, diplopia, pain and vision loss, being impaired motility frequently disproportionate to proptosis[7].

Goldberg categorizes orbital metastatic disease in syndromes: mass (primary mass effect, palpable, displacement of the globe); infiltrative (infiltration of orbital tissues, with diplopia, enophthalmos, limitation of eye movements, firm orbit); functional (cranial nerve function deficit, out of proportion to mass or infiltration); inflammatory (inflammatory signs, pain, chemosis, injection, pain on eve movements, erythema, lid swelling); silent (no orbital symptoms)[7].

Diagnosis is histological. Suspicion is raised from clinical presentation, and whenever there's a doubt, biopsy must be obtained. Fine needle biopsy is a reliable method[11]. Sometimes open incisional biopsy is required and here, transnasal routes are preferable for lesions located medial to the optic nerve, while those in the lateral orbit may be accessed anteriorly. Lateral apical lesions may require a transcranial approach.

Treatment of metastatic disease must always be thought as systemic, as it is a systemic condition. Orbital disease can be addressed with surgery and radiotherapy, but in most cases, treatment with a curative intent will cause a significant impact on quality of life, and this must be weighed too. Even in patients with a limited survival, preservation of vision has a dramatic impact on the quality of life.

Metastatic disease is certainly a heterogenous group of malignant diseases and its behavior is mainly a reflection of the primary tumor behavior. We must keep a high level of suspicion and aim for a precocious diagnosis.

Ethical Disclosures

Conflicts of Interest: The authors have no financial conflicts

Confidentiality of Data: Patient consent obtained.

Corresponding author

João Subtil

joaosubtil@gmail.com

REFERENCES

1. Selva D, White VA, O'Connell JX, Rootman J. Primary bone tumors of the orbit. *Surv Ophthalmol.* 2004;49(3):328-342.
2. Karcioglu ZA. *Orbital tumors : diagnosis and treatment, 2nd edition.* New York, NY: Springer Science+Business Media; 2014.
3. Whitson WE, Orcutt JC, Walkinshaw MD. Orbital osteoma in Gardner's syndrome. *Am J Ophthalmol.* 1986;101(2):236-241.
4. Ciappetta P, Delfini R, Iannetti G, Salvati M, Raco A. Surgical strategies in the treatment of symptomatic osteomas of the orbital walls. *Neurosurgery.* 1992;31(4):628-634; discussion 634-625.
5. Bibby K, McFadzean R. Fibrous dysplasia of the orbit. *Br J Ophthalmol.* 1994;78(4):266-270.
6. DeKlotz TR, Stefko ST, Fernandez-Miranda JC, Gardner PA, Snyderman CH, Wang EW. Endoscopic Endonasal Optic Nerve Decompression for Fibrous Dysplasia. *J Neurol Surg B Skull Base.* 2017;78(1):24-29.
7. Goldberg RA, Rootman J, Cline RA. Tumors metastatic to the orbit: a changing picture. *Surv Ophthalmol.* 1990;35(1):1-24.
8. Ducasse A, Segal A, Delattre JF, Burette A, Flament JB. [Participation of the external carotid artery in orbital vascularization]. *J Fr Ophtalmol.* 1985;8(4):333-339.
9. Heufelder AE, Bahn RS, Boergen KP, Scriba PC. [Detection, localization and modulation of hyaluronic acid/CD44 receptor expression in patients with endocrine orbitopathy]. *Med Klin (Munich).* 1993;88(4):181-184, 277.
10. Demirci H, Shields CL, Shields JA, Honavar SG, Mercado GJ, Tovilla JC. Orbital tumors in the older adult population. *Ophthalmology.* 2002;109(2):243-248.
11. Dresner SC, Kennerdell JS, Dekker A. Fine needle aspiration biopsy of metastatic orbital tumors. *Surv Ophthalmol.* 1983;27(6):397-398.

15. Vascular Lesions of the Orbit and Orbital Venous Hypertension

NEUROSURGERY, OPHTHALMOLOGY
Christian Matula, MD PhD; Julius Lukas, MD PhD

Summary

Vascular lesions and venous hypertension are commonly put together as one subgroup within all orbital mass lesions due to their special appearance, slightly different diagnosis but especially because of their different treatment algorithm. Vascular lesions represent 6% - 12% of all orbital tumors and have a higher incidence in children than in adults. The most frequent are capillary and cavernous hemangiomas, representing approximately 80% of the tumoral lesions. In addition, one should not forget traumatic carotid-cavernous fistulas (CCF), which appear more frequently than thought. Angiosarcomas, lymphangiomas, hemangiopericytomas, as well as -extremely rare, but seen- leiomyomas represent a kind of subgroup due to their different appearance, treatment and sometimes biological behavior. Hemangiopericytomas in particular show a very high recurrence rate, up to 30%, with a chance of becoming malignant in about 40% of cases under certain circumstances. In general, vascular lesions are benign lesions with a high cure rate. Main treatment options are surgical resection, depending on the type, combined with radiation, radiosurgery or even, in specific cases, chemotherapy. Endovascular treatment is the choice for all arterio-venous hemangiomas and any kind of fistulas. Venous hypertension may be one of the first clinical syndromes of other pathological lesions of the skull base (e.g. cavernous sinus) and represent in such cases a part of the so-called "cavernous sinus syndrome". In general, vascular lesions of the orbit can be treated very properly if it is done by an experienced group of people having all treatment options available.

Keywords:
Arterio-venous Malformations; Orbit/blood supply; Orbital Neoplasms/diagnosis; Orbital Neoplasms/diagnostic imaging; Orbital Neoplasms/therapy

INTRODUCTION

Literature on the history of orbital tumors is scarce, sometimes not well documented and if so, then mostly shown in illustrative historical drawings and sketches. Concerning the histological appearance of orbital tumors, an ancient publication can be found describing a hemangiopericytoma for the first time in 1942 by Stout *et al.*, which seems to be one of the first reports reflecting that topic in a structured way, and with a specific focus on vascular tumors.[1]

Vascular tumors, as well as vascular malformations, represent a significant group of orbital space-occupying lesions. The incidence is reported to be 6% - 12% of all histological documented orbital tumors. Günalp *et al* showed, in a retrospective study of 85 patients diagnosed and treated in a period between 1963-1993,[2] the frequency of orbital vascular tumors (Table 1). Notably, 43 of the 85 tumors (approximately 51%) were diagnosed in children and adolescents under the age of 18 years. Although the individual vascular tumors are of different histological origin, one often finds besides a primary tumor a secondary tumor of a different origin and correspondingly different histology. Xiao *et al.* evaluated in a study the importance of ultrasound and computed tomography in the diagnosis of orbital vascular tumors and vascular malformations.[3] With the help of ultrasound, 98% of the tumors could be diagnosed, the false negative rate being 2%. In 93% of the diagnosed tumors, their type could be determined correctly preoperatively. On the other hand, 100% of the tumors could be detected in the computed tomography (CT) scan, but the tumor type was only correctly classified in 92%. However, CT angiography and magnetic resonance (MR) angiography remain as important additive diagnostic tools, especially in the possibility of further treatment.

Table 1: Percentage frequency of vascular tumors of the orbit

Capillary Hemangioma	43,5 %
Cavernous Hemangioma	41,2 %
Orbital Varix	3,5 %
Arteriovenouse Malformation & Fistulas	3,5 %
Angiosarkoma	3,5 %
Lymphangioma	3,5 %
Haemangioperizytoma	1,2 %

Since different types of tissue coexist in tumors, it is important to determine the predominant tissue for proper treatment and prognosis: Immunoreactivity with CD 31 demonstrates the existence of endothelial cells, e.g. in capillary hemangioma, cavernous hemangioma, and angiosarcoma. Lymphangioma is CD 31 and CD 34 negative, hemangiopericytoma is positive for vimentin and CD 34.[2]

1. VASCULAR LESIONS OF THE ORBIT

1.1. CAPILLARY HEMANGIOMA (FIG. 1)

Definition: This tumor type, also called "blood sponge", is characterized by an increase in dermal capillaries.

Epidemiology: Most common orbital tumor in childhood, usually present at birth or occurring within the first 8 weeks

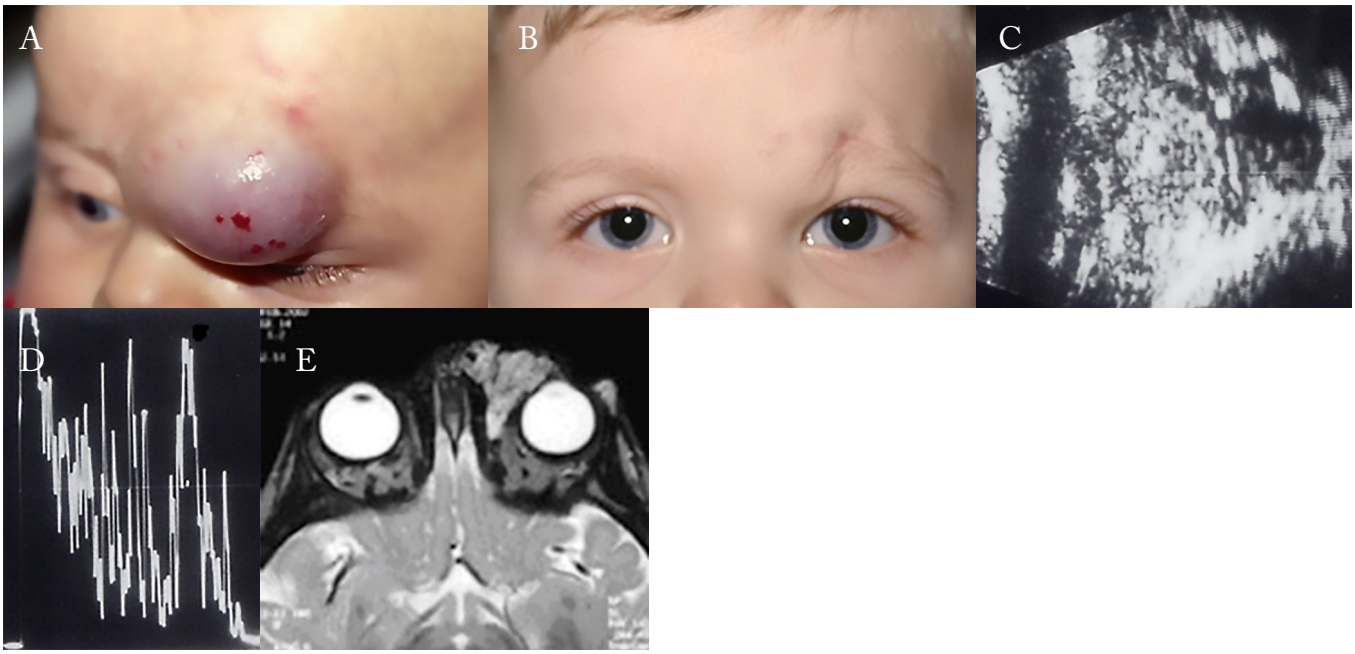


Figure 1. Capillary hemangioma

of life. The incidence is 0.7% - 2.2% of all orbital masses. Girls are affected up to 2 - 5 times more often than boys. In addition, a significantly higher incidence in premature babies below 1500 g and a 10-fold higher incidence in children of mothers after chorionic villus sampling were described.[4]

Localization: Frequently the anterior upper orbit or eyelids are affected. In only about 17% of cases the capillary hemangioma appears in the deeper orbit.

Etiopathology: As a benign hamartoma, capillary hemangioma have their point of origin from endothelial cells.

Clinical features: The lesions vary from small, isolated and clinically irrelevant, sometimes asymptomatic tumors, to large, disfiguring masses that can severely affect vision.[5]

It presents a reddish-livid and palpable tumor; the size increases as the baby screams and also if a Valsalva maneuver is performed. The most common symptoms are ptosis, strabismus and anisometropia with resulting amblyopia. Capillary hemangioma is characterized in the first 6 to 12 months of life by a proliferative phase with rapid growth, which is followed by 70% probability of an involute phase with a slow regression tendency to the age of 7 years. In an individual case, however, the course cannot be predicted. An additional occurrence of lesions in other visceral organs (especially the lungs or the skin) may be possible.

Imaging:

CT: Shows an inhomogeneous, irregularly infiltrating formation with heterogeneous internal structure.

Magnetic Resonance Imaging (MRI): Within the lesion, signal-free areas typically develop, which are produced by heavily perfused vessels.

A-scan ultrasound (US): variable, predominantly medium to low reflectivity; the sound attenuation varies depending on the density, size and distribution of the blood vessels. Typical are the pronounced internal blood flow and the soft consistency of the tumor when exerting pressure with the transducer.

B-scan (US): An irregularly shaped tumor appears, the size of which can only be indicated to a very limited extent due to the indistinct limitation; with also heterogeneous inner echoes.

Doppler US: This finding is highly positive due to the pronounced vascularization.

Histopathology: This is characterized by a proliferation of endothelial cells (Weibel-Palade bodies). Macroscopically, there is a lobular structure of densely packed and thin-walled vessels, traversed by fibrous connective tissue septa. Not encapsulated.

Treatment: Possible options are: (1) Observation if there is no risk of amblyopia; (2) Intralesional injection of corticosteroids, taking advantage of the vasoconstrictive effect of these substances; (3) systemic administration of corticosteroids; the indication for this is given for large tumors that do not respond to an injection; (4) Systemic administration of interferon alpha-2 is justified in cases of extensive hemangiomas with a lack of response to the previously mentioned therapeutic options; (5) Surgical resection of the tumor is considered in anterior lesions that are not responsive to intralesional application of the corticosteroid; however, there is the risk of a massive bleeding.[6]; (6) Laser therapy, namely Nd-YAG laser treatments, with the goal of photocoagulation. [7] Nowadays, the best treatment option is systemic propranolol with practically no side effects. It has proved to be highly effective (29).

Prognosis: In principle very good.

Comment: Sometimes capillary hemangiomas results in the Kasabach-Merritt-syndrome, which is pathophysiologically known as thrombocytopenia due to entrapment of platelets. Concerning the nosologic entity, capillary hemangiomas differ presumably from cavernous hemangiomas histologically in the following way: cavernous hemangiomas arise with muscle cells, capillary hemangiomas with pericytes.

1.2. CAVERNOUS HEMANGIOMA (FIG. 2)

Definition: Cavernous hemangioma is a vascular malformation with large, cavernous cavities, which results from the proliferation and ecstatic expansion of dermal and deep capillaries.

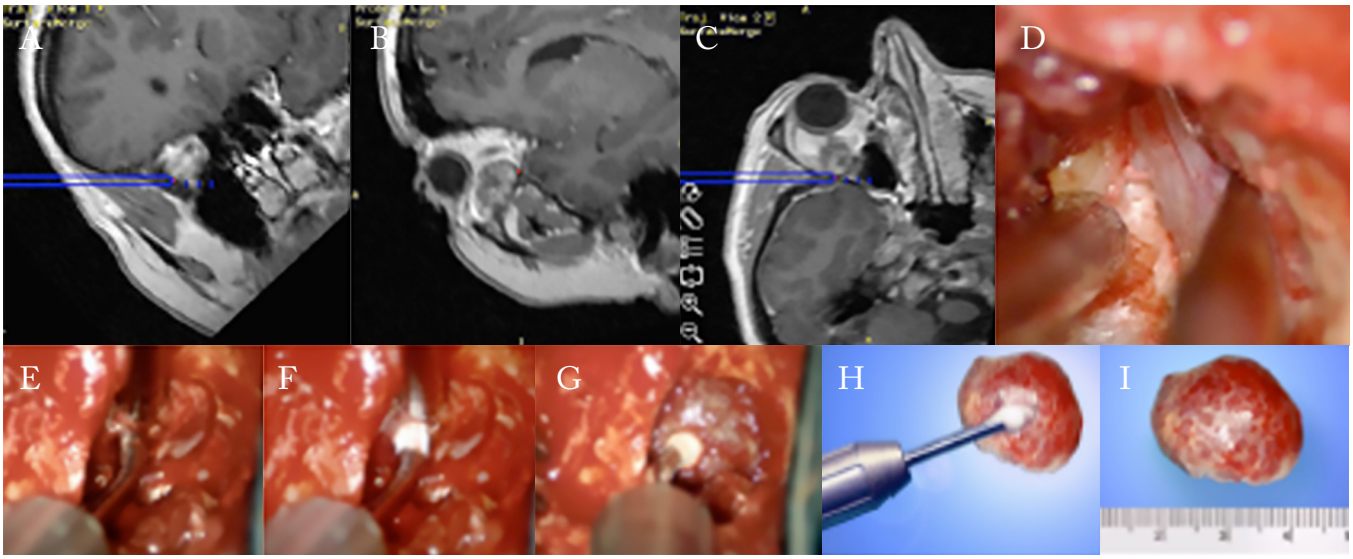


Figure 2. Cavernous hemangioma

Epidemiology: Most common benign orbital tumor in adulthood, usually diagnosed between the ages of 40 and 60. The incidence is reported as 3% - 9% among orbital tumors.[4]
Localization: Intraconal, usually temporal to the optic nerve, with larger lesions extending to the extraconal area. In contrast to the capillary hemangiomas, the cavernous type is not associated with a generalized appearance.
Etiopathology: As a benign hamartoma, cavernous hemangioma has their point of origin from endothelial cells.
Clinical features: Cavernous hemangioma typically results in a painless, slowly progressive proptosis, which is the leading symptom with a probability of occurrence of 74%.[8] If the tumor lies in the immediate vicinity of the globe, its compression causes choroidal folds and relative hyperopia, which may persist even after complete removal of the hemangioma.[9] The compression of the optic nerve results in a decrease of visual acuity, compression of the extraocular muscles leads to restricted mobility and consequently to double vision.
Imaging:
CT: Well-demarcated, oval to circular, homogeneous mass with a higher density compared to that of a muscle. If large neoplasms persist for longer, bony changes and small calcifications can be seen. Contrast enhancement is mild to moderate due to the low vascularization of the hemangioma.
MRI: Contrast agent administration typically shows an irregular enrichment, which spreads homogeneously to the entire tumor after some time.[10]
A-scan (US): The hemangioma has a regular, septate internal structure with high reflectivity and medium continuous sound attenuation (so-called "kappa angle" at approximately 45°). Because of the usually stagnant blood flow within the tumor, no vascularization is detectable. Characteristic is the solid consistency and delayed compressibility by the transducer.
B-scan US: Here is also a round to oval lesion with a regular surface. The tumor causes a moderate level of attenuation, which often limits the posterior surface. Large hemangiomas show a slight flattening of the bulb posterior wall according to Lukas J.
Doppler US: There are no vascular signs.
Histopathology: The macroscopic image of this tumor is characterized by large, well-encapsulated, cavernous, vascular cavities, lined by flat endothelial and smooth muscle cells, interspersed with thin fibrous septa. Since these cavities are mostly filled with stagnant blood, the occurrence of intravascular thrombosis is common.
Treatment: Complete surgical resection of the hemangioma is highly recommended. The surgical approach depends on the location and extent of the tumor, and might be done either via a cutaneous or transconjunctival approach, subfrontal transorbital approach, a lateral orbitotomy according to Krönlein, or even transsphenoidal, or endoscopic route.[11] In order to prevent bleeding, first a blunt dissection of the tumor is required; for subsequent removal, a cryode is helpful.
Prognosis: In principle very good, in case of an incomplete resection recurrence may occur even years after the initial surgery.
Comment: Cavernous hemangiomas are sometimes associated with Maffuci syndrome and blue rubber bleb nevus syndrome. They are not associated with other hemangiomas, e.g. the capillary hemangioma.

1.3. ORBITAL VARICES

Definition: An orbital varix is a pathological extension of an orbital vein. The primary orbital varix is confined to the veins within the orbit and is not associated with orbital or intracranial arteriovenous malformation. In contrast, the secondary orbital varix develops in association with intracranial arteriovenous malformations that divert blood into the venous system of the orbit and consequently secondary venous dilatation.
Etiopathogenesis: As an initial event, a progressive weakness of the vein wall is considered, which leads to a stagnation of the blood flow, especially since there are no valves in the orbital veins. The increased accumulation of venous blood in connection with the sluggish blood flow results in a proximal dilatation and thus leads to the formation of an orbital varix.
Epidemiology: Varices of orbital veins are a very rare disease; their incidence is given as 0% - 1.3%. Typically, the diagnosis is made between the ages of 10 and 30, and in principle, it can occur in any age group.[4]
Localization: Most often the superior ophthalmic vein is affected.

Clinical features: Over a long period of time, a slowly progressive, intermittent proptosis develops. If the patient takes a forward-leaning position or performs the Valsalva maneuver, it will increase in size. In the case of thrombus formation or acute bleeding into the affected vein, this can directly lead to painful proptosis, compression of the optic nerve and a reduction in visual performance.
Imaging:
CT and MRI: Show a lesion mostly localized in the posterior orbit, with heterogeneous signal densities consistent with the presence of blood at different stages of degradation. Especially in a symptomless interval, it is sometimes only possible to diagnose orbital varices with the help of a Valsalva maneuver during CT / MRI.[12] Phleboliths associated with this type of lesion are easier to visualize in the CT image.
A-scan US: Here, the extended vein can be detected very well. The stagnant blood flow shows no vascular signs.
B-scan US: As well as described above, a significant increase in the size of the varix when performing a Valsalva maneuver. Not infrequently, the S-shaped course of the enlarged vein can be displayed.
Doppler US: During a Valsalva maneuver, an increased blood flow in the color-coded Doppler ultrasound examination is shown.[13]
Histopathology: There are single or multiple ecstatic veins. The vessel walls may be fibrotic, the lumen may be acutely thrombotic or contain a phlebolith as a result of the calcification of an old thrombus.
Treatment: The surgical removal of a varix can be very difficult, as varices often collapse when the patient is supine. This requires performing jugular compression or positioning the patient in a Trendelenburg position (deep-set head) to ensure a successful surgery. Unless symptoms are present, therapeutic management may consist of close visual control and computer perimetry, optic nerve optical coherence tomography (OCT), color vision, and ultrasound examinations.
Prognosis: In the case of just a subtotal excision, it is quite likely that recurrence will occur. Otherwise, prognosis in general is very good. If everything is removed, normally no recurrence will occur.

1.4. ARTERIOVENOUS MALFORMATION AND FISTULAS (FIG.3)

Definition: The term "arteriovenous fistula" refers to an abnormal connection between two vessels and has to be distinguished from "classical arterio-venous" malformations (AVM), a tumorous convolute of vessels (classical AVM's). Arteriovenous malformations are congenital abnormalities whereas the origin is aneurismal varieties. To describe any kind of possible AVM's see relevant special literature. In case of fistulas, three different types of arteriovenous fistulas are described:
(1) *Carotid sinus cavernous fistula* arises between the carotid artery and the cavernous sinus, usually due to a traumatic event or rupture of an atherosclerotic cavernous sinus aneurysm (1.5% of cases).[14]
(2) *Cavernous fistula:* forms between the meningeal branches of the internal and external carotid and the cavernous sinus. These vessels have very thin walls that can rupture spontaneously, especially in the presence of arterial hypertension, or after trauma.
(3) *Orbital arteriovenous fistula:* Occurs after a traumatic rupture of the ethmoid artery that then develops connections to the orbital venous system.
Clinical features: Orbital symptoms result from the retrograde transmission of the increased venous pressure emanating from the cavernous sinus. Typical consequences include venous dilation, flow turbulence, retrograde flow direction, and thrombosis.
The clinical symptoms include proptosis, restricted mobility of the globe, chemosis, dilatation and tortuosity of the

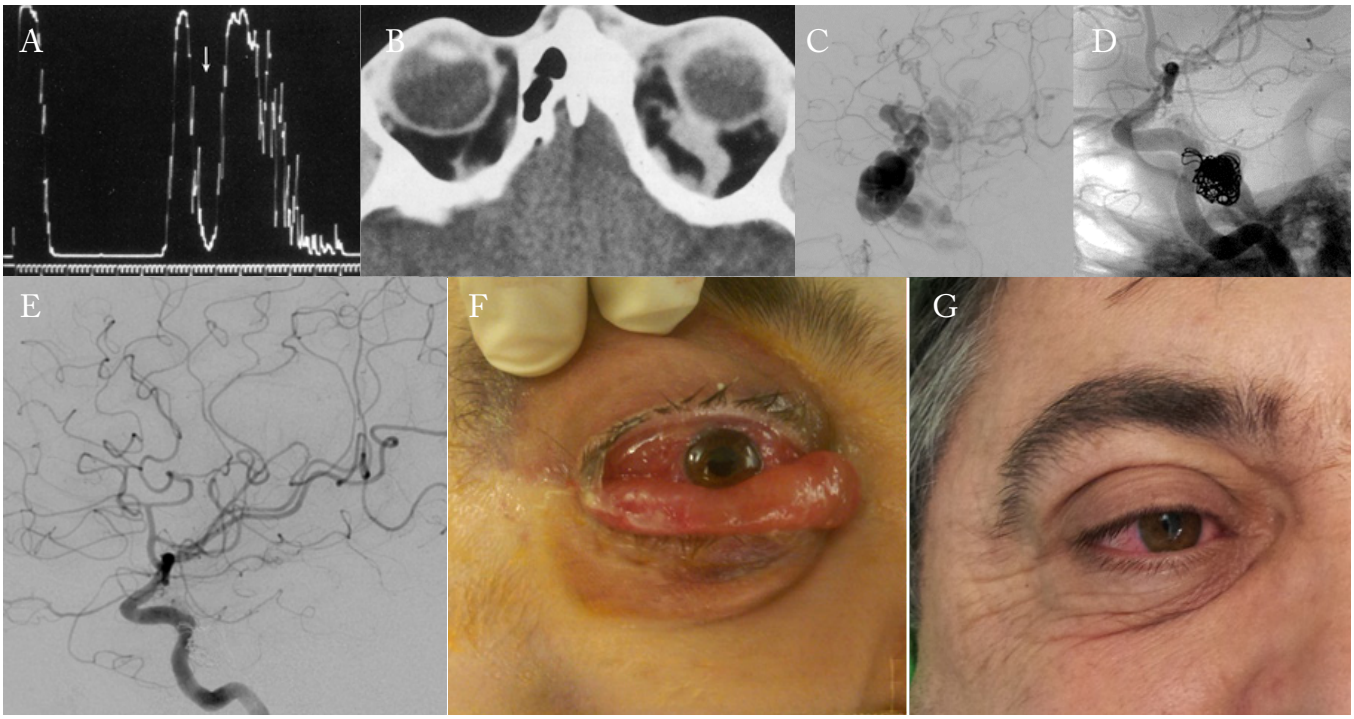


Figure 3. Arterio-venous malformation & fistulas

conjunctival and episcleral vessels (caput Medusae) and secondary glaucoma. Visual acuity reduction with visual field limitations occurs in up to 50% of affected patients.

Imaging:

US, CT and MRI show thickened extraocular muscles and an enlarged superior ophthalmic vein (30). An area of lower density and lack of contrast enhancement within a vessel represents thrombosis. CT, MRI angiography provides information on the characteristics of blood flow but not on the underlying pathology. Digital subtraction angiography is the method of choice for diagnosing arteriovenous fistula. A similar picture can be seen in the color-coded Doppler ultrasound, which is also used for the postoperative course management of a patient.[15]

Treatment: First, the pathophysiological classification into a strongly or weakly perfused ("high" or "low flow/drainage") arteriovenous (AV) fistula determines further therapeutic management.

Carotid sinus cavernous fistulas have the highest therapeutic requirement due to their high flow rate. Endovascular treatment is the method of choice and could be done either by coiling, stenting or using a different kind of balloons with a success rate of 70% - 92%.[16] Other possibilities associated with angiography include ligation and clipping of small afferent arterial vessels. The indications for angiographic intervention include visual impairment, double vision, severe headache, pronounced proptosis with lagophthalmos (corneal exposure), or secondary glaucoma. The following complications clearly confirm the indication for angiography: bleeding, persistence of the fistula, paralysis of a cranial nerve, formation of a secondary aneurysm by an early unfolded balloon, and closure of the internal carotid artery leading to cerebral or ocular ischemia. Twenty five percent of the cavernous sinus fistulas close spontaneously, which justifies a purely conservative therapeutic management. Only in case of symptoms mentioned above angiography is required. Alternatively, manual compression of the carotid artery by the patient may be performed with the contralateral hand. Prognosis: very good if total occlusion can be achieved. Sometimes in case of complex AVM's additional radiosurgery (Gamma Knife, Cyber Knife, Proton beam, Carbon ion) is recommended. Nowadays only in very rare selective cases surgery must be performed.

1.5. ANGIOSARCOMA

Definition and genesis: Angiosarcomas are extremely rare but may occur after radiation, and should therefore be at least very shortly addressed here for the sake of completeness.

Clinical features: Children are more frequently affected than adults. Painful proptosis, aggressive growth, invasion of the bone and metastatic dissemination are characteristic clinical features of angiosarcomas.

Imaging: usually done by a standard program consisting of ultrasound, CT and MRI.

Treatment: Aggressive surgery with en-bloc resection having negative margins, mostly as interdisciplinary procedures, might be performed in selective cases.[17]

Prognosis: In general, commonly bad, thus wide surgical exenteration might be necessary, followed by any kind of radiotherapy.

1.6. LYMPHANGIOMA/ LYMPHATIC MALFORMATIONS (FIG. 4)

Definition: Lymphangioma is a benign vascular malformation, more specifically a pathological neoplasm of lymphatic capillaries that spread between healthy tissues without direct hemodynamic connection to the large arteriovenous vessels.

Epidemiology: Lymphangiomas occur typically during infancy and childhood. Females are more frequently affected than males. A common childhood orbital tumor with an incidence of 0.3% - 1.5%, which usually occurs before reaching the age of ten.

Localization: May appear both intra- and extraconal and involve all orbital components, but more frequently are located in the extraconal space as well as in superficial regions with involvement of the conjunctiva and lid. Infiltration is seen commonly.

Etiopathology: The origin of lymphangiomas is still unclear since lymphatic tissue or a lymphatic drainage system is not normal in the orbit. The tumor increases if respiratory tract infection arises.

Clinical features: Lymphangiomas usually show a size increase proportional to the growth of the child and show no spontaneous regression tendency. There is also a painless, slowly progressive proptosis, which characteristically worsens in the case of an upper respiratory tract infection, in addition to ptosis, globe displacement and motility limitations.[18] Lower lesions may initially be clinically unremarkable. However,

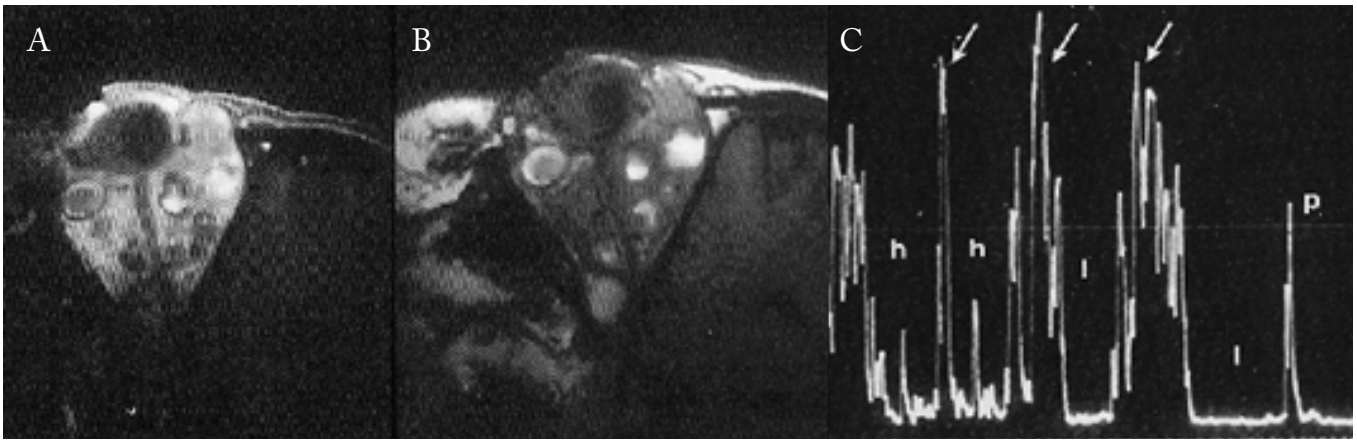


Figure 4. Lymphangioma

lymphangiomas tend to spontaneously bleed leading to a massive increase in size. This acute event manifests with ecchymosis of the eyelids, subconjunctival hemorrhage, and acute proptosis. Optionally, in combination there may be a compressive optic neuropathy (due to the acutely increased intra-orbital pressure) and loss of vision. Recurrent bleeding is the most common complication of lymphangioma.

In a subcutaneous involvement by the lymphangioma, the eyelids are lividly discolored. Very large lesions extending into the intracranial space can result in an intracranial pressure increase. Since the skin and the soft palate may have similar lesions, it is, therefore, necessary to examine them closely.

Imaging:

CT: Irregular, heterogeneous, poorly defined multicystic lesion with infiltration of healthy, adjacent orbital structures, transgressing anatomical boundaries. Large lesions can spread to the adjacent paranasal sinus and middle fossa.

MRI: A diffusely infiltrating mass with cystic cavities can be visualized. Looped, signal-less zones within the lesion represent vessels filled with rapidly flowing blood. Within cysts, acute bleeding can be diagnosed. Older bleeding ("chocolate cysts") can be differentiated by the release of methemoglobin due to erythrocyte lysis.[19]

A-scan US: Blood-filled areas show low reflectivity. The high echo signals represent the endothelium-lined vascular walls and septa. Lymphangiomas are devoid of vascular signs and, due to their cystic structure, are soft and compressible with the transducer.

B-scan US: The tumor produces a heterogeneous echo due to numerous vessels (either blood or lymph) and connective tissue.

Histopathology: Infiltrative tumor with ecstatic lymphatic vessels of variable sizes, ranging from capillaries to cavernous spaces. An already expired hemorrhage into a cyst is called a "chocolate cyst". Chronic recurrent bleeding leads to fibrosis. Until now no cases of malignant transformation were published in the literature.

Treatment: In most cases, conservative management under regular observation is the best approach, as the infiltrative properties of the lymphangioma make surgical therapy very difficult. In case of an acute hemorrhagic cyst, drainage and possibly a partial resection should be sought. Surgical resection is indicated for large lesions leading to severe cosmetic compromise of the patient, proptosis or signs of optic nerve compression. However, this may be extremely difficult to perform (neurosurgery). The use of electrocautery to prevent or reduce intraoperative bleeding may be useful, as well as using neuronavigational techniques, piezoelectric surgery and cryode stick.[17]

However, as the indication for surgical removal needs to be narrowed down, new therapeutic options are in research: Imatinib (Gleevec®) is a PDGF receptor blocker that mediates inhibitory effects on angiogenesis by inhibiting the emergence of new blood vessels from pre-existing ones.[20]

Prognosis: In most cases complete surgical removal is not possible due to the type of growing (see above). Over a period of several years, a high percentage (50%) develop recurrent bleeding. Re-operations are very frequent and have to be done time by time.

Comment: Lymphangiomas may resemble cavernous hemangiomas. Association to arteriovenous malformation has been described.

1.7. HEMANGIOPERICYTOMA

Definition: Hemangiopericytomas are benign tumors originating from the cells of the adventitia, the pericytes.

Epidemiology: Very rare occurrence with an incidence of 0.1% - 1.2% of all orbital masses. The clinical symptoms occur between the age of 20 and 70 years.

Localization: Appear frequently in the upper orbit, and involvement of the choroid, lacrimal gland, optic nerve, paranasal sinus, and intracranial space may be possible.

Etiopathology: Pericytes of orbital blood vessels are the point of origin of these rare tumors.

Clinical features: A slow progressive proptosis with downward displacement of the globe, possibly accompanied by pain, reduced visual performance, and intermittent swelling of the upper eyelid suggest the diagnosis of hemangiopericytoma.[21]

Imaging:

CT and MRI: In addition to the sharply defined, homogeneous, round to elongated tumor, phleboliths and a possible extra orbital involvement can be detected.

A-scan US: The highly reflective spike on the posterior surface of the tumor stands for its sharp boundary. Hemangiopericytomas are not compressible.

B-scan US: Allows the diagnosis of small cystic cavities within the tumor.

Histopathology: The macroscopic picture shows a red tumor composed of pericytes with different shapes. Unlike other vascular tumors, where a network of reticulin fibers surrounds cell clusters, each cell is enveloped. In immunohistology, the pericytes react positively with vimentin and CD34 antibodies. Cellular anaplasia, focal necrosis and bleeding, mitotic forms> 4 per HPF (HPF = high power field: term used in microscopy, field of view at maximum resolution) and a lack of reticulin fibers are considered to have a malignant potential. This conclusion can be drawn on the basis of histopathological findings, not by the clinical manifestation or tumor evolution.

Treatment: Due to the well-defined appearance of the hemangiopericytoma, in principle a total surgical removal should be sought. Postoperative radiotherapy[22]and brachytherapy[23] are recommended after an incomplete excision or resection of recurrence to prevent recurrences. An aggressive histopathological manifestation may require an orbital exenteration.

Prognosis: Malignant transformation may be observed in up to 40% of cases. Incomplete excision is associated with a higher risk of local recurrence and metastases. The local recurrence rate is reported as 30% and can result in multiple excisions. The likelihood of metastasis and its spread to other organs is described in 15% of cases, with palliative chemotherapy being recommended.[24]

In addition to those groups of tumors described in detail above, other extremely rare types of tumors and tumor-like conditions like lymphosarcoma, hemangiosarcoma, liposarcomas may occur, described in the literature mostly as single case reports. Beneath those, leiomyomas should be addressed in more detail.

1.8. LEIOMYOMA

Definition: Angioleiomyomas are very rare benign tumors of the orbit, the origin of which is attributed to the degeneration

of smooth muscle cells of orbital blood vessels. They are recognizable by a slowly progressive proptosis.
Imaging and clinical features: Both clinical and radiographic differential diagnosis are very difficult.
Histopathology: Reveals a tumor composed of compact spindle cell bundles.
Treatment: The therapy of choice is a complete surgical excision,
Prognosis: Excellent after complete removal.

2. ORBITAL VENOUS HYPERTENSION

Definition: Per definition orbital venous hypertension is a kind of compartment syndrome typically presented as a more or less diffuse swelling within the orbit (25, 26).
Pathological reasons: The main pathological mechanism is a significant elevation of orbital venous pressure caused by several different reasons such as vessel venous obstruction (venous sinus thrombosis and superior vena cava syndrome), arteriovenous shunts or fistulas, Sturge-Weber syndrome, scleritis, thyroid related orbitopathy, orbital tumors, tumors of the optic nerve canal, or chiasmal processes (26).
CT, MRI and ultrasound: All structures within the orbit are swollen, and differentiation between anatomical structures is very difficult, sometimes impossible.
Treatment: Management consists in the treatment of the primary cause
Outcome: If the causing reason can be appropriately treated, the outcome, in general, is good.

CONCLUSION

Vascular lesions of the orbit are not common, sometimes extremely rare, and need special attention in their diagnosis, treatment, and aftercare. Nomenclature and classification, as well as treatment options of such lesions often present a big challenge and might be difficult, since these heterogenic entities are very often confusing and may overlapping. Differential diagnosis of this group of orbital lesions is usually possible based on clinical and imaging parameters; however, that field needs a long-lasting experience. Diagnosis requires an understanding of the classification of vascular lesions, integration of the individual patient's history with epidemiological data, and familiarity with the imaging features that are typical of specific lesions. Treatment in most cases comprises an individual plan, in which surgery is only one part. Depending on the special type of lesion, endovascular, radiosurgical, but also chemotherapeutic options must be considered. The use of appropriate imaging techniques (e.g., high-end ultrasound, thin slice high-resolution CT and MRI, sometimes super selective angiography) are often essential for an accurate diagnosis (30). The use of modern microsurgical techniques like neuronavigation, intraoperative imaging, piezoelectric surgery, cryosurgery and endoscopy revolutionized that field of surgery with excellent results for the patient. Endovascular techniques using coiling, stenting, etc. achieve undisputed perfect results and should be considered as first choices in case of AVM's and fistulas of the orbit.
Additional radiosurgical techniques like proton beam or carbon ion therapy are not only offering efficient additional treatment options, but are often the method of choice and have replaced conventional surgery. And last not but least, the aftercare of those patients has also changed significantly over the years. Vascular orbital lesions nowadays can be treated very properly, with perfect results, if done by an experienced group of people using a strict interdisciplinary strategy and having all treatment options available.

Acknowledgment:
The authors would like to thank Katharina Erb and Kathrin Ziegler for the excellent work with their master thesis to get the doctors degree, which builds the basis for this manuscript. We are also very grateful to our friend and colleague Wolfgang Hauff for his tireless input and inspiration in the field.
We further like to dedicate this work to our friend and colleague Franz Josef Steinkogler who unfortunately passed away much too early, we will never forget him!

Ethical Disclosures
Confidentiality of Data: Patient consents obtained.
Conflicts of Interest: The authors have no financial interest

Corresponding author
Christian Matula
christian.matula@meduniwien.ac.at

REFERENCES

1. Stout AP, Murray MR. Haemangiopericytoma: vascular tumor featuring Zimmermann´s pericytes. Ann Surg. 1942; 116:26-33.
2. Günalp I, Gündüz K. Vascular tumors of the orbit. Doc Ophthalmol. 1995;89:337-45.
3. Xiao LH, Lu XZ, Wei H. Diagnosis by ultrasonography and CT scan in orbital vascular tumors and malformations. Zhonghua Yan Ke Za Zhi. 2004;40:364-7.
4. Karcioglu ZA, editor. Orbital Tumors: Diagnosis and Treatment. Berlin: Springer; 2014.
5. Haik BG, Karcioglu ZA, Gordon RA, Pechous BP. Capillary hemangioma (infantile periocular hemangioma). Surv Ophthalmol. 1994;38: 399-426.
6. Levi M, Schwartz S, Blei F, Ceisler E, Steele M, Furlan L, et al. Surgical treatment of capillary hemangiomas causing amblyopia. J AAPOS. 2007;11:230-4.
7. Clymer MA, Fortune DS, Reinisch L, Toriumi DM, Werkhaven JA, Ries WR. Interstitial Nd:YAG photocoagulation for vascular malformations and hemangiomas in childhood. Arch Otolaryngol Head Neck Surg. 1998;124:431-6.
8. Wollenberg B., Zimmermann F. Kopf- und Hals-Malignome. Zuckschwerdt Verlag Tumorzentrum München. 2003;255.
9. Harris GJ, Jakobiec FA. Cavernous hemangioma of the orbit. J Neurosurg. 1979;51:219-28.
10. Orhan S, Durak AC, Mavili E, Akdemir H. MRI findings of orbital hemangiomas. Tani Girisim Radyol. 2004;10:26-30.
11. Brusati R, Goisis M, Biglioli F, Guareschi M, Nucci P, Gianni AB, et al. Surgical approaches to cavernous haemangiomas of the orbit. Br J Oral Maxillofac Surg. 2007;45:457-62.
12. Rubin PA, Remulla HD. Orbital venous anomalies demonstrated by spiral computed tomography. Ophthalmology. 1997;104:1463-70.
13. Lieb WE, Merton DA, Shields JA, Cohen SM, Mitchell DD, Goldberg BB. Colour Doppler imaging in the demonstration of an orbital varix. Br J Ophthalmol. 1990;74:305-8.
14. van Rooij WJ, Sluzewski M, Beute GN. Ruptured cavernous sinus

aneurysms causing carotid cavernous fistula: incidence, clinical presentation, treatment, and outcome. AJNR Am J Neuroradiol. 2006;27:185-9.
15. Costa VP, Molnar LJ, Cerri GG. Diagnosing and monitoring carotid cavernous fistulas with color Doppler imaging. J Clin Ultrasound. 1997;25:448-52.
16. Keltner JL, Satterfield D, Dublin AB, Lee BC. Dural and carotid cavernous sinus fistulas. Diagnosis, management, and complications. Ophthalmology. 1987;94):1585-1600.
17. Matula C. Surgical therapy of orbital tumors from a Neurosurgeons perspective. Neurologisch. 2015:22-30.
18. Tunç M, Sadri E, Char DH. Orbital lymphangioma: an analysis of 26 patients. Br J Ophthalmol. 1999;83:76-80.
19. Bond JB, Haik BG, Taveras JL, Francis BA, Numaguchi Y, Mihara F, et al. Magnetic resonance imaging of orbital lymphangioma with and without gadolinium contrast enhancement. Ophthalmology. 1992;99:1318-24.
20. Colletti G, Biglioli F, Poli T, Dessy M, Cucurullo M, Petrillo M, et al. Vascular malformations of the orbit (lymphatic, venous, arteriovenous): Diagnosis, management and results. J Craniomaxillofac Surg. 2018 (in press).
21. Sullivan TJ, Wright JE, Wulc AE, Garner A, Moseley I, Sathananthan N. Haemangiopericytoma of the orbit. Aust N Z J Ophthalmol. 1992;20:325-32.
22. Setzkorn RK, Lee DJ, Iliff NT, Green WR. Hemangiopericytoma of the orbit treated with conservative surgery and radiotherapy. Arch Ophthalmol. 1987;105:1103-5.
23. Tijl JW, Koornneef L, Blank LE. Recurrent hemangiopericytoma and brachytherapy. Doc Ophthalmol. 1992;82:103-7.
24. Croxatto JO, Font RL. Hemangiopericytoma of the orbit: a clinicopathologic study of 30 cases. Hum Pathol. 1982;13:210-8.
25. Ding D. Symptomatic orbital venous hypertension associated with intracranial vascular malformations. J Neurol Sci. 2014;341:174.
26. Parsa CF. Focal venous hypertension as a pathophysiologic mechanism for tissue hypertrophy, port-wine stains, the Sturge-Weber syndrome, and related disorders: proof of concept with novel hypothesis for underlying etiological cause (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc. 2013;111:180-215.
27. Smoker WR, Gentry LR, Yee NK, Reede DL, Nerad JA. Vascular lesions of the orbit: more than meets the eye. RadioGraphics. 2008; 28:185–204.
28. Matula C, Lukas J, Hauff W, editors. Color Atlas of Orbital Mass Lesions – Diagnosis, Treatment and After care. Stuttgart: Thieme;2019.
29. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo J-B, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008; 358: 2649–51.
30. Lukas J. Clinical diagnostic and standardized ultrasound of orbital mass lesions. Neurologisch. 2015:17-20.

Section 5

Trauma

16. Orbital Fractures

MAXILLOFACIAL SURGERY
Hugo Pereira; MD

Summary

Orbital fractures are common injuries after facial trauma. Although road accidents are now less frequent, sports injuries, interpersonal violence and falls have assumed relevance as everyday causes of facial fractures. The author explains the mechanism, consequences, diagnosis and management of these lesions through a synthetic review of this topic. Relevant anatomic features and their correlation with clinical aspects are detailed, in addition to functional and aesthetic repercussions. Treatment and surgical approaches are also discussed as well as the sequels due to untreated or insufficiently treated fractures.

Keywords: *Orbital Fractures/diagnostic imaging; Orbital Fractures/etiology; Orbital Fractures/surgery; Orbital Fractures/treatment;*

Figure 1. Orbital anatomy

INTRODUCTION

The orbital rim and the ocular globe occupy a prominent position on the face, particularly exposed to impact trauma which often results in fractures of the orbital cavity.[1] These are common injuries, and several specialties are involved in their treatment. They can have important functional and aesthetic implications.[2]

Injuries can be minor, such as simple linear fractures, or as complex as craniofacial fractures involving different orbital walls and extensive comminution. Every presentation is possible. A direct traumatic mechanism to the rim can produce a fracture involving the anterior third of the orbit, which is represented superiorly by the supraorbital portion of the frontal bone, medially by the nasal and ethmoid bones, and inferiorly by the zygomatic-malar area (Fig.1). If the trauma involves the globe, the force of the blow on the eye is transmitted to the orbital walls where a fracture occurs in order to absorb the impact, as a natural mechanism to prevent the eye from rupturing.[1] In this case, it is the thin midportion of the orbit that fractures (mainly the medial wall and floor), allowing the imposing force to be transmitted to the maxillary and ethmoidal sinuses instead of the eye.[3] The posterior third of the orbit is rarely implicated in orbital fractures.[4]

For a long time, the choice between a conservative, non-surgical approach versus early surgical repair was heavily debated.[5,6] Today, there is more consensus in the treatment of orbital fractures. When there is a clear involvement of the orbital rim with an aesthetic implication, the fracture should be reduced or reconstructed as soon as possible, after other conditions, for example edema, have already healed.[5] Cases presenting with symptoms such as diplopia or enophthalmos can either be surgically treated or benefit from a conservative approach, detailed below[6].

After the first historical medical descriptions of orbital fractures in the 19th century, the work of Converse and Smith, Manson in the 20th century, and also the contribution of Putterman were unquestionably important, extending throughout the 50's and 60's, and continuing into the 80's and 90's.[2,4,6,7] The most relevant contribution for the knowledge of anatomy was, by far, the thin-slice computerized tomography (CT) scan.[8] After that, the advent of 3D reconstruction (and sometimes the use of magnetic resonance imaging) has left no further secrets in the orbit.[9,10] Nevertheless, a solid clinical examination continues to be crucial for the decision-making process and surgical planning.

1. RELEVANT ANATOMY

There are noteworthy details in the anatomical concepts discussed in the previous chapters. It is of special clinical importance to divide the orbit into an anterior, middle and posterior sections. The strong orbital rim, constituting the anterior third, benefits from an open reduction and fixation after almost all displacements. It is also currently accepted that the integrity of the rim does not exclude fractured orbital walls.[1] The middle third is constituted by the roof, the medial and lateral walls, along with the orbital floor. The roof is a bowed surface that prolongs the rim, and when dislocated inferiorly it may produce exophthalmos. Rarely, if dislocated superiorly, it may cause enophthalmos and/or interference with muscle function. Also, the skull base may be implicated

in a frontal fracture. When displaced, the medial orbital wall, being a thin bone in contact with ethmoidal cells and septae, greatly influences orbital volume[11](Fig.2) In this case, it is uncommon to find muscle incarceration, but diplopia is a frequent feature. The lateral wall is constituted by the sphenoid bone and the frontal process of the zygoma, and, when fractured, may expand or contract orbital volume, being muscular entrapment rarely seen.[4,11,12] In this area, the rim allows surgical frontal fixation when reducing a zygomatic-malar complex fracture. The floor and lower medial wall have also anatomical details to take into consideration. The first segment of the floor, posterior to the rim, is a bowed surface that soon after becomes convex, before reaching the posterior third of the orbital cone (Fig. 3). When fractured, this "step" is the primary factor responsible for the considerable increase of orbital volume that leads to enophthalmos.[11]

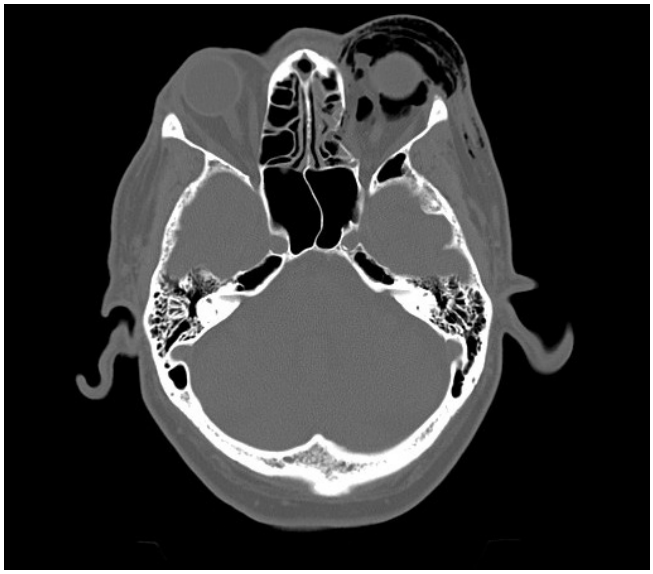


Figure 2. Volume expansion and the thicker bone of the posterior third of the orbit in a medial wall fracture

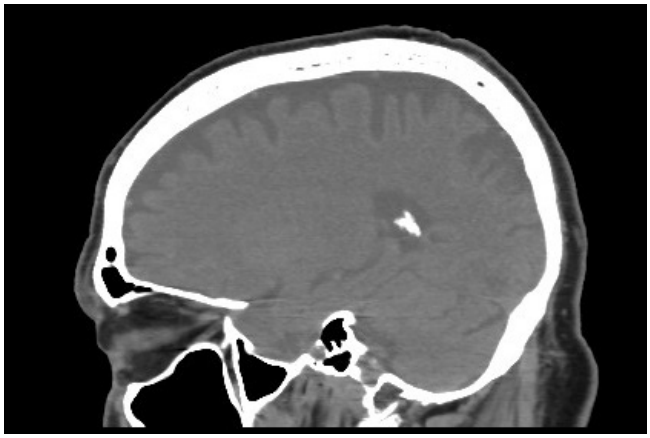


Figure 3. Anatomic detail of the orbital floor

The infraorbital nerve, which runs between the lateral two-thirds and medial third of the orbital floor, is another sensitive area of a fragile anatomy.

The orbital apex or posterior third, having a thicker bone, does not usually fracture. (Fig.s 1 and 2). The main reason is that the thinner anterior bone offers an impact absorption area that protects the posterior section, where the superior and inferior orbital fissures and the optic foramen are located. Nevertheless, some fractures here may require optic canal decompression.[2,4]

2. MECHANISMS OF INJURY

Orbital fracture is usually the result of a direct trauma over the orbital rim.[1] Even in the absence of a rim fracture, the forces are transmitted to the thin areas just behind it, and the fracture occurs in the floor or medial wall.[1] Direct trauma to the globe is yet another means to fracture those same thin areas, generally only producing orbital expansion. On the contrary, the force of the impact onto the rim can fracture and move bone segments reducing orbital volume.[1] Extraocular muscles are located near the orbital walls, protected by fat.[4] Sometimes, a fracture over these tissues may lead to muscle entrapment (Fig. 4).

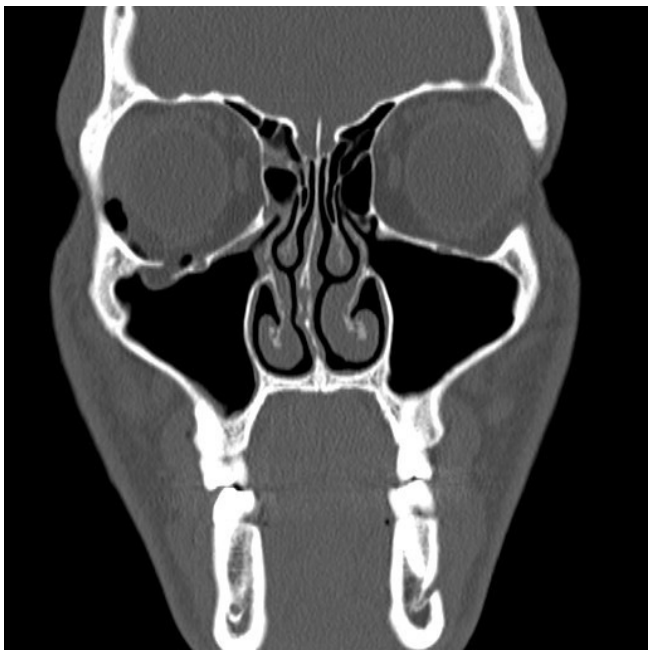


Figure 4. Blowout fracture - "trap door"

3. ETIOLOGY

The etiology of orbital fractures has changed over the last two decades, given the decrease in speed limits while driving. Also, the improvement in car safety, with safety belts, airbags and new motor cycle helmets decreased facial trauma from traffic accidents.[13] Now, sports, interpersonal violence and falls amongst the erderly, have become the most common causes of simple orbital fractures.[13]

Panfacial trauma may occur due to high-speed traffic accidents and often involves the orbits. Recently, in some European countries, the adoption of new kinds of mobility by the elderly, like electric bikes reaching 25 or 30 km per hour, have led to an increase in facial trauma, especially as adequate protection helmets have not yet been adopted. In addition, working accidents are also an important reality in certain countries.[13]

4. CLINICAL PRESENTATION

Medical history should include the type and direction of

injury, subjective symptoms (paresthesia, dysesthesia or anesthesia) and any vision problems. A careful physical examination will detect cutaneous wounds, ecchymosis, edema, hematoma, subconjunctival hemorrhage and changes in globe position like enophthalmos, exophthalmos and vertical dystopia. Due to swelling, vertical dystopia can be difficult to recognize during the initial examination (Fig. 5). A thorough eye examination by an ophthalmologist with visual acuity and fundoscopy documentation is critical. With the head immobilized, eye movements should be explored to detect entrapment of extraocular muscles. By anesthetizing the conjunctiva topically, a forced duction test may be performed by grasping near the inferior limbus with a forceps, moving the globe upward and downward. Any limitation indicates a positive test, suggesting muscle and/ or periorbital tissue entrapment in the fracture. Compromised ocular motility and globe position are the main clinical features that support the need for surgical repair of a fracture, however, due to edema and hematoma, early findings cannot predict late globe position (Fig. 5).

Figure 5. Orbital fracture. Day 1 (left) and day 20 (right) with a conservative treatment

5. DIAGNOSIS AND MANAGEMENT

Plain radiographs are of little use, although a Water's incidence as an initial screening plain film can be acceptable. The relevant orbital anatomy can only be clearly understood with 1 to 3 mm sliced CT scans with axial, coronal and 3D reconstructions, complemented by digital contrasts (Fig. 6) and volume measurements of the orbit.[8,10,11,14,15] This gives information about fracture patterns, muscle relationships, and displacement of bone and soft tissue.

The term "blowout fracture" refers to an expansion of a fractured inferior or medial wall. A "trap door" fracture occurs with periorbital fat or muscle incarceration (Fig. 4). In order to make the best treatment decision, it is important to use precise imaging to more fully evaluate anatomical regions, and understand the correlation with clinical findings. Repeated evaluation as the edema and hematoma are reabsorbed (ex: day 1,5 and 8) are required to clarify a surgical indication.

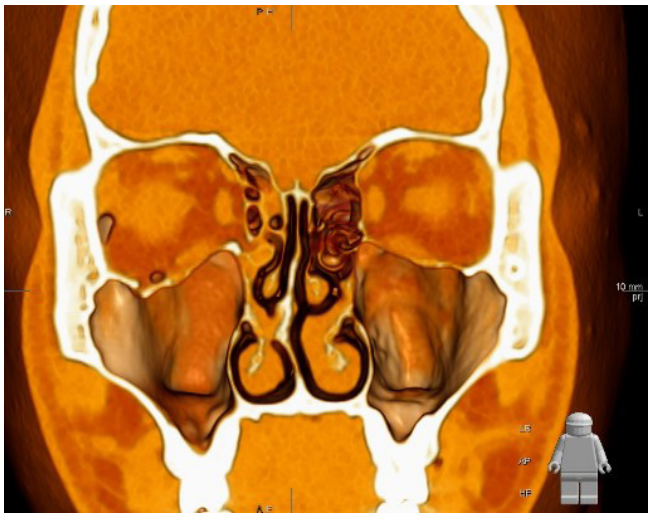


Figure 6. Relationships between periorbital muscles and the fracture site

SURGICAL APPROACH

Currently, the preferred surgical accesses to the medial, inferior and lateral walls of the orbit are the subciliary or the transconjunctival approaches.[21] To the orbital roof, the bicoronal access has advantages in complex fractures or reconstructions (Fig.7).

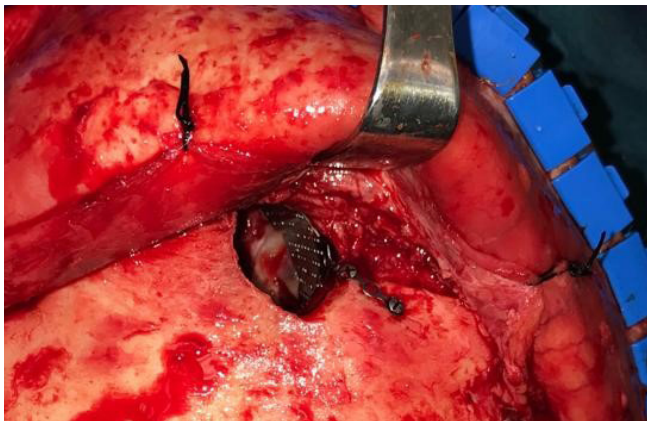


Figure 7. Medial wall reconstruction via bicoronal approach - titanium mesh

The subciliary approach may result in ectropion or scleral show, while with the transconjunctival approach entropion is more frequent.[21] We prefer the transconjunctival approach, choosing the retroseptal extended incision[22,23] associated with a specific closure technique featuring one or two inverted 5/0 absorbable sutures, if any at all.

Patients with disturbing diplopia, aesthetically unacceptable enophthalmos, vertical dystopia, positive forced duction test and CT- evidence of soft tissue entrapment should be operated within the first three weeks of trauma,[5,6] after resolution of the edema and hematomas, in order to be able to evaluate the globe position more accurately.

SURGICAL DECISION MAKING

The guides for surgery are the anatomic restoration of the bony orbit by repositioning the displaced bony segments to achieve a correct orbital volume,[10,16] and the release of soft

tissue .[1,17] It is acceptable to compare the volume and anatomy of the orbit with the opposite, intact orbit[8], although a pre-existing facial asymmetry should be taken into consideration. A centripetal reconstruction must start with the restoration of orbital contour and the repositioning of the zygomatic-malar complex with osteosynthesis of the rim and the pyramidal process using mini or micro titanium plates and screws. A correct reduction of the fractured three-dimensional bone is critical for the following correction of the fractured orbital walls, when those injuries are not isolated.

As fat is distributed differently through the muscle cone of the orbit, being more intra-conal in the posterior part of the orbit and more extra-conal in the anterior area, globe dystopia caused by a fracture may lead to a supratarsal hollow as fat fades away from the upper lid. Intra-conal fat displacement is more likely the mechanism of an enophthalmos, being bone reconstruction the only way to push this intra-conal fat into its proper position. Globe retrocession in the bony orbit by more than 2 to 3 mm - enophthalmos- is apparently related to an increase in orbital volume of 2.5 to 3 cc.[14] Apart from the functional effects of the disturbed ocular motility on binocular vision, vertical dystopia may be cosmetically unacceptable. Small linear fractures with small entrapments of periorbital tissues indicate surgery.

The correct anatomy and functioning of the orbital cavity can be re-established in many ways, ranging from the use of a simple non-rigid and absorbable membrane applied on the orbital floor after soft tissue release in a small linear non-displaced fracture, to bone grafts of the calvaria or the iliac crest in complex reconstructions of one or several walls of the orbit.[18] Shaped titanium mesh, custom-made implants, porous polyethylene shell[19] and several other absorbable polymers (ex: poly-L/DL-lactide, polycaprolactone)[20] have been used with different levels of success. In every case, the purpose is always to bridge the defect and to restore the anatomy while avoiding periorbital or muscle entrapment.

NON-SURGICAL TREATMENT

In patients with a favorable prognosis, it is generally acceptable an initial conservative treatment with systemic corticosteroids in the first 21 days, even when a gradually resolving diplopia (caused by edema or hematoma) is present, leading to good results while avoiding surgery in many cases.[6] However, if surgery is considered, it should be performed as soon as possible.[6] Patients with fractures of the medial wall and floor should be treated with broad-spectrum antibiotics due to the risk of periorbital cellulitis. Initial care and recommendations include ice, head elevation, and the treatment of external cutaneous lesions either by cleaning and disinfection or by suturing).

6. FINAL CONSIDERATIONS

After surgical corrections, the presence of hypoesthesia or anesthesia of the infraorbital nerve, enophthalmos, vertical dystopia, diplopia, ectropion, entropion, and unacceptable scars are sequels that must be evaluated and treated with different techniques, whose choice depends on a comprehensive diagnosis based on accurate CT imaging. Some patients can be observed initially already with sequels, frequently after a prolonged admission in intensive care units due to life-threatening conditions such as cranial trauma. Repeated clinical observations, when there is no apparent large defect in the orbital walls, are crucial to evaluate a possible regression of diplopia or disturbed ocular movement. These symptoms may fade away when swelling, and hematoma disappear or, if persistent, may constitute an early surgical indication, even in the absence of an obvious entrapment on a fracture site.

Ethical Disclosures

Confidentiality of Data: Patient consent obtained.

Conflicts of Interest: The author has no financial interest in the products or procedures mentioned in this chapter

Corresponding author

Hugo Manuel Gil Pereira

hugo.pereira@jmellosaude.pt

REFERENCES

1. Waterhouse N, Lyne J, Urdang M, Garey L. An investigation into the mechanism of orbital blowout fractures. Br J Plast Surg. 1999;52:607–12.
2. Manson PN. The orbit after Converse: seeing what is not there. J Craniofac Surg. 2004;15:363–7.
3. Manson PN. Pure orbital blowout fracture: new concepts and importance of the medial orbital blowout fracture. Plast Reconstr Surg. 1999;104:878–82.
4. Manson PN, Clifford CM, Su CT, Iliff NT, Morgan R. Mechanisms of global support and posttraumatic enophthalmos: I. The anatomy of the ligament sling and its relation to intramuscular cone orbital fat. Plast Reconstr Surg. 1986;77:193–202.
5. Manson PN, Iliff N. Management of blow-out fractures of the orbital floor. II. Early repair for selected injuries. Surv Ophthalmol.1991;35:280–92.
6. Putterman AM. Management of orbital floor blowout fractures. Adv Ophthalmic Plast Reconstr Surg. 1987;6:281–5.
7. Converse JM, Smith B, Obear MF, Wood-Smith D. Orbital blowout fractures: a ten-year survey. Plast Reconstr Surg. 1967;39:20–36.
8. Blumer M, Gander T, Kruse Gujer A, Seifert B, Rücker M, Lübbers HT. Influence of mirrored computed tomograms on decision-making for revising surgically treated orbital floor fractures. J Oral Maxillofac Surg. 2015;73:1982.e1-9.
9. Kim YC, Jeong WS, Park T, Choi JW, Koh KS, Oh TS. The accuracy of patient specific implant prebented with 3D-printed rapid prototype model for orbital wall reconstruction. J Cranio-Maxillofacial Surg. 2017;45:928–36.
10. Diaconu SC, Dreizin D, Uluer M, Mossop C, Grant MP, Nam AJ. The validity and reliability of computed tomography orbital volume measurements. J Cranio-Maxillofacial Surg. 2017;45:1552–7.
11. Schönegg D, Wagner M, Schumann P, Essig H, Seifert B, Rücker M, et al. Correlation between increased orbital volume and enophthalmos and diplopia in patients with fractures of the orbital floor or the medial orbital wall. J Cranio-Maxillofacial Surg. 2018;46:1544–9.
12. Hosal BM, Beatty RL. Diplopia and enophthalmos after surgical repair of blowout fracture. Orbit. 2002; 21:27-33.
13. Blumer M, Kumalic S, Gander T, Lanzer M, Rostetter C, Rücker M, et al. Retrospective analysis of 471 surgically treated zygomaticomaxillary complex fractures. J Cranio-Maxillofacial Surg. 2018;46:269–73.
14. Sugiura K, Yamada H, Okumoto T, Inoue Y, Onishi S. Quantitative assessment of orbital fractures in Asian patients: CT measurement of orbital volume. J Cranio-Maxillofacial Surg. 2017;45:1944–7.
15. Nilsson J, Nysjö J, Carlsson A-P, Thor A. Comparison analysis of orbital

shape and volume in unilateral fractured orbits. J Craniomaxillofac Surg. 2018;46:381–7.
16. Andrades P, Cuevas P, Hernández R, Danilla S, Villalobos R. Characterization of the orbital volume in normal population. J Cranio-Maxillofacial Surg. 2018;46:594–9.
17. Sozzi D, Gibelli D, Canzi G, Tagliaferri A, Monticelli L, Cappella A, et al. Assessing the precision of posttraumatic orbital reconstruction through "mirror" orbital superimposition: A novel approach for testing the anatomical accuracy. J Cranio-Maxillofacial Surg. 2018;46:1258–62.
18. Boyette JR, Pemberton JD, Bonilla-Velez J. Management of orbital fractures: Challenges and solutions. Clin Ophthalmol. 2015;9:2127-37.
19. Bratton EM, Durairaj VD. Orbital implants for fracture repair. Curr Opin Ophthalmol. 2011;22:400–6.
20. Young SM, Sundar G, Lim TC, Lang SS, Thomas G, Amrith S. Use of bioresorbable implants for orbital fracture reconstruction. Br J Ophthalmol. 2017; 101:1080-5.
21. Al-Moraissi EA, Thaller SR, Ellis E. Subciliary vs. transconjunctival approach for the management of orbital floor and periorbital fractures: A systematic review and meta-analysis. J Cranio-Maxillofacial Surg. 2017;45:1647–54.
22. Ishida K. Evolution of the surgical approach to the orbitozygomatic fracture: From a subciliary to a transconjunctival and to a novel extended transconjunctival approach without skin incisions. J Plast Reconstr Aesthetic Surg. 2016;69:497-505.
23. Barcic S, Blumer M, Essig H, Schumann P, Wiedemeier DB, Rücker M, et al. Comparison of preseptal and retroseptal transconjunctival approaches in patients with isolated fractures of the orbital floor. J Cranio-Maxillofacial Surg. 2018 Mar;46:388–90.

Section 6

Orbital Rehabilitation

17. Orbital Implants and Prosthesis

OPHTHALMOLOGY
Sandra Prazeres, MD; Renata Rothwell, MD

Summary

The use of orbital implants and ocular prosthesis after enucleation and evisceration procedures is fundamental to restore facial aesthetics and to normalize social interactions. With this goal and to minimize surgical complications, the material and design of orbital implants have evolved over the last decades. The advantages and disadvantages of the different types of orbital implants, the use of pegs, wrapping of the orbital implant and the indications for primary and secondary implants are discussed in this chapter. The fabrication process, evaluation and maintenance of ocular prosthesis are reviewed.

Keywords: *Eye Enucleation; Eye Evisceration; Eye, Artificial; Orbital Implants*

INTRODUCTION

Following the removal of the eye, an orbital implant is inserted into the anophthalmic socket in order to provide satisfactory volume replacement and restore the aesthetic appearance of a normal eye. Prior to the advent of artificial orbital implants, prosthesis gave patients an unnatural immobile appearance.

ORBITAL IMPLANTS

The first orbital implants were produced by Mules in 1885, who used hollow glass spheres restore the anophthalmic cavity volume.[1] Since their introduction, orbital implants have significantly varied regarding to material, design, shape and size, with silicone and polymethylmetacrylate (PMMA) implants gaining in popularity (Fig. 1A). They are smooth, non-porous, and non-integrated implants, which are inert and cause little reaction in the host. However, the success of these implants decreased due to the development of complications such as late migration and extrusion. [2,3]

In 1985, Perry introduced the coralline porous hydroxyapatite (HA) material into orbital implants.[4] The implant is biocompatible, causes minimal tissue inflammation and allows vascular tissue ingrowth as a result of its porous structure. With tissue ingrowth, the HA implant resists migration, a common problem with PMMA or silicone implants.

Many surgeons were encouraged to use the porous or integrated implants as a new option to solve the problems of extrusion that occurred with the non-integrated implants. The use of natural hydroxyapatite was followed by other porous implants, such as synthetic hydroxyapatite and porous polyethylene (PE).[5-7]

Porous PE implants are typically well tolerated by orbital soft tissues and have a smooth surface, which restrains irritation of the overlying conjunctiva following placement and results in a diminished risk of postoperative complications. The major commercial example is the so-called "Medpor implant". This material is pliable enough to allow direct suturing of the extraocular muscles to the implant, thereby potentially avoiding the use of a covering material. Smooth surface tunnel spheres (Medpor SST) have a smooth, porous anterior surface and suture tunnels to allow easy attachment of rectus muscles. Suture holes and curved tunnels of Medpor SST may allow an easier insertion of the ophthalmic needles used to attach the extraocular muscles to the implant.[8,9]

In 2002, a survey of members of the American Society of Ophthalmic Plastic and Reconstructive Surgery found that PE was used in 42.7% of the primary enucleations.[10] The superiority of PE has been reported[11] but others note that porous polyethylene has the same rate of complications as other porous orbital implants.[12]

At the end of the 1990s, a new porous implant made of aluminum oxide (alumina) was introduced under the name of bioceramic orbital implant from FCI S.A.S, Paris, France (Fig. 1B).[13] It has excellent biocompatibility by virtue of a lower reactivity when in contact with tissue. The alumina implant is lighter than HA reducing the pressure over the lower eyelid. Jordan *et al* found that aluminum oxide has a smoother surface compared to HA, which may reduce late exposure / extrusion.[14] Based on the results currently available, it would be difficult to nominate one porous material showing superior performance over the others.[15]

The follow-up of patients was decisive for identifying problems that may occur with the integrated implants, which were at least as common as those with the non-integrated implants.[16] It is possible that the stiffness of current porous implants may be contributing to the development of complications such as exposure, which remains a major problem of porous implants.[15]

Dehiscence of the conjunctiva and sclera were increasingly frequent with porous implants, and the exposure rates ranged from 0% to 7.6%, influenced by many factors such as the surgical technique employed (enucleation or evisceration), the use of wraps or their absence, the length of follow-up, and systemic diseases.[5,14,15,17-24]

After an initial enthusiasm for integrated implants,[25] the same complications that occurred with the non-integrated implants were soon reported.[26,27] Some studies suggest that there is little difference between porous and non-porous implants.[28,29] A retrospective study of 542 cases on the complications associated with orbital implants concluded that silicone implants have the least amount of complications.[19] However, most studies have a short follow-

up period, and implant exposure is a long term complication in the majority of cases, occurring up to 5 years after surgery.[2] A meta-analysis conducted by Schellini in 2016 concluded that porous PE implants showed a lower chance of exposure than bioceramic implants for anophthalmic sockets.[11] A protocol of a Cochrane systematic review about the new options to be employed in the treatment of the anophthalmic cavity was not able to draw any conclusions on the efficacy and safety of integrated versus non-integrated implants in the reconstruction of the ophthalmic cavity because of insufficient evidence.[30]

Due to the fibrovascularization of porous implants, it is possible to drill a hole in the implant and insert a peg. Pegging the porous orbital implant improves the motility of the prosthesis and hence the overall cosmetic result. This is generally not done until at least 6 months after the primary procedure in order to allow time for adequate fibrovascularization of the implant.

The main reason for using integrated implants with a coupling system between the implants and the external prosthesis is to improve mobility. However, if pegging is not planned, there is no advantage in terms of mobility when using porous orbital implants instead of solid silicone spheres.[5] Insertion of a peg requires a second procedure and imaging studies to confirm the vascularization of the implant (with associated costs) and there is also a relatively high complication rate.[31-33] Therefore, the pegging system is now rarely used.[16]

The quasi-integrated orbital implants have irregularly shaped anterior surfaces that create an indirect coupling mechanism between the implant and the prosthesis. The first examples were the acrylic Iowa and Universal implants. The quasi-integrated design was adapted to Medpor implants providing the advantage of porous materials of a low risk of extrusion, without the need for a secondary pegging procedure.[34]

Recently, other implants have been developed by associating different materials, i.e., composites that combine PMMA, silicone, hydroxyapatite, porous polyethylene, aluminum, polytetrafluorethylene, and other materials. In the 1980s, Guthoff and coworkers developed a composite implant constituted by an anterior part made of synthetic HA to allow tissue integration and a posterior silicone hemisphere (Fig. 1C).[35] The horizontal and vertical rectus muscles are sutured cross-wise in front of the implant to ensure better stability and motility. A more recent example of a composite device is Medpor-Plus orbital implant, a combination of porous PE with synthetic bone graft particulate. Implant vascularization is faster with Medpor-Plus implants compared with Medpor implants.[36]

The use of autologous tissues to restore the orbital volume can be advisable in some cases. A dermis fat graft can be used for primary orbital implantation for economical reasons (synthetic implants are more expensive) or can be preferred in the pediatric population.[37,38] The dermis fat graft is a good option as a secondary orbital implant (Fig. 2) and in case of contracted sockets.[39]

Figure 1. Orbital implants. A – Silicone; B – Bioceramic; C – Guthoff.

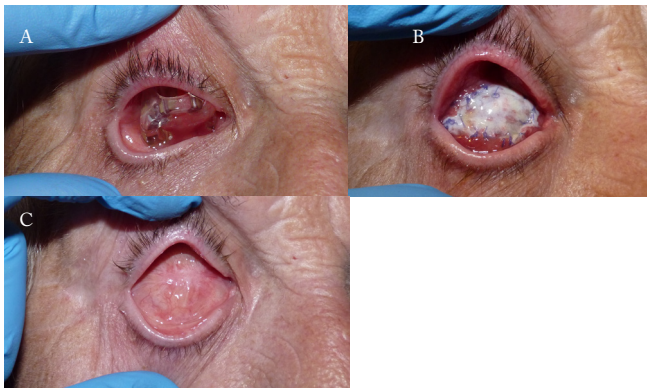


Figure 2. A – Large implant exposure of a non-porous implant; B – the implant was removed and a dermis fat graft was used as a secondary implant; C – integrated dermis fat graft 2 months postoperatively.

1.1 CLASSIFICATION

Baino *et al* recently suggested a seven-type general classification of orbital implants.[5]

1. Non-integrated: glass, silicone sphere, PMMA sphere
2. Quasi-integrated: Cuttler implant I, Allen implant, Iowa implant, Universal implant
3. Magnetically integrated: Ropper Hall implant
4. Mechanically integrated (pegged): Cuttler implant II
5. Porous: hydroxyapatite, polyethylene, aluminum oxide
6. Porous quasi-integrated: Gutthof implant
7. Biogenic: biological graft or implants wrapped by biological tissue sheets (sclera, dermis, fascia)

1.2 SHAPE

Conic, pear shaped, quasi-integrated and other implant formats are available, although the most widely used implant format is spherical.[5]

1.3 SIZE

Evisceration and enucleation procedures create an orbital volume deficit of 6 to 7 mL. This is partially replaced with the orbital implant. An 18 mm spherical implant has a volume of only 3.1 mL, meaning that the ocular prosthesis must be over the average 2 mL to make up the difference. For this reason, whenever possible, an implant of 19 mm or larger should be used.[24,40]

If the implant is of insufficient size, the ocular prosthesis will have to be larger than desirable in an attempt to reduce the volume deficit. The patient will then exhibit features referred to as the post-enucleation socket syndrome.[41]

The advantage of a large orbital implant is that the ocular prosthesis can then be lighter, reducing the incidence of lower lid laxity and post-enucleation socket syndrome. The disadvantages of a large implant are an increase in implant vascularization time, and increased pressure on the surgical wound with a higher risk of conjunctival dehiscence and implant exposure.

1.4 WRAPPING OF THE ORBITAL IMPLANT

Wrapping the implant may help the surgeon insert it into the orbit smoothly, by protecting the anterior part of the orbital soft tissues from the rough surface of the porous implant. It also provides attachment sites for the extraocular muscles after enucleation.[24]

Unwrapped PMMA implants may migrate into the orbital cavity, thereby leading to poor stability for the external prosthesis, as well as yielding an unaesthetic effect. Thus, non-integrated implants should be wrapped, and the extraocular muscles should be sutured to the wrapping material in their normal anatomical positions. Integrated implants were designed to allow greater mobility of the external prosthesis, and it was assumed that the vasculature needed to grow through the center of the implant. The wrapping material may reduce the contact between the host and the implant, so this coating should either not be present or have discontinuities, thereby facilitating the vascularization of the implant. Initially, polyethylene implants were frequently placed in the anophthalmic cavity without wrapping. However, the rates of dehiscence of the conjunctiva increased over time, leading surgeons to wrap the anterior surface of the implant while leaving the posterior surface free for the process of vascularization. Currently, this is the preferred method when using porous polyethylene implants.

In conclusion, implants must be coated in enucleation procedures, at least on their front face where they come into contact with the delicate conjunctival surface, which will reduce the chance of exposure.[5,15] The posterior face should not be covered so that fibrovascular invasion of the implant can occur.

Materials used for wrapping orbital implants:

Homologous materials (sclera, dura mater, fascia lata or temporal fascia) have a risk of disease transmission and have been abandoned. **Autologous** tissues may also be employed, such as fascia lata, temporalis fascia, auricular cartilage, dermis or even the autologous sclera (Fig. 3). However, the use of autologous tissues increases the cost, time and morbidity of the procedure. **Haloplastic** materials, such as meshes of absorbable threads like synthetic polymeric materials, e.g., polyglactin mesh, a composite of poly (lactic acid) and poly (glycolic acid), have been widely proposed.[15,24]

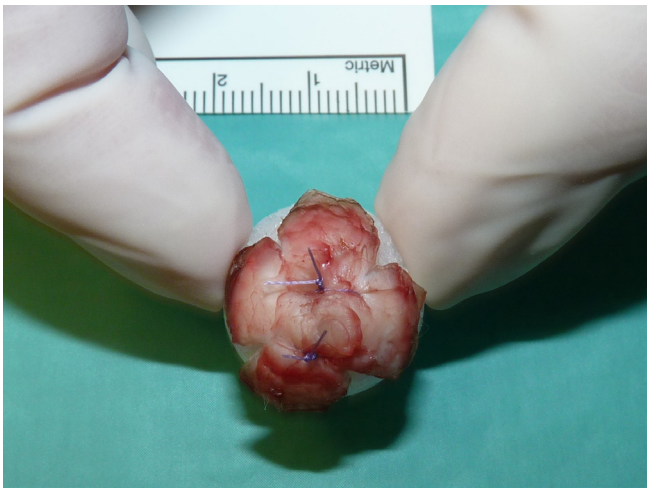


Figure. 3. Porous polyethylene implant with autologous sclera covering its anterior surface.

1.5 COMPLICATIONS

The most common complication is chronic discharge from the socket, occurring in 4.7% to 15.9% of cases.[19,24] Other complications include implant exposure (Fig. 4), infection, conjunctival thinning, persistent pain or discomfort, pyogenic granuloma, migration of the orbital implant and transient socket edema.[19]

One of the most important complications is orbital implant exposure. This is related to delayed fibrovascular ingrowth into the implant at the point of contact of the prosthesis with the conjunctiva.[24] Its incidence varies widely with the type of surgery and wrapping material, although it has continued to decline over time. In 2004, a survey of American Society of Ophthalmic Plastic and Reconstructive Surgery members reported that the rate of exposure for unpegged HA implants was 3.2%.[10]

The most feared complication is implant infection, which implies its removal. While titanium pegs have the lowest complication rate, the placement of any peg increases the risk of complications.[24]

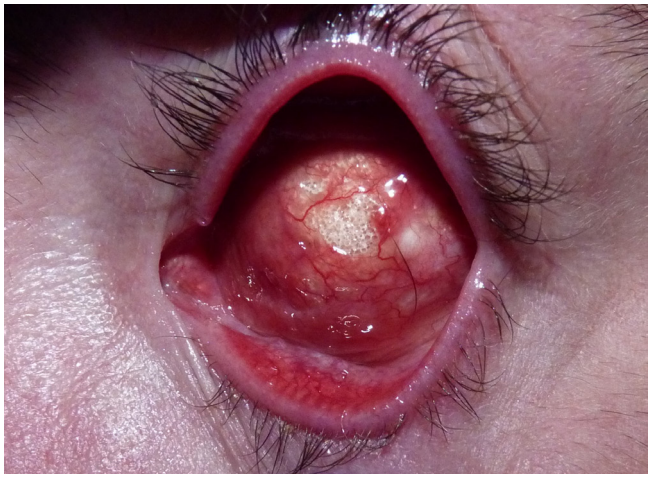


Figure. 4. Exposure of a porous implant.

1.6 PRIMARY ORBITAL IMPLANTS

An orbital implant should be placed at the time of enucleation or evisceration surgery, whenever possible, for better global surgical results and a reduction of long term complications. However, a primary orbital implant is contraindicated in cases of severe ocular and orbital trauma or infection. Primary implantation is also not recommended in evisceration cases in the context of panophthalmitis or endophthalmitis, due to the risk of intraoperative contamination of the porous implant. A secondary porous implant or a primary acrylic implant can be used after the infection is controlled.

The surgeon might consider not placing a primary implant in cases of enucleation where radiotherapy treatment is anticipated, since the radiation increases the risk of conjunctival dehiscence and consequent implant exposure.[42]

In children, the implant must be appropriate for the size of the orbit and should be replaced according to the growth of the child's orbit until they reach the adult size. The use of porous implants in the pediatric population has been advocated[18]; however, if implant exchange is required later, its removal is more difficult due to fibrovascularization. Therefore, the majority of surgeons prefer non-porous implants for children.[5,43]

1.7 SECONDARY ORBITAL IMPLANTS

An orbital implant can be placed in the orbit in a second surgical procedure (Fig. 5). The surgical technique is more difficult, less predictable, with more potential complications,

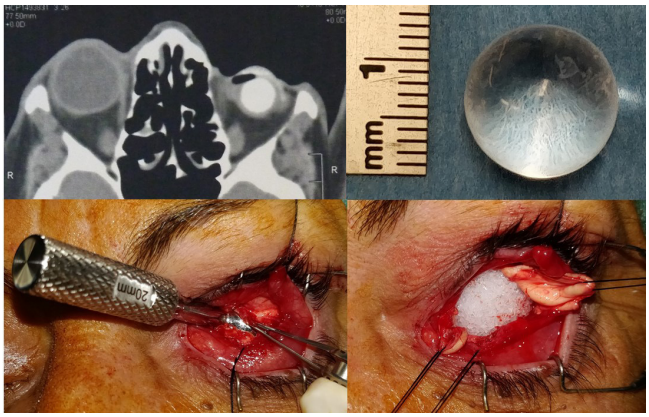


Figure 5. Substitution of a 14 mm PMMA implant for a 20 mm porous implant.

such as exposure, pyogenic granuloma, transient socket edema and socket edema requiring a surgical debulking procedure.

Conformers

At the end of the evisceration or enucleation surgery, a conformer should be placed in the conjuntival fornices in order to maintain an adequate depth for the stability of the future ocular prosthesis. The conformer also allows the patient to become familiar with the use of an ocular prosthesis from the immediate post-operative period.

The size of the conformer is selected so that the eyelid can close without effort. Large conformers that produce excessive tension on the fornices should be avoided because they predispose tissue to early dehiscence. There are three standard sizes (small, medium and large), from 20 to 26 mm largest diameter. Another option is aesthetic conformers like Natural Iris Conformers® , which feature a painted iris and sizes ranging between 24 to 28 mm. These conformers have a better aesthetic result, better acceptance and can reduce the time off work. Moreover, the larger diameter of the aesthetic conformers relative to the classic transparent acrylic conformers is more similar to the volume of the future prosthesis.[44]

Ocular Prosthesis

The ocular prosthesis is designed to improve the cosmesis of an anophthalmic socket after evisceration or enucleation. A custom-made prosthesis can be manufactured as soon as the postoperative inflammation has settled, usually between 6 to 12 weeks after surgery.[5,45]

3.1 FABRICATION OF THE OCULAR PROSTHESIS

Fabricating custom-made prosthesis requires a series of sequential steps beginning with taking an impression of the anophthalmic socket onto a first mould, the formation of a plaster cast, the final acrylic model, painting of the iris and other details on the prosthesis, and, lastly, polishing.[42,45]

Impression: The first mould of the prosthesis is obtained by filling the cavity with a paste-like material. Today, elastomers (such as dental silicone) are preferred over hydrocholloids (alginates) since they do not produce toxic by-products and are less prone do dehydration and volume contraction. Elastomers are, however, more costly than alginates. The material is carefully injected through a cannula into the anophthalmic cavity, with the patient looking straight ahead (Fig. 6). The patient must maintain primary gaze and relax all facial muscles for two minutes to allow the material to solidify. The imprinting of the surface of the anophthalmic socket onto the future prosthesis enables a larger contact surface, a factor that is essential for good mobility and comfort.

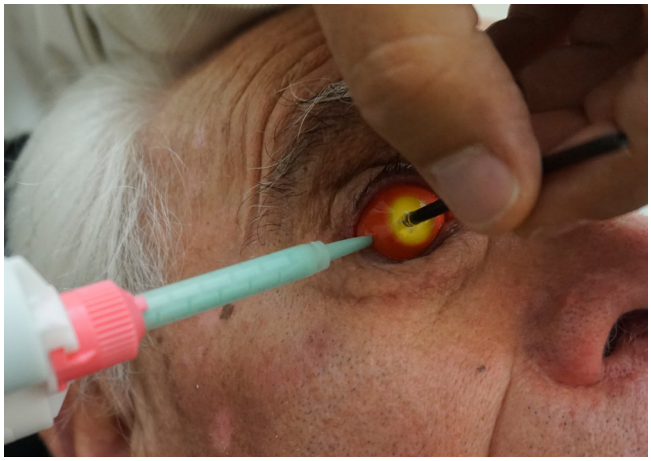


Figure 6. A silicone mould is obtained by injecting silicone into the anophthalmic socket, a process known as impression.

Plaster mould: A plaster mould is obtained from the silicone model using dental plaster (Fig. 7). From the plaster cast, as many PMMA (acrylic) copies as needed can be produced.

Figure 7. Plaster mould of the ocular prosthesis.

PMMA prosthesis: Once there is a plaster cast of the prosthesis, a copy in PMMA can be fabricated from resin. The resin polymerizes when activated by ultraviolet light or high pressure. Acrylic is notable for its transparency, biocompatibility, durability, ease of cleaning and low cost.[46]

Painting of the surface of the prosthesis: The PMMA prosthesis is placed inside the cavity and the position of the pupil is determined with the patient looking straight ahead into a light, such as in the Hirschberg test. The diameter of the iris is measured. In order to select the color, the contralateral iris should be observed in daylight and varying light conditions, and an intermediate tone should be selected. The iris can be painted directly on the prosthesis; or, an acrylic button can be fixed on the body of the prosthesis. Once the paint is dry, a layer of transparent acrylic is applied.

Polishing: Finally, the surface is polished to remove irregularities that might cause discomfort and facilitate bacterial adhesion, and to provide a final shiny and natural appearance to the surface of the prosthesis (Fig. 8).

Figure 8. Polishing the ocular prosthesis.

3.2 PLACING AND REMOVING THE PROSTHESIS

The insertion and removal of an ocular prosthesis consists of a series of simple but precise maneuvers that are facilitated by the use of a suction cup. The prosthesis is positioned by locating the notch on the superior nasal edge, where the trochlea of the superior oblique lies. The patient is asked to look down while the upper eyelid is held. Then, the upper border of the prosthesis is inserted into the superior fornix. Next, the inferior border is inserted with slight traction of the lower eyelid. To remove the prosthesis, the wet tip of the suction cap is placed on the zone of the prosthesis corresponding to the cornea. Both wetting the suction cap and the convexity of the cornea improve adhesion.[42] The patient is asked to look up and the inferior border of the prosthesis is moved away from the cavity with slight traction on lower eyelid.

It should be noted that an ocular prosthesis should be used 24 hours a day[47] and should never be removed for several days at a time, to avoid the risk of cavity retraction.[48]

3.3 CLEANING AND MAINTENANCE OF THE OCULAR PROSTHESIS

There is no absolute consensus on the frequency of cleaning of the prosthesis; however it is advisable to **clean** the prosthesis once a month, at most, using neutral soap and water.[42,49] More frequent regimens, such as weekly washing, have been associated with irritation symptoms and secretions.[50] Products such as alcohol and abrasive substances should be avoided since they damage the surface of the prosthesis,[51] as does drying the prosthesis with a towel or tissue. After washing, the prosthesis should be left to air dry spontaneously.[49] At least once a year the prosthesis should have professional **polishing**. This should take place more frequently in the presence of irritation of the eyelid rim or giant papillary conjunctivitis[49] or if deposition of protein material is observed on the surface of the prosthesis (Fig. 9).[42]

Depending on the patient's occupation and care of the prosthesis, **substitution** of the prosthesis is recommended in up to 6 years of use in adults.[42,48,49,52] In children, due to the growth of the orbit, a change of prosthesis is required between 18-26 months following placement.[53]

Patients should have **artificial tears** prescribed and be encourage to use them multiple times per day. Artificial tears help lubricate the hydrophobic surface of the prosthesis, thereby reducing friction and inflammation of the mucosa.[42]

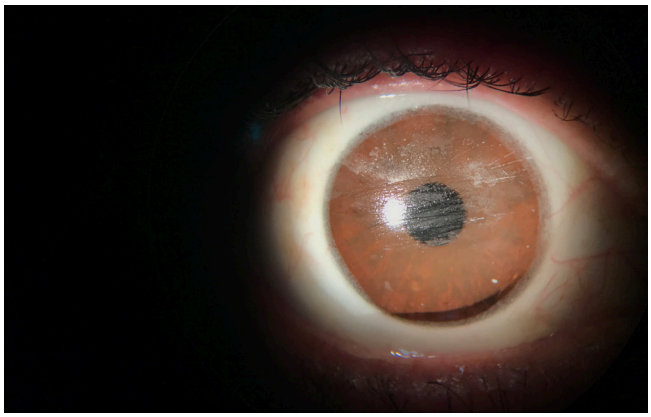


Figure 9. Deposit buildup on ocular prosthesis.

3.4 EVALUATION OF THE PROSTHESIS AND CAVITY

The observation of patients with an anophthalmic socket comprises the external examination of the eyelids and orbit, the mobility, size and surface of the prosthesis, as well as inspection of the conjunctiva.

Post-enucleation socket syndrome (PESS) occurs in a significant portion of these patients. PESS consists in a combination of enophthalmos, deep superior sulcus, lower lid laxity and upper lid ptosis, all of which may become disfiguring and require rehabilitation (Fig. 10).[41,54]

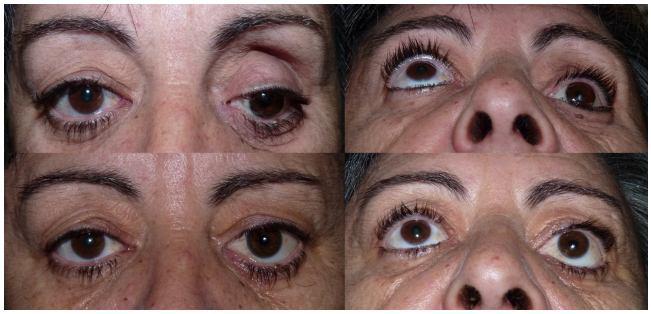


Figure 10. Post-enucleation socket syndrome – pre (A, B) and post-operative (C, D) appearance after substitution of the implant (clinical case of Fig. 5).

The **mobility** of the prosthesis constitutes an important aspect of the final aesthetic result. Movements of the prosthesis are transmitted by the orbital implant underneath. The movement can never be complete, especially in extreme gaze, due to the space occupied by the extremities of the prosthesis in the cavity. However, it should be observed if there is significant and uniform mobility of the prosthesis.

Evaluate the **size and volume** of a small prosthesis by determine the presence of excessive displacing using a cotton swab.[42,49] A large and heavy prosthesis, used to mitigate the lack of volume in the cavity can impede the spontaneous, full closer of the eyelids and could, in fact, contribute to PESS by distending the canthal ligaments and increasing lower lid laxity.

The **surface of the prosthesis** should be observed at each visit with the help of the slit-lamp, to make sure there are no significant irregularities and scratches, in order to avoid

discomfort and an increased risk of bacterial deposits and deterioration.[49]

The **conjunctiva** of the anophthalmic socket should be vascularised, pinkish and homogeneous. The dimensions of the **fornices** and the presence of synechiae should be noted, as they may impede the correct positioning and stability of the ocular prosthesis in the socket. **Giant papillary conjunctivitis** is an allergic reaction secondary to a mechanical stimulus such as contact lenses or an ocular prosthesis. It is a relatively frequent condition in patients with ocular prosthesis, and its incidence increases with unkempt surfaces or defective fabrication.[48]

Epithelial inclusion cysts can form in 3% - 7% of cases.[55] They have a translucid appearance and consist of a fibrous capsule with an epithelial lining, containing mucous fluid.[56] They can expand impeding the retention of the prosthesis, and can be treated with surgical excision or steroid infiltration.[42]

Pyogenic granulomas have a friable and hemorrhagic appearance and are mostly found around suture remnants.[42]

The surface should also be inspected for possible **exposure of the orbital implant** as an immediate correction can prevent future failure of the orbital implant.

Scleral shells

A scleral shell is a custom-made, thin, ocular prosthesis that fits over a blind eye.[57] Scleral shells provide good-to-excellent prosthetic motility and are often cosmetically superior to results from enucleation or evisceration, while also avoiding the operative and post-operative complications of those procedures (Fig. 11).[58] Their use should be considered in blind, unaesthetic eyes that are not painful.

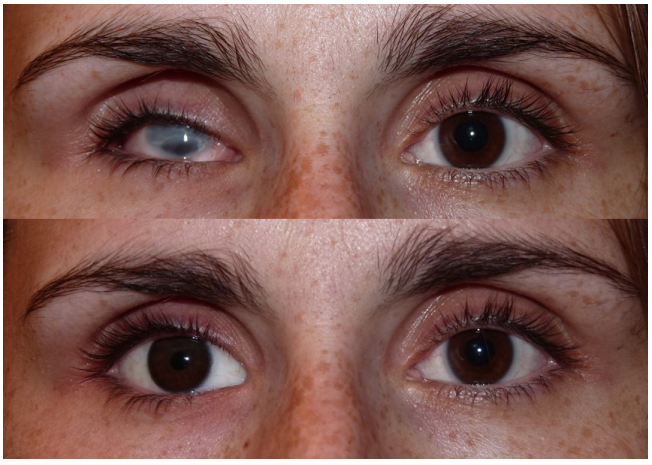


Figure 11. Adaptation of a scleral shell on a blind and painless eye.

Most patients can tolerate the fit of a shell even with normal corneal sensation because the posterior face of the shell is vaulted to sit off the cornea (Fig. 12).[57] However, some patients may require a Gunderson flap, a Tenon-conjunctival flap or a full-thickness mucous membrane graft to tolerate the scleral shell.[58-61]

In phthisical eyes with chronic pain, severe phthisis, or any active intraocular processes such as infection or tumor, evisceration or enucleation remain the gold standard.[60]

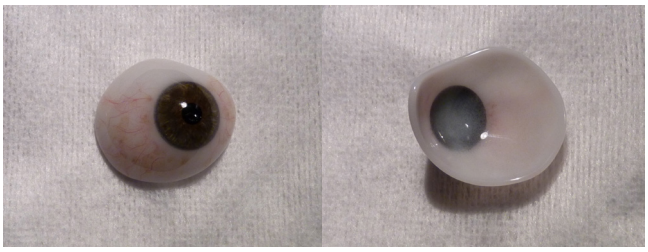


Figure 12. Front and back surfaces of a scleral shell.

Acknowledgements: we would like to thank the Ocularists Mr. Paulo Ferreira and Mr. Lúcio Ferraz, for their collaboration in the fabrication of the ocular prosthesis and the photographic documentation undertaken during this process.

Ethical Disclosures

Confidentiality of Data: Patient consents obtained.
Conflicts of Interest: The authors have no financial interest in the products or procedures mentioned in this chapter

Corresponding author
Sandra Prazeres
prazeresandra@gmail.com

REFERENCES

1. Mules PH. Evisceration of the globe with artificial vitreous. 1884-1895. Adv Ophthalmic Plast Reconstr Surg. 1990;8:69-72.
2. Fan JT, Robertson DM. Long-term follow-up of the Allen implant. 1967 to 1991. Ophthalmology. 1995;102:510-6.
3. Chuah CT, Chee SP, Fong KS, Por YM, Choo CT, Luu C, et al. Integrated hydroxyapatite implant and non-integrated implants in enucleated Asian patients. Ann Acad Med.. 2004;33:477-83.
4. Perry AC. Integrated orbital implants. Adv Ophthalmic Plast Reconstr Surg. 1990;8:75-81.
5. Baino F, Perero S, Ferraris S, Miola M, Balagna C, Verne E, et al. Biomaterials for orbital implants and ocular prostheses: overview and future prospects. Acta Biomater. 2014;10:1064-87.
6. Karesh JW, Dresner SC. High-density porous polyethylene (Medpor) as a successful anophthalmic socket implant. Ophthalmology. 1994;101:1688-95; discussion 95-6.
7. Jordan DR, Munro SM, Brownstein S, Gilberg SM, Grahovac SZ. A synthetic hydroxyapatite implant: the so-called counterfeit implant. Ophthalmic Plast Reconstr Surg. 1998;14:244-9.
8. Mahoney NR, Grant MP, Iliff NT, Merbs SL. Exposure rate of smooth surface tunnel porous polyethylene implants after enucleation. Ophthalmic Plast Reconstr Surg. 2014;30:492-8.
9. Choi YJ, Park C, Jin HC, Choung HK, Lee MJ, Kim N, et al. Outcome of smooth surface tunnel porous polyethylene orbital implants (Medpor SST) in children with retinoblastoma. Br J Ophthalmol. 2013;97:1530-3.
10. Su GW, Yen MT. Current trends in managing the anophthalmic socket after primary enucleation and evisceration. Ophthalmic Plast Reconstr Surg. 2004;20:274-80.
11. Schellini S, Jorge E, Sousa R, Burroughs J, El-Dib R. Porous and nonporous orbital implants for treating the anophthalmic socket: A meta-analysis of case series studies. Orbit. 2016;35:78-86.
12. Jung SK, Cho WK, Paik JS, Yang SW. Long-term surgical outcomes of porous polyethylene orbital implants: a review of 314 cases. Br J Ophthalmol. 2012;96:494-8.

13. Jordan DR, Mawn LA, Brownstein S, McEachren TM, Gilberg SM, Hill V, et al. The bioceramic orbital implant: a new generation of porous implants. Ophthalmic Plast Reconstr Surg. 2000;16:347-55.
14. Jordan DR, Gilberg S, Mawn LA. The bioceramic orbital implant: experience with 107 implants. Ophthalmic Plast Reconstr Surg. 2003;19:128-35.
15. Chalasani R, Poole-Warren L, Conway RM, Ben-Nissan B. Porous orbital implants in enucleation: a systematic review. Surv Ophthalmol. 2007;52:145-55.
16. Schellini SA, El Dib R, Limongi RM, Morschbacher R. Anophthalmic socket: choice of orbital implants for reconstruction. Arq Brasil Oftalmol. 2015;78:260-3.
17. Li T, Shen J, Duffy MT. Exposure rates of wrapped and unwrapped orbital implants following enucleation. Ophthalmic Plast Reconstr Surg. 2001;17:431-5.
18. Iordanidou V, De Potter P. Porous polyethylene orbital implant in the pediatric population. Am J Ophthalmol. 2004;138:425-9.
19. Shoamanesh A, Pang NK, Oestreicher JH. Complications of orbital implants: a review of 542 patients who have undergone orbital implantation and 275 subsequent PEG placements. Orbit. 2007;26:173-82.
20. Jordan DR, Gilberg S, Bawazeer A. Coralline hydroxyapatite orbital implant (bio-eye): experience with 158 patients. Ophthalmic Plast Reconstr Surg. 2004;20:69-74.
21. Dutton JJ. Coralline hydroxyapatite as an ocular implant. Ophthalmology. 1991;98:370-7.
22. Smith RJ, Prazeres S, Fauquier S, Malet T. Complications of two scleral flaps evisceration technique: analysis of 201 procedures. Ophthalmic Plast Reconstr Surg. 2011;27:227-31.
23. Jordan DR, Klapper SR, Gilberg SM. The use of vicryl mesh in 200 porous orbital implants: a technique with few exposures. Ophthalmic Plast Reconstr Surg. 2003;19:53-61.
24. Yoon JS, Lew H, Kim SJ, Lee SY. Exposure rate of hydroxyapatite orbital implants a 15-year experience of 802 cases. Ophthalmology. 2008;115:566-72.e2.
25. Hornblass A, Biesman BS, Eviatar JA. Current techniques of enucleation: a survey of 5,439 intraorbital implants and a review of the literature. Ophthalmic Plast Reconstr Surg. 1995;11:77-86; discussion 7-8.
26. Shields CL, Shields JA, De Potter P, Singh AD. Problems with the hydroxyapatite orbital implant: experience with 250 consecutive cases. Br J Ophthalmol. 1994;78:702-6.
27. Shields CL, Shields JA, De Potter P. Hydroxyapatite orbital implant after enucleation. Experience with initial 100 consecutive cases. Archives Ophthalmol. 1992;110:333-8.
28. Christmas NJ, Gordon CD, Murray TG, et al. Intraorbital implants after enucleation and their complications: A 10-year review. Arch Ophthalmol. 1998;116:1199-203.
29. Trichopoulos N, Augsburger JJ. Enucleation with unwrapped porous and nonporous orbital implants: a 15-year experience. Ophthalmic Plast Reconstr Surg. 2005;21:331-6.
30. Schellini S, El Dib R, Silva LR, Farat JG, Zhang Y, Jorge EC. Integrated versus non-integrated orbital implants for treating anophthalmic sockets. Cochrane Database Syst Rev. 2016;11:Cd010293.
31. Lin CJ, Liao SL, Jou JR, Kao SCS, Hou PK, Chen MS. Complications of motility peg placement for porous hydroxyapatite orbital implants. Br J Ophthalmol. 2002;86:394-6.
32. Edelstein C, Shields CL, De Potter P, Shields JA. Complications of motility peg placement for the hydroxyapatite orbital implant. Ophthalmology. 1997;104:1616-21.
33. Jordan DR, Chan S, Mawn L, Gilberg S, Dean T, Brownstein S, et al. Complications associated with pegging hydroxyapatite orbital implants. Ophthalmology. 1999;106:505-12.
34. Anderson RL, Yen MT, Lucci LM, Caruso RT. The quasi-integrated porous polyethylene orbital implant. Ophthalmic Plast Reconstr Surg. 2002;18:50-5.
35. Guthoff R, Vick HP, Schaudig U. Zur Prophylaxe des Postenukleationssyndroms: Das Hydroxylapatitsilikon-implantat. Experimentelle Vorarbeiten und erste klinische Erfahrungen. . Ophthalmologe. 1995;92:198-205.
36. Naik MN, Murthy RK, Honavar SG. Comparison of vascularization of Medpor and Medpor-Plus orbital implants: a prospective, randomized study. Ophthalmic Plast Reconstr Surg. 2007;23:463-7.
37. Tarantini A, Hintschich C. Primary dermis-fat grafting in children. Orbit. 2008;27:363-9.
38. Quaranta-Leoni FM, Sposato S, Raglione P, Mastromarino A. Dermis-fat graft in children as primary and secondary orbital implant. Ophthalmic Plast Reconstr Surg. 2016;32:214-9.
39. Nentwich MM, Schebitz-Walter K, Hirneiss C, Hintschich C. Dermis fat grafts as primary and secondary orbital implants. Orbit. 2014;33:33-8.
40. Viswanathan P, Sagoo MS, Olver JM. UK national survey of enucleation, evisceration and orbital implant trends. Br J Ophthalmol. 2007;91:616-9.
41. Tyers AG, Collin JR. Orbital implants and post enucleation socket syndrome. Trans Ophthalmol Soc U K. 1982;102:90-2.
42. Fernández Hermida R, Berasategui Fernández B. Cavidad Anoftálmica y Prótesis Oculares. Madrid: Mac Line; 2016.
43. Baino F, Potestio I. Orbital implants: State-of-the-art review with emphasis on biomaterials and recent advances. Mater Sci Eng C Mater Biol Appl. 2016;69:1410-28.
44. Avisar I, Norris JH, Quinn S, Allan D, McCalla M, Dugdale D, et al. Temporary cosmetic painted prostheses in anophthalmic surgery: an alternative to early postoperative clear conformers. Eye. 2011;25:1418-22.
45. Gomez P. Prótesis oculares: "una mirada a las prótesis oculares". Invest ANdina. 2010;12.
46. Goiato MC, Bannwart LC, Haddad MF, dos Santos DM, Pesqueira AA, Miyahara GI. Fabrication techniques for ocular prostheses--an overview. Orbit. 2014;33:229-33.
47. Bailey CS, Buckley RJ. Ocular prostheses and contact lenses. I--Cosmetic devices. BMJ. 1991;302:1010-2.
48. Laiseca J, Laiseca D, Laiseca A. Prótesis oculares y cirurgía reconstructiva de cavidades. Madrid: Prensa Hispoanoamericana; 1991.
49. Bonaque-Gonzalez S, Amigo A, Rodriguez-Luna C. Recommendations for post-adaption care of an ocular prosthesis: A review. Cont Lens Anterior Eye. 2015;38:397-401.
50. Vasquez RJ, Linberg JV. The anophthalmic socket and the prosthetic eye. A clinical and bacteriologic study. Ophthalmic Plast Reconstr Surg. 1989;5:277-80.
51. Parr GR, Goldman BM, Rahn AO. Postinsertion care of the ocular prosthesis. J Prosthet Dent. 1983;49:220-4.
52. Pine KR, Sloan B, Jacobs RJ. Deposit buildup on prosthetic eyes and implications for conjunctival inflammation and mucoid discharge. Clin Ophthalmol. 2012;6:1755-62.
53. Raizada D, Raizada K, Naik M, Murthy R, Bhaduri A, Honavar SG. Custom ocular prosthesis in children: how often is a change required? Orbit. 2011;30:208-13.
54. Shah CT, Hughes MO, Kirzhner M. Anophthalmic syndrome: a review of management. Ophthalmic Plast Reconstr Surg. 2014;30:361-5.
55. Junemann A, Holbach LM. Epitheliale riesenimplantationszyste 50 jahre nach enukleation ohne orbitaimplantat. Klin Monbl Augenheilkd.1998;212:127-8.

56. Smit TJ, Koornneef L, Zonneveld FW. Conjunctival cysts in anophthalmic orbits. The British journal of ophthalmology. 1991;75(6):342-3.
57. Nerad J. Techniques in Ophthalmic Plastic Surgery. Amsterdam: Saunders Elsevier; 2010.
58. Ma'luf RN, Awwad ST. Mucous membrane graft versus Gunderson conjunctival flap for fitting a scleral shell over a sensitive cornea. Ophthalmic Plast Reconstr Surg. 2005;21:356-8.
59. Gundersen T. Conjunctival flaps in the treatment of corneal disease with reference to a new technique of application. AMA Arch Ophthalmol. 1958;60:880-8.
60. Galindo-Ferreiro A, Akaishi PS, Al-Aliwi M, Niespodzany E, Galvez-Ruiz A, Cruz AAV. Five years' experience with tenon-conjunctival flaps in phthisical eyes. Semin Ophthalmol. 2017;32:642-6.
61. Ding J, Chen T, Hou Z, Qin Y, Hao L, Li D. Cosmetic shell fitting over a sensitive cornea in mild phthisis bulbi using total conjunctival flap. Aesthetic Plast Surg. 2013;37:398-401.

18. The Anophthalmic Orbit

OPHTHALMOLOGY
Guilherme Castela, MD; Nádia Lopes, MD

Summary

Acquired anophthalmia refers to the loss of one eye as the result of either trauma or surgery. The main surgical procedures for eye removal are enucleation and evisceration. To restore volume loss after these procedures, an implant is placed inside the orbit. Current concepts for the prevention and treatment of implant migration, post-enucleation socket syndrome (PESS) and socket contraction are described in this chapter.

Keywords: *Adipose Tissue/transplantation; Anophthalmos/surgery; Eye, Artificial; Eye Enucleation; Eye Evisceration; Orbit/surgery; Orbital Implants; Postoperative Complications;*

INTRODUCTION

After an enucleation or evisceration procedure a close follow up is needed, as complications may occur. Implant migration and extrusion may result from soft tissue changes that occur over time in the anophthalmic socket. Also, the absence or an implant too small may lead to a post-enucleation socket syndrome (PESS). This condition is characterized by an orbital volume deficit (enophthalmos), laxity of the lower lid, ptosis and a deep upper eyelid sulcus. Finally, a progressive socket contraction can develop in cases where soft tissue and conjunctiva shrinkage occurs over time.
All these complications may lead to an uncomfortable, poorly positioned and unstable prosthesis.

1. EVISCERATION / ENUCLEATION

The main indications for eye removal are:
1. Atrophy of a non-seeing eye (phthisis bulbi) resulting in a volume deficit (Fig.1).
2. Pain control in a blind eye. Common causes of ocular pain include corneal decompensation, epithelial defects, uveitis, high intraocular pressure, and ocular ischemia.
3. Severe intra-ocular infection (endophthalmitis).
4. Reducing the risk of sympathetic ophthalmia (SO). This bilateral diffuse granulomatous intraocular inflammation usually develops within days or even months after surgery or a penetrating trauma to one eye. The injured eye is known as the exciting eye, while the fellow eye (which develops the inflammation) is called the sympathizing eye.
5. Cosmetic improvement of a disfigured eye (Fig. 2).
6. Eye tumor.

There are two surgical techniques to remove an eye. The removal of the eye contents preserving the scleral shell, extraocular muscles and other orbital adnexa is called **evisceration**. The complete removal of the eye itself is called **enucleation**.

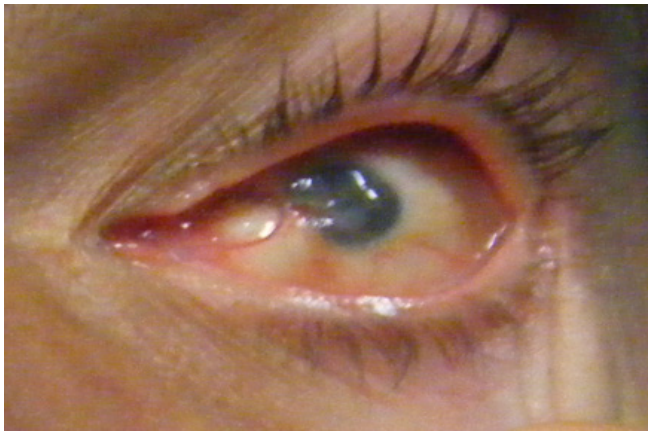


Figure 1. Left atrophic eye

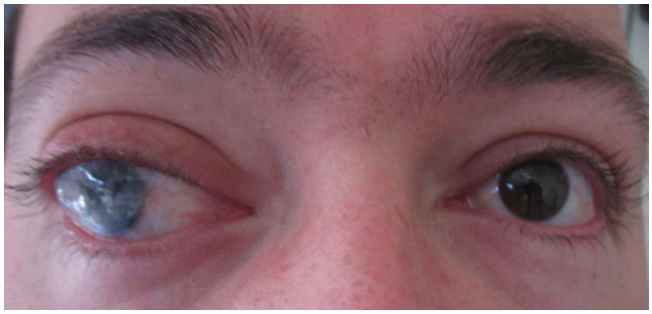


Figure 2. A right disfigured eye

The decision between the two techniques depends on the surgeon's experience, the type of implants available, and the risk of SO.
In trauma, evisceration is usually preferred over enucleation as it allows a better preservation of orbital volume, ocular motility and has a lower risk of implant migration. Evisceration usually provides a superior cosmetic and functional result. In an eye with a tumor or suspected tumor, however, enucleation is the only option.
Concerns regarding the risk of visual loss in the opposite eye secondary to SO is often the reason why some specialists prefer enucleation over evisceration in trauma cases. Nevertheless, the risk of SO following evisceration is now considered to be low, and this association has never been clearly proven.

1.1 EVISCERATION

Surgical Technique (Fig. 3)

Several different techniques have been described for evisceration (with or without keratectomy, two or four

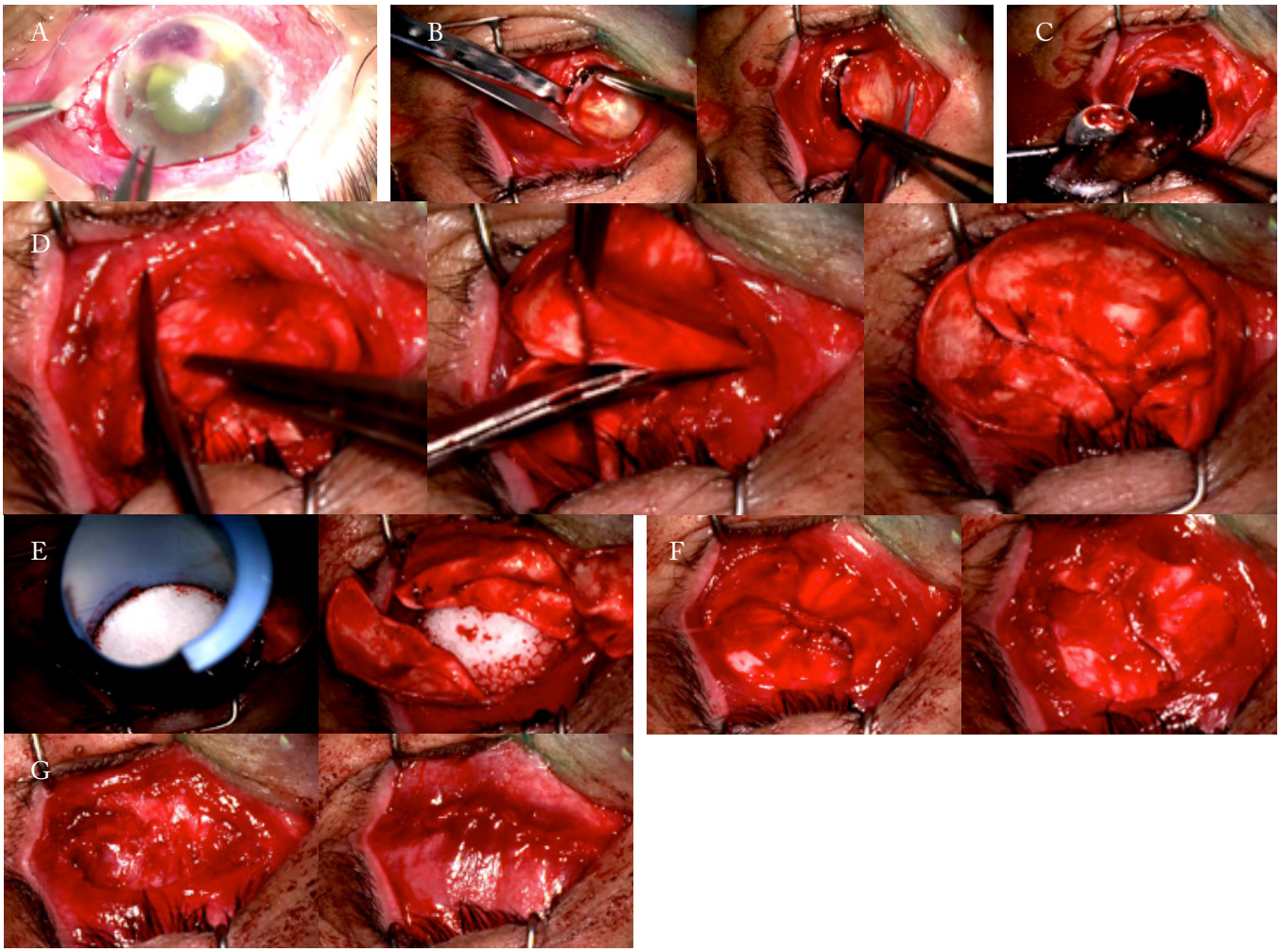


Figure 3. A: 360º conjunctival opening, B: Keratectomy, C: Removal of the eye contents, D: Two sclerotomies performed from the limbus to the optic nerve, E: Implant placement between the two scleral flaps, F: Suture of two scleral flaps using 5-0 prolene suture, G: Closure of conjunctiva and Tenon´s capsule with an absorbable 6-0 interrupted suture

sclerotomies, etc). It is not possible to outline each one in detail. The technique preferred by the authors consists of two sclerotomies with keratectomy. This is a quick, easy and reproducible procedure, which allows the use of large implants.

1. A 360º opening of the conjunctiva is performed (Fig. 3A)
2. Blunt dissection is undertaken to separate the conjunctiva and Tenon's capsule from the globe
3. Keratectomy of the cornea including 1mm of adjacent limbus (Fig. 3B)
4. Cornea and choroidal tissue is removed, leaving only the sclera (Fig. 3C)
5. Two sclerotomies are performed from the limbus, between the superior and medial rectus, and the inferior and lateral rectus, up to the optic nerve, leaving the optic nerve and the posterior sclera completely separated. This allows the expansion of the cavity and the introduction of a large implant (Fig. 3D)

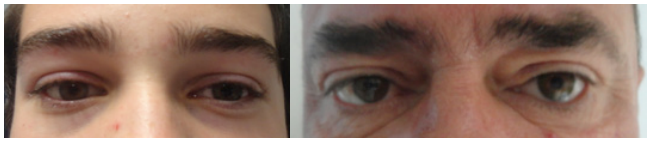


Figure 3H. Post-operative aspect of patients undergoing unilateral evisceration

6. An orbital implant is placed between the two scleral flaps (Fig. 3E)
7. The two flaps are sutured to each other superiorly using 5-0 polypropylene (Prolene®) sutures (Fig. 3F)
8. The conjunctiva and Tenon capsule are sutured separately using an absorbable 6-0 (Vicryl®) interrupted suture (Fig. 3G,H)

OTHER TECHNIQUES FOR EVISCERATION

Four-Petal Evisceration

This procedure consists of a quadri-section of the sclera, which is sutured in two layers, allowing the placement of a large orbital implant with few complications. It is a more time-consuming technique.

Evisceration with Cornea Preservation

Preserving the cornea provides a larger and more suitable socket for the adaptation of the external prosthesis, resulting in a better functional and aesthetic appearance. Contraindications are: keratitis, corneal ulcers, thin corneas with a risk of rupture, and degenerations. With this technique, it is difficult to introduce a large implant.

1.2 ENUCLEATION

Surgical Technique (Fig. 4)

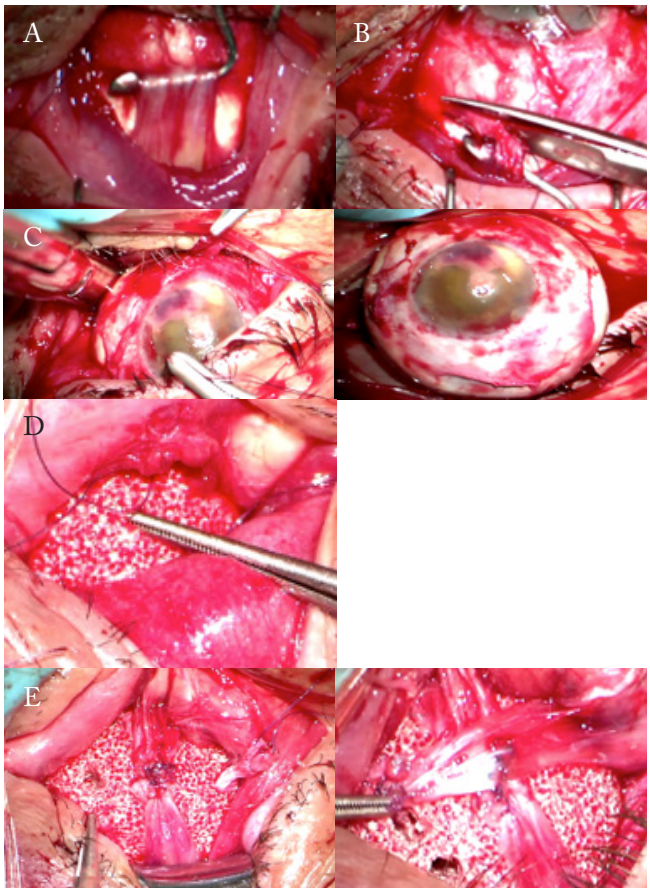


Figure 4. A: The four rectus muscles are isolated and sutured with 6-0 double armed absorbable suture, B: The muscles are detached close to the sclera, C: Optic nerve transection, D: The implant is placed in the cavity, E: The four rectus muscles are sutured to the implant

1. A 360º opening of the conjunctiva is performed (see evisceration technique)
2. Blunt dissection is used to separate the conjunctiva and Tenon's capsule from the globe
3. The four rectus muscles are isolated with 6-0 double-armed absorbable (Vicryl®) sutures, 2 mm from their insertion (Fig. 4A)
4. The rectus muscles insertion is cut close to the sclera (Fig. 4B)
5. The two oblique muscles are also cut and left loose inside the orbit
6. The optic nerve is transected using enucleation scissors, ensuring a good hemostasis by applying direct pressure or using a bipolar cautery (Fig. 4C)
7. The chosen implant is placed inside the cavity (Fig. 4D)
8. The four rectus muscles are sutured directly to the implant if a porous implant is chosen, or to the wrapping material of a non-porous implant (Fig. 4E)
9. The conjunctiva and Tenon's capsule are sutured independently with absorbable 6-0 (Vicryl®) interrupted suture (see evisceration technique)

2. ORBITAL IMPLANTS

An orbital implant is a rounded device implanted in the orbit following evisceration or enucleation. An ocular prosthesis (artificial eye) is usually placed anteriorly to the orbital implant for cosmetic purposes.
Ideally, the orbital implant should provide a good orbital volume, transmit mobility to the prosthesis, and be biocompatible.
Implants are classified in two groups: autologous and heterologous (synthetic). This last group can be divided into porous (Fig. 5A) and non-porous (Fig. 5B) implants. The selection of the implant depends on many factors. These include extrusion rates, availability, desired mobility, and surgeon preference.

2.1 SYNTHETIC

Porous orbital implants have become popular since the introduction of the coralline hydroxyapatite (HA) implant in the late 1980s. Today, they are preferred by most of the oculoplastic surgeons. Porous materials (coralline hydroxyapatite, synthetic hydroxyapatite, porous polyethylene, aluminum oxide) allow the growth of fibrovascular tissue into their porous channels, and therefore a more biological integration into orbital contents. This decreases the risk of infection, extrusion and migration. They also allow the possibility of using a peg, which is placed anteriorly to the implant and connected to the ocular prosthesis in order to give it a wider range of movements.
The non-porous orbital implants (silicone and polymethyl methacrylate - PMMA) are cheaper but are not integrated into the tissues. This may result in a higher rate of implant migration and extrusion. The extrusion of silicone implants is actually a well-known complication after the repair of orbital fractures, the same occurring in cosmetic procedures such as chin and nasal augmentation.
In enucleation procedures, most implants need to be wrapped in order to create a reattachment point for the extraocular muscles. Several wrapping materials have been used: preserved donor sclera (Fig. 5C), dura-mater, bovine pericardium, fascia lata, as well as synthetic substances like teflon. Medpor® implants, the preferred for most authors in cases of enucleation, allow direct muscle suturing, therefore eliminating the need of wrapping.
More recently, hydrophilic osmotic implants have been developed. Hydrogel implants gradually increase in size as they absorb water from the surrounding tissues, having the capacity to swell tenfold their size. This implant is better for children who depend on a growing eye for a normal development of the socket.

2.2 AUTOLOGOUS

Autologous implants (dermal fat grafts) have the advantage of not being rejected and can be used as both primary or secondary implants. They are ideal for children due to their growth potential.

Figure 5. A: Porous implant, b: Nonporous implant, c: Sclera used for implant wrapping

Choosing the implant size

The implant should be 2-3 mm smaller than the axial length of the opposite eye. The remaining volume comes from the

external prosthesis. The most frequent implant sizes used in adults are 20 and 22 mm. In general, the bigger the implant, the better the final cosmetic result. If the external prosthesis is thick to compensate for a deficient volume, it will be heavier, which may limit its retention and cause a systematic drooping.

3. COMPLICATIONS

Immediate complications
- Infection
- Hemorrhage
- Implant extrusion

Long-term complications
- Sunken / deep superior fornix (cf enophthalmos)
- Lower eyelid laxity and ectropion
- Upper eyelid ptosis
- Socket contraction
- Conjunctival cyst formation (Fig. 6)
- Implant migration
- Late extrusion of the implant

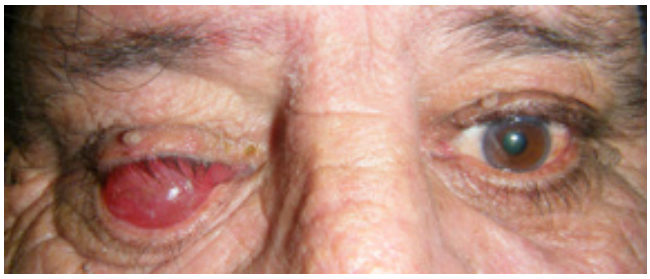


Figure 6. Conjunctival cyst

3.1 IMPLANT EXPOSURE / EXTRUSION

Implant exposure is an important complication of porous implants and occurs in up to 2% to 10% of cases (Fig. 7)
Many factors are thought to be associated: larger implant sizes, tension on the conjunctival wound, the contact between the textured surface of the implant and its covering layers with a possible progressive breakdown. In a porous implant an inadequate fibrovascular ingrowth is the most important factor for exposure/extrusion. Also, non-wrapping an implant may become an important predisposing feature.
When planning surgical correction of an exposed porous implant, an important aspect to take into account is the degree of fibrovascular integration that has already occurred. The exposure of a partially vascularized implant may improve following implant salvaging techniques, but an entirely avascular, nonintegrated, porous implant often requires complete removal. In non-porous implants, the implant should always be removed, since the exposure ends in extrusion in most cases.
In small exposures (up to 3 mm) of porous implants, a "wait and see" approach is a valid option, as long as signs of infection are not identified. Washings can be made using polyvinylpyrrolidone diluted to 50%. Larger exposures may be covered with labial mucosa or an autologous dermal fat graft (with minimal fat). When the implant is partially integrated, a dermal fat graft can be placed over the implant after removing the avascular part. However, when the implant is completely avascular, or in cases of relapse, the only option is to replace it with another heterologous or autologous implant.
Another technique (preferred by the authors) in cases of exposure/extrusion associated with a conjunctival deficit is the simultaneous placement of a dermal fat graft with a porous implant. It addresses both the volume and the lack of conjunctival tissue.
The most critical factors in preventing exposure/extrusion are the initial surgical technique (the posterior placement of the implant and the separate suture of Tenon and conjunctiva avoiding tension across the wound) and choosing an appropriate implant size.

3.2 PESS (POST-ENUCLEATION SOCKET SYNDROME)

The absence or a small implant after an evisceration/ enucleation procedure may result in a post-enucleation socket syndrome (PESS). This is characterized by an orbital volume deficit (enophthalmos), laxity of the lower lid, ptosis and a deep upper eyelid sulcus (Fig.8).
The primary goal when rehabilitating a PESS patient is to correct the orbital volume together with eyelid malposition.

3.3ORBITAL VOLUME OPTIMIZATION

Many different materials are available for the correction of orbital volume: dermal fat graft, fat graft, and also biomaterials. Different surgical techniques are used for reconstruction.

Autologous Dermal Fat Graft

Dermal fat grafts are composed of dermis and the underlying subcutaneous fat. The dermis quickly becomes vascularized,

Figure 7A, B, C: Cases of implant exposure

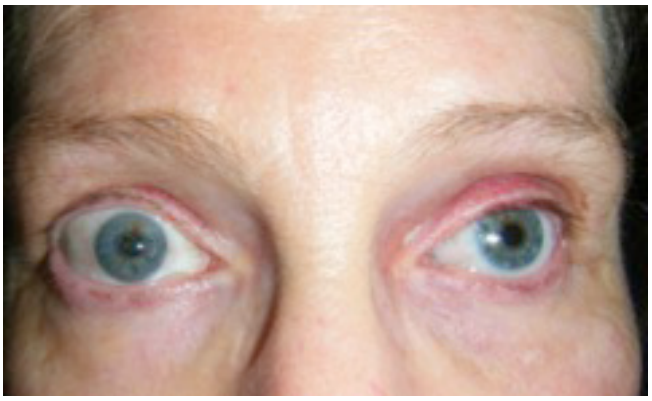


Figure 8. A patient with a left post-enucleation socket syndrome: enophthalmos and a deep upper eyelid sulcus are visible

which is believed to reduce the incidence of fat atrophy, compared to a fat only graft. Fat reabsorption is more significant in the first six months. Unfortunately, its extent is unpredictable and ranges from 25% to 30%. Factors such as severe trauma, irradiation and multiple interventions increase these rates.

Donor sites used to harvest the graft vary and include the gluteal and lower abdomen. Some specialists prefer adipose tissue from the gluteal area because the dermis is thicker and, apparently, present more fibroblasts and fibrocytes, believed to reduce fat reabsorption.

Complications occur in approximately 5% of cases. These include: graft ulceration, infection, conjunctival granuloma, hair growth and keratinization of the socket.

Surgical Technique (Fig. 9)

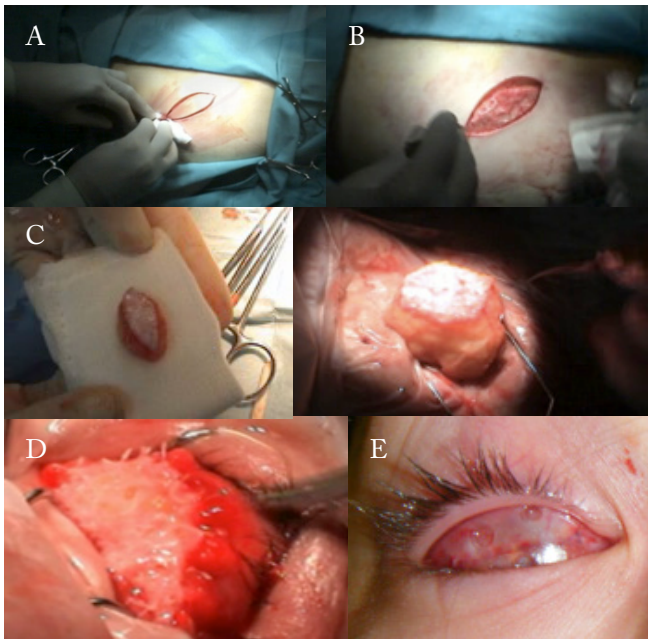


Figure 9. A: The graft is harvest from the gluteal area, B: The epidermis is dissected from de dermis, C: The graft is introduced in the orbit, D: The extra-ocular muscles and the conjunctiva are sutured to the dermis, E: Conformer placed over the conjunctiva

1. A graft with approximately 2.5 / 3 cm dimension is harvested from the gluteal area (or elsewhere) (Fig. 9A)
2. The epidermis is dissected from the underlying dermis (Fig. 9B)
3. The graft is introduced into the orbit (Fig. 9C)
4. The extra-ocular muscles and the conjunctiva are sutured to the dermis using absorbable 6-0 (Vicryl®) interrupted suture (Fig. 9D)
5. A rigid conformer is positioned to maintain the socket cavity volume and fornices until an external prosthesis is adapted (Fig. 9E).

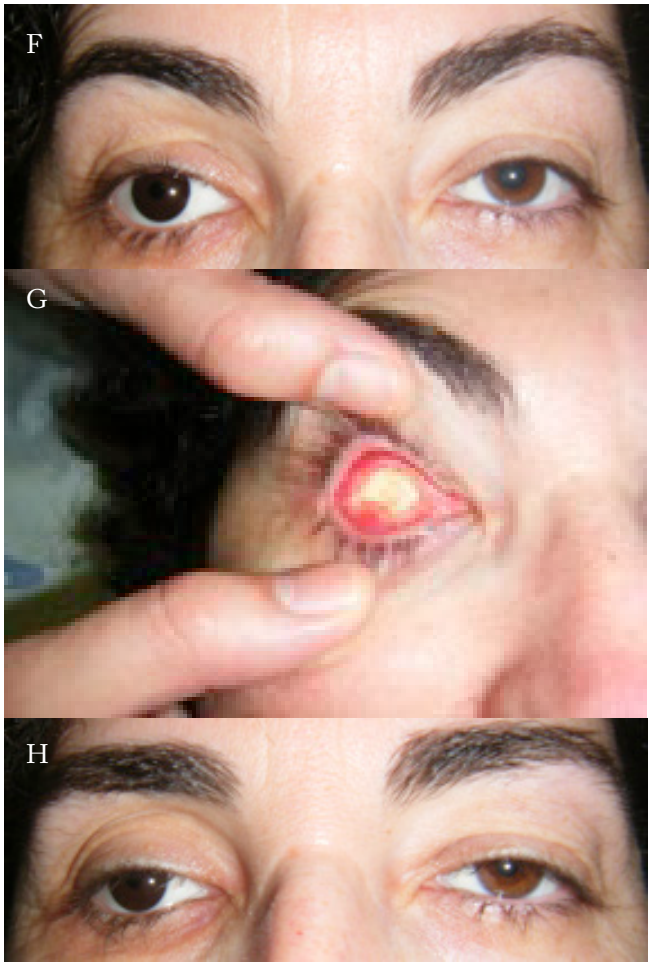


Figure 9. F: A patient with right orbital volume deficit, G: One month after a dermal fat graft (partial epithelialization of the graft), H: Four months after the procedure

Autologous Fat Graft

Micro-fat grafting or 'lipostructure' was initially described by Coleman, and is sometimes referred to as the 'Coleman fat transfer technique'. Autologous fat can be considered as an ideal soft-tissue graft because it is abundant, readily available, inexpensive, host-compatible, and can be harvested repeatedly. However, it has unpredictable reabsorption rates. The technique consists of carefully harvesting adipocytes using a non-traumatic liposuction technique. The fat is then refined by centrifugation in order to separate the intact cells from the remaining ruptured cells, liquid fat, etc. The cells are finally injected into the areas to be filled. One of the advantages of this technique is its versatility. Fat can be used not only to correct the orbital volume, but also to correct volume deficits in the upper and lower eyelid regions. This may be useful if one wants to mask minor enophthalmos.

The most common complication of this technique is under-correction. The rate of fat reabsorption can reach up to 30%. A small amount of overcorrection is therefore recommended

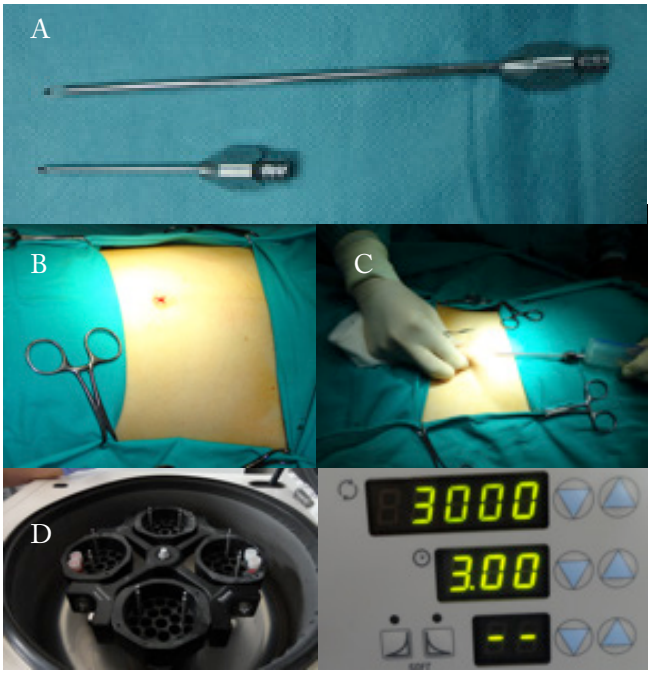


Figure 10. A: Liposuction (above) and injection (below) cannulas, B: The graft is harvest from the abdominal region, C: A cannula is inserted into the donor site and a negative pressure is created by pulling back the syringe plunge, D: The material is purified by centrifugation (3000 revolutions/minute during 3 minutes)

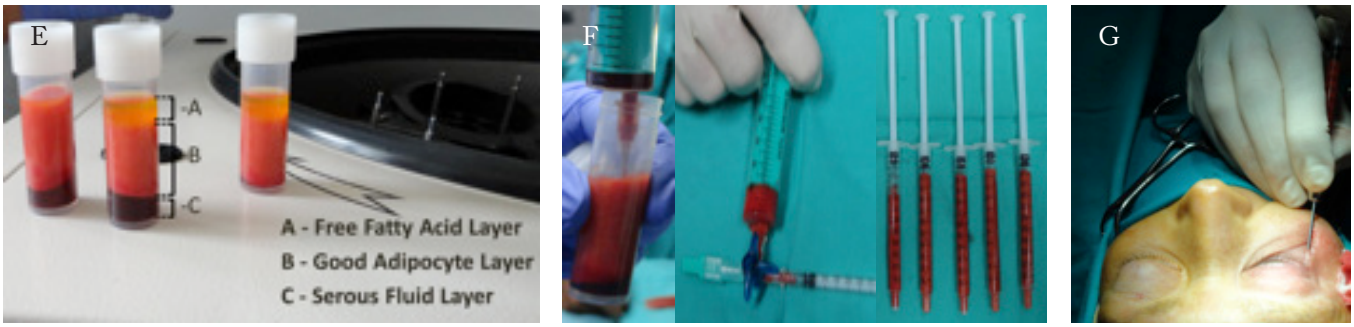


Figure 10 (continuation) E: Separation of layers by centrifugation, F: The oil, blood and water are decanted and the fat is transferred to 1 mL syringes, G: The fat is injected

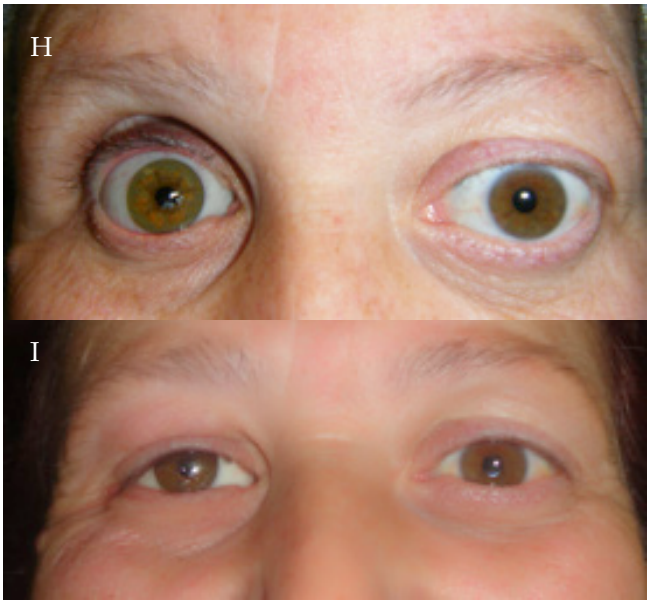


Figure 10. H: Patient with a right orbital volume deficit, I: Two months after an autologous fat graft

by some specialists. A permanent overcorrection is a rarer complication and can result in fat necrosis and pseudocyst formation. Other complications include damage to the surrounding nerves, muscle and vessels. An intra-vascular fat embolus is a rare, but serious complication. The use of a blunt cannula and the injection of small boluses can avoid these complications (Fig. 10A). Also, fat should be injected when the cannula is being withdrawn, preventing intravascular injection.
Autologous fat graft is generally an effective and safe procedure for the treatment of volume deficits in the orbit. Fat presents several advantages when compared with other autologous and heterologous materials. Using the correct technique, the results obtained in the long-term are usually very satisfactory.

Surgical Technique
1. The graft is harvest from the abdominal region or medial thigh (Fig. 10B)
2. A 15 cm two-hole Coleman cannula (see Fig. 10C) is inserted into the donor site
3. Some negative pressure is created on the syringe by pulling back the plunger (Fig. 10C)
4. The negative pressure and the curetting movement of the cannula allow the entry of fatty material through the cannula
5. The material is purified by centrifugation (3000 revolutions/minute for 3 minutes), in the end of which three layers are obtained: the upper level corresponding to oil, the middle portion fatty tissue, and the lower level blood and water (Fig.s 10D,E)
6. The oil, blood, and water are decanted (Fig. 10F)
7. The fatty material is injected using a Coleman infiltration cannula (Fig. 10G)

3.3 EYELID MALPOSITION
A poorly fitted prosthesis and/or levator disinsertion may cause a ptosis. This situation can be corrected by altering the prosthesis or by a levator resection. It is important to distinguish a ptosis from a pseudo-ptosis resulting from the lack of orbital volume. Ectropion is caused by the laxity of the supporting tissue of the inferior eyelid, which is aggravated by the weight and pressure from the prosthesis. It is treated through a canthoplasty procedure (lateral tarsal strip). On the other hand, an entropion may occur due to the contracture of cicatricial tissue near the lash margin. This condition is managed through a tarsal rotation procedure (Jones entropion repair).

3.4 SOCKET CONTRACTION
A contracted socket may occur after any case of enucleation/evisceration. Previous radiotherapy, trauma, an inadequate prosthesis or infection may predispose to this problem. Socket contraction results in an unstable external prosthesis, irritation and chronic discharge. The main goals of its management are the reconstitution of orbital volume (as previously described) and the restoration of the contracted fornices. Several materials (autologous and alloplastic) and different surgical techniques may be used.
Contracted sockets are classified as minimal, moderate and severe. The lower fornix usually is the first to contract.

Minimal Contracted Socket
This is characterized by a vertical shortening of the conjunctiva resulting in a shallow inferior fornix. Treatment consists in performing a suture from the fornix to the inferior rim periosteum. (Fig. 11A)

Surgical Technique
1. An infratarsal conjunctival incision is made, and dissection proceeds until reaching the lower rim periosteum (Fig. 11B)
2. The conjunctiva is sutured to the periosteum using 3-4 U sutures of nylon 4.0 (Fig. 11C)
3. Sutures are removed after three weeks.

Moderate and Severe Contracted Socket (Fig. 12)
When the fornix is obliterated, the contraction is classified as moderate. An obliterated inferior fornix associated with shortening of the eyelid is defined as a severely contracted socket (Fig.s 12 A,B).

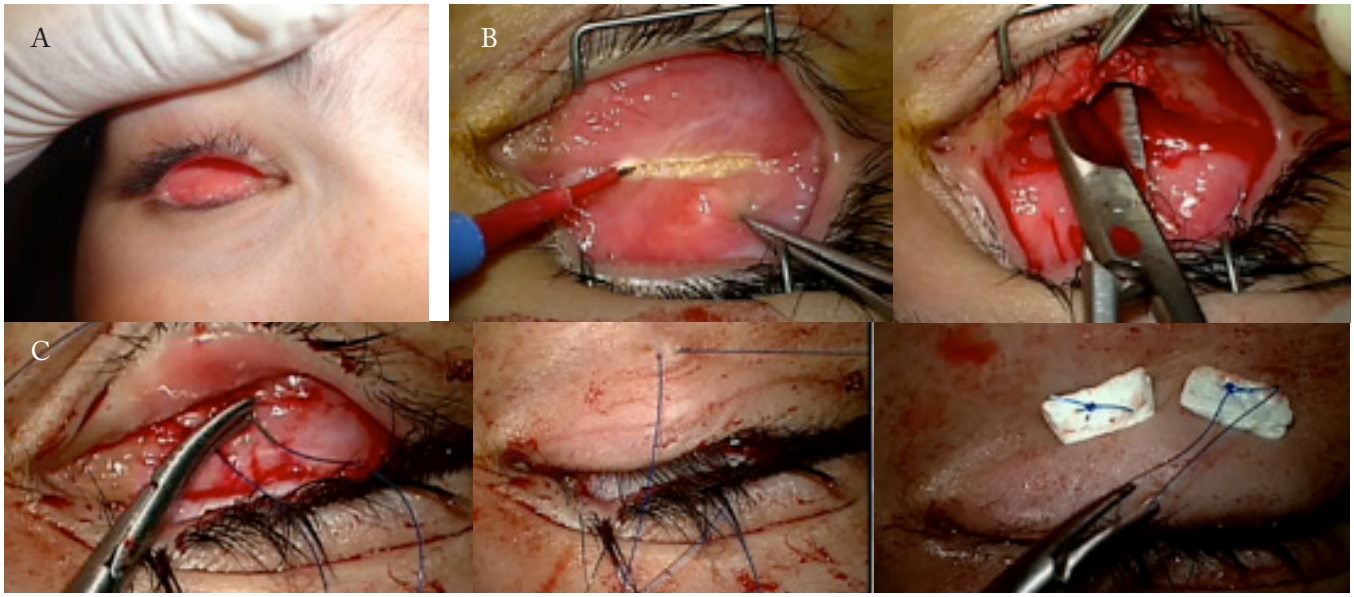


Figure 11 A: Minimal contracted socket, B: An infratarsal conjunctival incision is made, and dissection is undertaken until reaching the periosteum, C: The conjunctiva is sutured to the periosteum using 3-4 U sutures of nylon 4.0

Available Materials for the Management of a Contracted Socket

1. Labial Mucosa
It is effective for posterior lamella expansion; however, it may contract over time. It is therefore indicated only in cases of minimal/moderate retraction (Fig. 12C).

2. Hard Palate Mucosa
It is composed of a dense connective tissue that offers a good support to the eyelid. This reduces the risk of retraction. However, some complications have been associated with its use. These include severe bleeding and fistula formation at the donor site.

3. Auricular Cartilage
This is an excellent graft due to its intrinsic strength. It can be used to support the conjunctival sac in the presence of a severe retraction associated with palpebral retraction (Fig. 12D).

4. Dermal Fat Graft
This is also an option, and it can be used to correct any volume deficit associated with a contracted socket. The dermis can be left without cover, being re-epithelialized and therefore allowing the increase of the conjunctival cavity and fornices enlargement.

5. Amniotic Membrane
This is a good alternative to a mucosal graft. It promotes conjunctival reepithelialization, reducing inflammation and preventing fibrosis.

In both cases, a new conjunctival sac should be created. Various materials are used for its reconstruction, such as: labial mucosa, hard palate mucosa, auricular cartilage, dermal fat graft and amniotic membrane from human placenta.

Surgical Technique

1. A deep incision is made through the contracted conjunctiva of the inferior fornix (Fig. 12E)
2. The graft is sutured to the conjunctiva using an absorbable 6-0 (Vicryl®) interrupted suture (Fig. 12F)
3. A rigid conformer is placed
4. A tarsorrhaphy is made so that the socket cavity can expand. It is usually opened after four weeks. In severe cases, it is opened after three months (Fig. 12G).

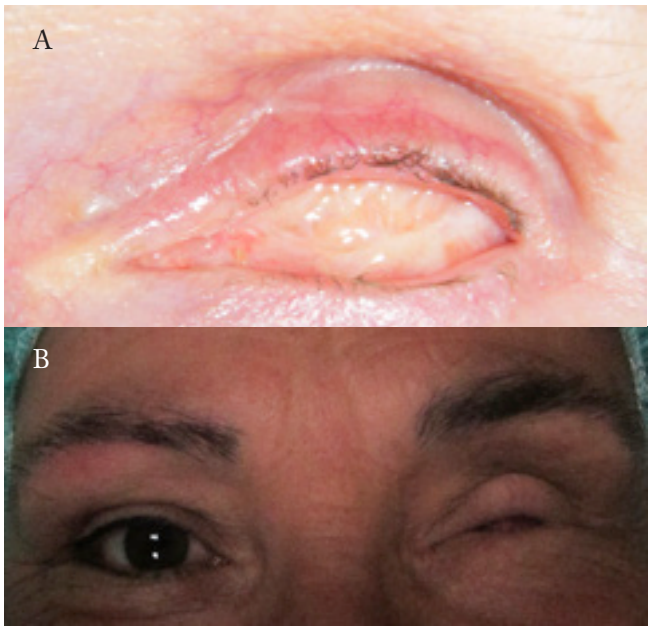


Figure 12. A,B: Severely contracted left socket

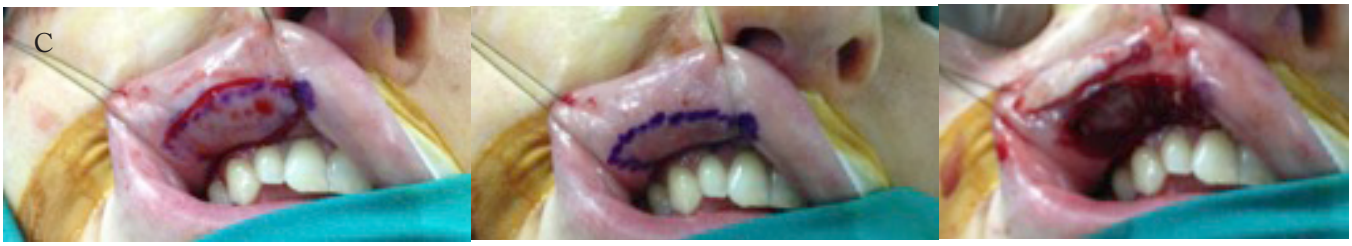


Figure 12C: Oral mucosa graft

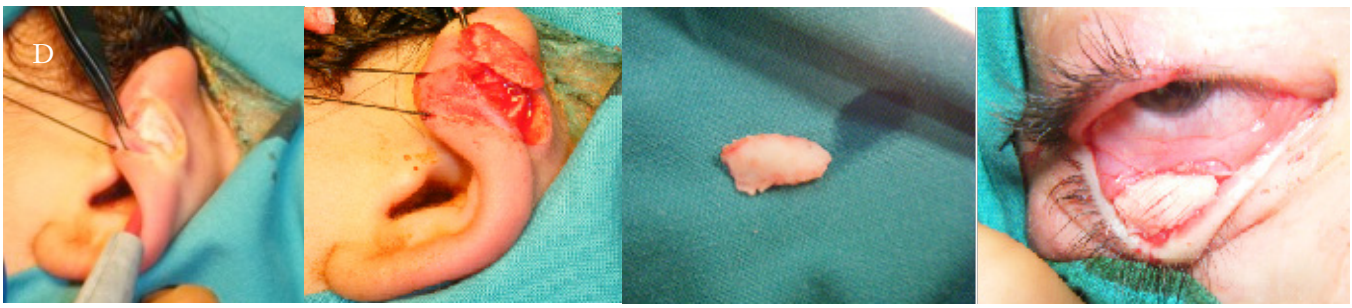


Figure 12D: Auricular cartilage graft

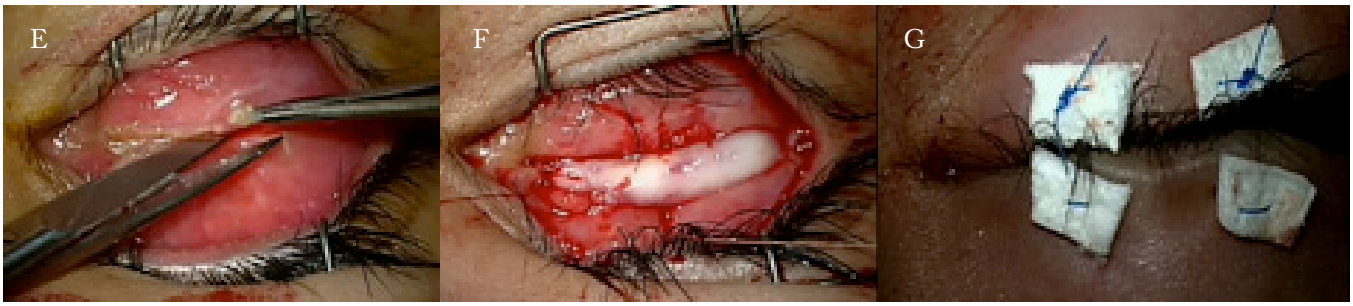


Figure 12 E: A deep incision is made through the contracted conjunctiva of the lower fornix, F: The graft is sutured to the conjunctiva using an absorbable 6-0 interrupted suture, G: Final tarsorrhaphy

CONCLUSION

Enucleation and evisceration are the two existing options for patients who present either with severe eye injuries that cannot be anatomically repaired, or have a permanently blind and painful unaesthetic eye.

Except for cases of ocular malignancy, evisceration is usually the procedure of choice, with better results especially regarding volume and mobility, and a lower risk of exposure and extrusion.

The choice of the implant depends mostly on the surgeon preference and costs. Implants should be placed posteriorly in the orbital cavity. Suturing of the sclera, conjunctiva and Tenon's capsule should be interrupted, not continuous. The Medpor® porous implant is currently the only implant which allows direct suturing of the muscles, without the need for wrapping.

The dermal fat graft presents many advantages. It can be used as a primary or a secondary implant. In addition to correcting volume deficits it also allows the treatment of any conjunctival contraction - problems that often coexist in patients with PESS syndrome. Being an autologous graft, it does not undergo rejection. However, its main complication is a fat reabsorption that can reach 30%.

The 'lipostructure' technique (described initially by Coleman) is a useful adjunct in periorbital rehabilitation. It can provide volume not only within the orbit but also in the superior and inferior palpebral sulcus. This may allow 'fine tuning', resulting in a better symmetry with good aesthetic and functional results.

Ultimately we should not forget the patients themselves. Many have frequent feelings of self-consciousness. For this reason, the aim is to achieve a symptom-free conjunctival cavity that, after the placement of a custom-made external prosthesis, makes the anophthalmia almost imperceptible.

Ethical Disclosures

Confidentiality of Data: Patient consents obtained.

Conflicts of Interest: The authors have no financial interest in the products or procedures mentioned in this chapter

Corresponding author
Guilherme Castela
gcastela@hotmail.com

REFERENCES

1. Gilhooly MG, Faloner PT, Wood GA. Orbital subperiosteal abscess and blindness complicating a minimally displaced zygomatic complex fracture. Br J Oral Maxillofacial Surg. 1995;33:185-8.
2. JCollin JR. A manual of systematic eyelid surgery. 3rd ed. Amsterdam:Elsevier; 2006.
3. American Academy of Ophthalmology. Fundamentals and Principals of Ophthalmology. Section 2 2011-2012. San Francisco: ACO; 2014.
4. Perry AC. Advances in enucleation. Ophthal Plast Reconstr Surg. 1991; 4:173.
5. Callahan MA. Evisceration and Enucleation.. In: Kuhn F, Pieramici DJ. Ocular Trauma. Berlin: Thieme; 2002. Chapter 31: p. 320-34.
6. Morgan-Warren PJ, Mehta P, Ahlewalia HS. Visual function and quality of life in patients who had undergone eye removal surgery: a patient survey. Orbit. 2013;32:285-93.
7. Dortzbach RK, Woog JJ. Choice of procedure. Enucleation, Evisceration, or prosthetic fitting over globes. Ophthalmology. 1985; 92:1249-55.
8. Manandhar A. Sympathetic ophthalmia: enucleation or evisceration? Nepal J Ophthalmol. 2011c;3:181-7.
9. Sales-Sanz M, Sanz-Lopez A. Four-petal evisceration: a new technique. Ophthalmic Plast Reconstr Surg. 2007;23:389-92.
10. Soares IP, França VP. Evisceration and enucleation. Semin Ophthalmol. 2010;25:94-7.
11. Jordan D, Brownstein S, Dorey M, Yuen V, Gilberg S. Fibrovascularization of polyethylene orbital implant in a rabbit. Ophthal Plast Reconstr Surg. 2004; 20:136-43.
12. Alwitry A, West S, King J, _ Foss AJ, Abercrombie LC. Long-term follow-up of porous polyethylene spherical implants after enucleation and evisceration. Ophthal Plast Reconstr Surg. 2007;23:11–23.
13. Trichopoulos N, Augsburger JJ. Enucleation with unwrapped porous and nonporous orbital implants: a 15-year experience. Ophthalmic Plast Reconstr Surg. 2005;21:331-6.
14. Mazzoli R, Raymond W, Ainbinder D, Hansen E. Use of self-expanding, hydrophilic osmotic expanders (hydrogel) in the reconstruction of congenital clinical anophthalmos. Curr Opin Ophthalmol. 2004; 15:426-31.
15. Quaranta-Leoni FM, Sposato S, Lorenzano D. Secondary orbital implant after enucleation and evisceration: Surgical management, morbidity, and long-term outcome. Ophthl Plast Reconstr Surg. 2014;31:115-8.
16. Lee BJ, Lewis CD, Perry JD. Exposed porous orbital implants treated with simultaneous secondary implant and dermis fat graft. Ophthalmic Plast Reconstr Surg. 2010;26:273-6.
17. Basterzi Y, Sari A, Sari A. Surgical treatment of an exposed orbital implant with vascularized superficial temporal fascia flap. J Craniofac Surg. 2009; 20: 502-4.
18. Tyers AG, Collin JR. Orbital implants and post enucleation socket syndrome. Trans Ophthalmol Soc UK. 1982;102:90-2.

19. Gotzamanis A, Ducasse A, Brugniart C, Sayag D. La greffe dermo-graisseuse, utilisation en chirurgie de reconstruction des cavitec. J Fr Ophthalmol. 2001;24:617-22.
20. Hwang K, Kim DJ, Lee IJ. An anatomic comparison of the skin of five donor sites for dermal fat graft. Ann Plast Surg. 2001; 46:327-31.
21. Bosniak SL. Complications of dermis-fat orbital implantation. Adv Ophthalmic Plast Reconstr Surg. 1990: 170-81.
22. Coleman SR. Facial recontouring with lipostructure. Clin Plast Surg. 1997; 24: 347-67
23. Lee BJ, Lewis CD, Perry JD. Exposed porous orbital implants treated with simultaneous secondary implant and dermis fat graft. Ophthalmic Plast Reconstr Surg. 2010;26:273-6.
24. Defossez T, Garson S, Benabid L, Berthout A, Malthieu D, Milazzo S. Comblement d'une cavite orbitaire evisceree par greffe d'adipocytes selon la technique de Coleman, apres expulsion d'implant. J Fr Ophtalmol. 2007;30:610-5.
25. Coleman SR. Avoidance of arterial occlusion from injection of soft tissues fillers. Aesthet Surg J. 2002; 22: 555-7.
26. Lopes N, Castela G, Andrés R, Lisboa M, Castela R, Loureiro R. Reconstruction de l'orbite anophtalme. J Fr Ophtalmol. 2011;34:608-14.
27. S. Morax, FMan, D Schapiro. Pathologie et chirurgie des cavités anophtalmes. Paris: Elsevier Masson; 2005.
28. Neuhaus RW, Hawes MI. Inadequate inferior cul-de-sac in the anophthalmic socket. Ophthalmology. 1992: 99:153-7.
29. Molgat Y, Hurwitz J, Webb MC. Buccal mucous membrane-fat graft in the management of the contracted socket. Ophthalmic Plast Reconstr Surg. 1993;9:267–9.
30. Holck D, Foster J, Dutton J, Dillon H. Hard palate mucosal grafts in the treatment of the contracted socket. Ophthalmic Plast Reconstr Surg. 1999; 15: 202-9.
31. Guyot L, Layour W, Richard O, Gola R. Greffe fibro-muqueuse palatine en chirurgie palpébrale. J Fr Ophtalmol. 2001; 1071-6.
32. Smith R, Malet T. Auricular cartilage grafting to correct lower conjuntival fornix retraction and eyelid malposition in anophtalmic patients. Ophthalmic Plast Reconstr Surg. 2008; 24: 13-8.
33. Bajaj MS, Pusker N, Singh K. Evaluation of amniotic membrane grafting in the reconctruction of contracted socket. Ophthal Plast Reconstr Surg. 2006; 22:116-20.

19. Lipofilling

OPHTHALMOLOGY
Benjamin Riesco, MD; Martín Devoto, MD

Summary

The lipofilling technique is an effective tool in the toolbox of orbital reconstruction. In this chapter we discuss its indications and contraindications, surgical technique and complications. Some clinical cases are shown, and the state of art of the procedure is reviewed.

Keywords: *Adipose Tissue/transplantation; Orbit/surgery; Reconstructive Surgical Procedures*

INTRODUCTION

Among the most frequent orbital problems, the loss of soft tissue volume is one of the most complexes. There is a wide range of possible causes and motivations for its correction. In general terms, the loss of soft tissue volume can be part of the normal aging process, however it can also be caused by trauma, congenital malformations as microphthalmia and anophthalmia, surgical procedures as enucleation or orbital tumor removal, or progressive disfiguring diseases such as Parry-Romberg syndrome or silent sinus syndrome. Historically, the treatment goal has been to fill the defect, either using local or free tissue flaps, alloplastic/autologous filler injections, or prosthesis.[1] Current trends for reconstruction and aesthetic improvement of mild to moderate defects goes toward the use of minimally invasive procedures, such as autologous fat transfer.

The ideal agent for volume restoration and filling has to meet some criteria: it has to be biocompatible, inexpensive, easy to use and obtain, it has to provide a natural aspect and texture, and it cannot be toxic. Autologous fat is an excellent choice as it fulfills the previous requirements. Although it was first described during the late XIX century, the use of fat for soft tissue augmentation only became popular after the introduction of lipoplasty techniques in the United States, during the 1980s. At this point the first limitation of lipofilling became visible: the intolerance of adipose tissue to hypoxia rapidly led to ischemia and fat reabsorption. Reabsorption rates between 20% and 80% have been reported since then.[2]

As other tissues, fat is constituted by main cells (adipocytes) and stromal cells. The stromal component plays an important role in lipotransfer, since it encompasses the multipotent adipose-derived stem cells (ADSCs), first isolated in 2002 by Zuk *et al*. This finding led to the development of cell-assisted lipofilling, a method in which grafts are enriched with freshly isolated fat tissue stromal fraction, containing ADSCs. A meta-analysis published in 2016 showed that fat survival was significantly higher in the cell-assisted lipotransfer group than in the non-assisted group.[3]

In general terms, the survival of the fat graft depends on the harvesting technique, processing and injection. Regarding the processing stage, the role of platelet-rich plasma (PRP) has been largely discussed. PRP is derived from fresh whole blood; its regenerative properties are thought to be related with the large amount of secretory proteins, including vascular endothelial growth factor, epidermal growth factor, platelet-derived growth factor and transforming growth factor, among others. Activated PRP was shown to maintain the volume and weight of fat grafts in a mouse model.[4]

In 2015 Bernardini *et al*[5] proposed a technique focused on obtaining "micro" fat. It included a new harvesting method, processing with PRP, and superficial injection. This superficial enhanced fat fluid injection (SEFFI) was shown to be a safe and effective method to correct age-related volume loss and reduce rhytids.

Another recent strategy also developed to improve fat graft survival was the preconditioning of the recipient site with micro needling. This procedure involves an instrument composed of a cylindrical part with a handle, with near to 190 micro-needles of 1.5 mm length spread over the cylindrical portion. The stimulus consists of 20 back and forward movements leading to visible petechia in the skin surface. The primary goal is to increase vascularity of the recipient bed, which in turn is thought to increase graft survival preventing its reabsorption. Microneedling showed to improve histological features such as vascularization and integrity of the recipient area, reducing inflammation and fibrosis, and significantly preserving the fat graft volume. Microneedling is also an easy technique, with a very low cost.[6]

In this chapter the surgical technique of lipofilling will be described, and indications for its use in orbital surgery will be reviewed.

1. INDICATIONS AND CONTRAINDICATIONS

Since lipofilling became a popular procedure in periocular and facial medicine, it has been applied in many distinct settings. It should be noted that most of the studies only provide low to moderate evidence, although some meta-analyses have been recently published.[3,7] Lipofilling is still an ongoing topic, and its current indications and contraindications should be reviewed.

1.1 INDICATIONS

In general terms, lipofilling is an option for soft tissue volume loss, particularly contour deformities in facial reconstructive surgery. A meta-analysis published in 2018,[7] including 53 clinical trials, stated that lipofilling is a safe and effective treatment. It described human immunodeficiency virus-associated lipodystrophy as the most common indication for lipofilling, with outstanding satisfaction rates among patients

and surgeons. Table 1 summarizes the main indications, outcomes and complications of lipofilling.

Indications can be classified into congenital and acquired.

Congenital

The use of lipofilling in the pediatric population is also a subject under debate. A meta-analysis published in 2018[7] describes patient´s and surgeon´s satisfaction rates close to 90% in congenital conditions. However, as lipofilling indications in children grow, it becomes necessary to improve fat graft survival, and deal with other implications not yet described in this specific population. A small 11 patient clinical trial[8] assessed a three-dimensional method for lipoestructure evaluation in children, reporting a 40% rate of fat graft survival within 1 year. However, the main question about this technique still persists: for how long will the fat in the injected area survive.

Craniofacial microsomia is a wide spectrum of congenital deformities that affect the normal development of the cranium. It usually presents with ear abnormalities involving the external ear (microtia or anotia) or the ear canal (absent or closed). Microphthalmia and some other eye abnormalities have also been described. In a study, 14 patients with craniofacial microsomia and unilateral deformity, phenotypes M0, M1 or M2, and S1 or S2 according to the "Orbit, Mandible, Ear, Nerve, and Soft Tissue–Plus classification" were enrolled to assess the efficacy and safety of ADSC-supplemented fat graft versus classical fat graft for facial recontouring.[9] Results were classified according to fat survival, being at least 50% of survival considered as good. The ADSC-supplemented fat graft group had 7 times more chance of obtaining an excellent result, without complications. The authors concluded that this lipofilling method is effective and safe.

Acquired

Scars are the result of an attempted tissue restoration after a cutaneous injury. An atrophic scar is a sunken lesion, frequently hypopigmented or hyperpigmented, thought to be derived from collagen or other fibrous tissue deficiency. A 20 patient clinical trial was designed to assess the effect of lipofilling on aesthetic and functional improvement of facial atrophic scars, using the Patient and Observer Scar Assessment Scale (POSAS) (see Table 1*).[10] According to patient's evaluation, lipofilling improved the color, stiffness, thickness, and irregularity of scar tissue, whereas in surgeon´s evaluation it improved pigmentation, thickness, relief, and pliability. No complications were reported.

Parry-Romberg syndrome (PRS) or Romberg disease is a clinical syndrome characterized by a progressive atrophy of hemifacial soft tissue, including skin, muscle, cartilage, and bone. Management of facial contour in PRS is a major challenge, and the classical approach comprises free dermal-fat flaps, silicone injections, autologous fat grafts, omental transfer, among others, with unpredictable outcomes and problems. Thirty six PRS patients were recruited in a clinical trial comparing the use of common fat graft versus bone marrow-derived mesenchymal stem cells (BMSC)-assisted fat graft for facial symmetry restoration.[11] Even though the group treated with BMSC-assisted fat graft required a lower number of injections, both procedures resulted in an effective and safe restoration of facial symmetry without complications.

A 98 patient clinical trial applied SEFFI[5] for *periorbital and facial volume correction*, in association with different cosmetic procedures. The main outcome was the restoration of volume, which was assessed by the senior authors with a 1-4 point scale (no effect; fair effect, good effect, excellent effect). Sixty-three percent of the cases were rated as good, whereas 37% were rated as excellent. Complications occurred in 4% of patients, all minor, as oil cysts.

The use of lipofilling in *post-traumatic facial deformities* was assessed in a 25 patient clinical trial,[12] which included maxillofacial problems such as malunited zygomatic-maxillary complex fractures, frontonasal depressions, or scared depressions. After 2 years of follow-up, the authors reported a 9.1/10 mean subjective satisfaction score and 8.8/10 objective assessment score, with only 4% postoperative complications.

Post-traumatic enophthalmos is commonly corrected with orbital reconstructive surgery. A 9 patient clinical trial reported the effect of retroseptal lipotransfer for the correction of enophthalmos involving amaurotic post-traumatic eyes. Six of nine patients achieved a symmetric facial morphology in a 12 months follow-up, with no reported complications.[13]

Deep superior sulcus is a very common periocular deformity, often associated with anophthalmic socket, but also present in many other orbital disorders. The use of a fat graft to correct superior sulcus deepening was successfully reported in five patients in 1986.[14] The use of dermis-fat graft for permanent superior sulcus deepening has also been proposed. At the 37th ESOPRS (European Society of Ophthalmic Plastic and Reconstructive Surgery) annual meeting in 2018,[15] Cetinkaya presented a case where a dermis-fat graft was obtained from the lower abdomen, transferred to the dermal side of the eyelid, and finally shaped to slightly overcorrect the deformity. Permanent correction of the hollow appearance was described, without eyelid or orbital structure compromise.

Anophthalmic socket syndrome after enucleation or evisceration is a major concern in orbital surgery. In general terms, the aesthetic alterations consist of enophthalmos, deep superior sulcus, ptosis and a shallow fornix. The goal in anophthalmic socket reconstruction is to obtain the best result after prosthesis adaptation. Dermis-fat graft has been for a long time the method of choice. A 41 patient study was completed to assess its results and common indications in anophthalmic socket syndrome. Exposure (30%), implant extrusion (27%) and volume insufficiency (24%) were the most common indications, and 75% of patients were able to use eye prosthesis for a mean follow-up time of 32 months.[16] Another 8 patient study evaluated the use of dermis-fat graft as a secondary orbital implant and for superior sulcus correction. A mean time of 6 to 8 weeks for graft epithelization was reported.[17] The lack of large studies comparing dermis-fat graft versus lipotransfer in this setting makes, however, a clinical recommendation difficult to establish. Recently, we have reported the successful use of lipotransfer with SEFFI technique in a 36-years old female who presented with post-traumatic enophthalmos after a previous eye evisceration.[18] In other unpublished cases, we also have had good results.

Table 1

References	Applications	Outcomes	Complications
Bernardini FP, Gennai A, Izzo L, Zambelli A, Repaci E, Baldelli I, et al. Superficial Enhanced Fluid Fat Injection (SEFFI) to Correct Volume Defects and Skin Aging of the Face and Periocular Region. Aesthet Surg J. 2015;35:504–15	Volume skin correction of face and periocular region (n = 98)	Restoration of volume: senior jury assessment 63% good, 37% excellent. Reduction of facial rhytids and skin quality improvement: senior jury assessment 63% good, 37% excellent	Minor local complications 4%
Tanikawa DYS, Aguena M, Bueno DF, Passos-Bueno MR, Alonso N. Fat Grafts Supplemented with Adipose-Derived Stromal Cells in the Rehabilitation of Patients with Craniofacial Microsomia. Plast Reconstr Surg. 2013;132:141–52	Facial contour improvement in cranial microsomia (n = 14)		None
Gu Z, Li Y, Li H. Use of Condensed Nanofat Combined With Fat Grafts to Treat Atrophic Scars. JAMA Facial Plast Surg. 2018;20:128	Aesthetical and functional treatment of facial atrophic scars (n = 20)	POSAS scale*: Statistically significant difference between pre and post intervention	None
Jianhui Z, Chenggang Y, Binglun L, Yan H, Li Y, Xianjie M, et al. Autologous Fat Graft and Bone Marrow–Derived Mesenchymal Stem Cells Assisted Fat Graft for Treatment of Parry-Romberg Syndrome. Ann Plast Surg. 2014;73:S99–103	Restoration of facial symmetry in PRS (n = 36)	Restoration of facial symmetry with: Classical fat graft: 24/26 patients. BMSC-assisted fat graft: 10/10 patients	None
Agrawal K, Bachhav M, Naik C, Tanwar H, Sankhe S. Autologous Fat Transfer for Esthetic Contouring of Face in Posttraumatic Nonfunctional Maxillofacial Deformities. Craniomaxillofacial Trauma Reconstr. 2015;9:113–20.	Post traumatic nonfunctional maxillofacial deformities (n = 25)	No gross asymmetry after the first surgical intervention: 84%. Subjective satisfaction: 9.1/10. Objective jury assessment: 8.8/10	Minor local complications 4%
Agostini T, Perello R, Arcuri F, Spinelli G. Retroseptal Lipotransfer to Correct Enophthalmos in the Postraumatic Amaurotic Eye. Plast Reconstr Surg. 2014;134:989e-90e.	Post traumatic enophthalmos correction (n = 9)	Similar facial morphology after 1yr follow-up: 67%	None

* POSAS (Patient and Observer Scar Assessment Scale) is a comprehensive scale designed to scar characterization. An interesting issue is the addition of patient's point of view in order to complete the scar evaluation. There are 6 items in the patients scale (thickness, pliability, itching, relief and pain), whereas the observer scale has 5 items (vascularization, pigmentation, pliability, thickness and relief).

1.2 CONTRAINDICATIONS

Lipofilling is a safe, minimally invasive procedure with an extremely low complication rate. However, it is necessary to establish criteria and conditions before its indication. Due to its intrinsic nature, there are no absolute contraindications for facial lipotransfer. However, potentially adverse scenarios include anticoagulation or antiplatelet therapy, allergy to the anesthetic or hematologic abnormalities. There are other situations in which a mental health practitioner could be useful,[19] i.e., for lipotransfer surgery in patients with unrealistic expectations or body dysmorphic disorder. In this set, an additional discussion or even a waiting period is highly recommended. It is also important to take medical conditions into account. Chronic non-treated diseases such as chronic liver disease, diabetes, hypertension or heart failure are prevalent in the general population and may contribute to complications and negative outcomes. A thorough evaluation before planning the procedure is recommended.

2. TECHNIQUE

Although there is no standardized method for the procedure, we review the autologous fat transfer (SEFFI) technique developed by Bernardini and colleagues,[5] which makes use of the current knowledge about ADSCs and PRP. A comprehensive step-by-step approach is provided in Table 2. The first step is to define the donor site. We recommend the knee/thigh region due to its accessibility (Fig. 1A). It also allows a second surgical team to proceed with an additional facial procedure while fat harvesting and processing is taking place. Both anesthesia and harvesting use a sterile technique. Another donor site option is the flank or the abdomen, using atraumatic harvesting and taking care not to penetrate the abdominal cavity. Previously liposuctioned areas must be avoided.

Local anesthesia (see details in Table 2) is injected with a 10 mL syringe and a 2 mm diameter cannula (Fig. 1B). Twenty mL are injected into deep fat and another 20 mL into the superficial area, with a total of 40 mL per knee/thigh region.

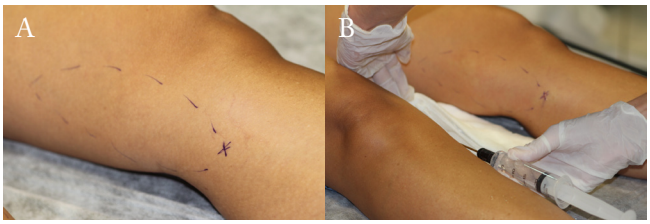


Figure 1. Knee/thigh region as the donor site. A. Marking B. Application of anesthesia under sterile technique.

The harvest should be symmetrical to prevent asymmetries. A gentle massage is given to the area, and harvesting is started after a 15 minutes interval. Currently, there is no conclusive evidence that local anesthesia can compromise the viability of adipocytes.[20]
Harvesting is done using blunt cannulas and a 10 mL syringe (Fig. 2A). During this step, a threshold of 2 mL of negative pressure must not be exceeded while absorbing. Harvesting should be done in a fan-like fashion, homogenously. We use Luer lock system syringes to avoid centrifugation losses (Fig. 2B). The centrifuge must be properly balanced, and fat can be centrifuged for 3 minutes at 3000 rpm. Currently, there is no conclusive evidence that centrifugation plays a role in graft survival,[20] so this step may be skipped and the fat simply left to decant for a couple of minutes.

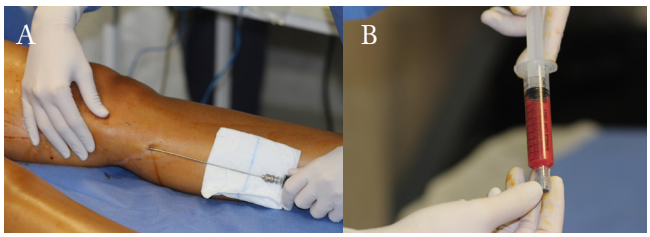


Figure 2. Harvesting. A. Blunt cannula. B. Luer lock system syringe in the centrifuge.

Once fat centrifugation is finished, the infranatant in the syringe (blood and anesthesia) and the supernatant (oil) need to be discarded to maintain pure fat inside the syringe (Fig. 3).

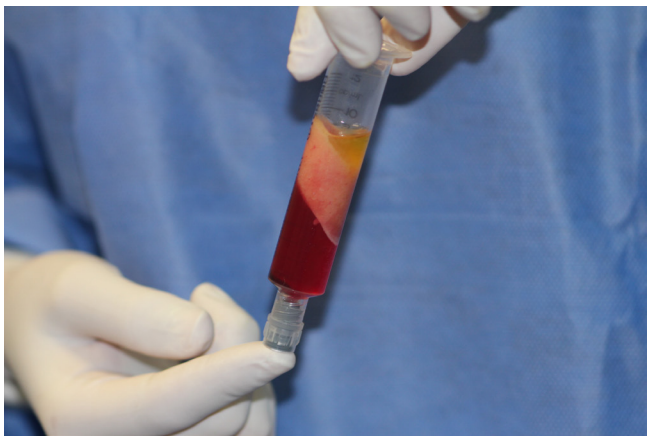


Figure 3. Supra and infranatant from harvesting centrifugation.

The fat is transferred into 10 – 20 mL syringes, depending on the volume needed for reconstruction.

PRP is obtained from 20 mL of patient's blood, centrifuged for 2 minutes at 1000 rpm (Fig. 4A). It is then mixed with fat in a 20% proportion. For the final application, we recommend to transfer the final product to a 5 mL syringe (Fig. 4B) and apply it with an injection cannula of 0.9 mm (Fig. 4C).

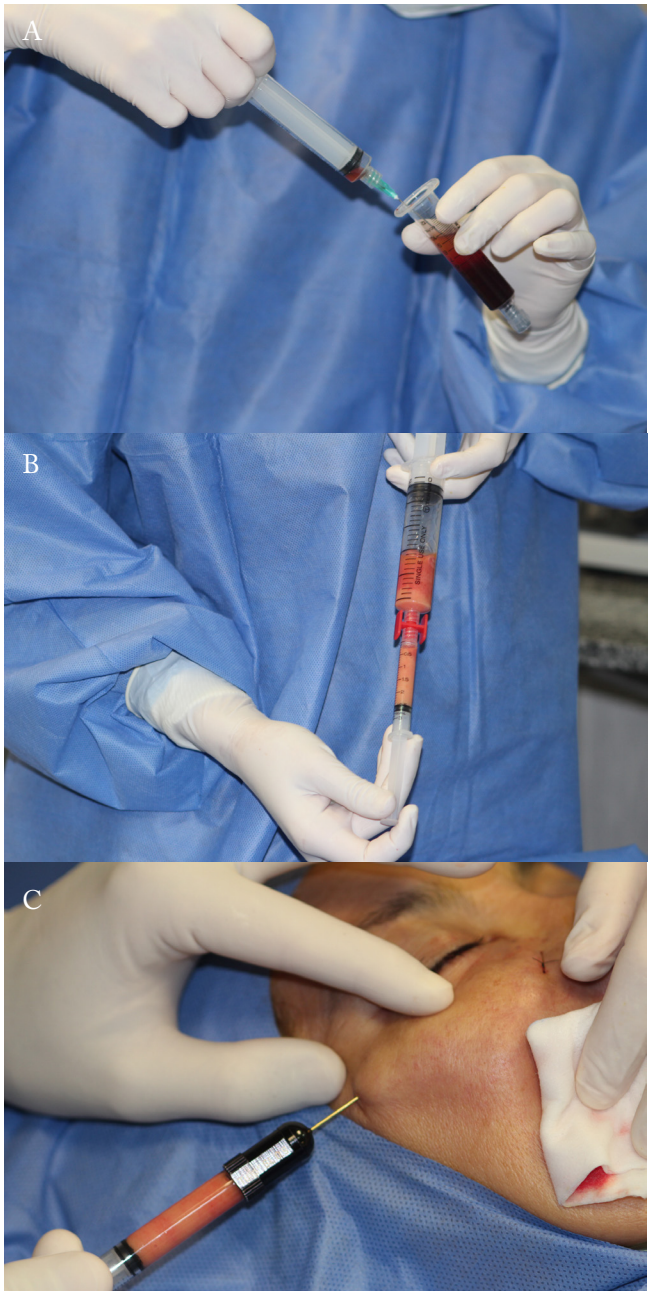


Figure 4. A. PRP after centrifugation. B. Transfer to 5 mL syringes. C. Application in an anophthalmic socket.

Evidence supports that lipotransfer should be performed as quickly as possible after harvesting.[20] The injection technique will vary depending on the recipient area. In the deep orbit we recommend a long cannula, while for superficial filling needles may be used (however with a more traumatic effect and a higher risk of embolic complications).
Finally, a patch is placed on the donor site, and a compressive bandage is recommended to minimize hematomas.

1- Anesthesia
Under sterile technique, at the same time as facial anesthesia
Donor site marking
Local Anesthesia: 500 mL saline solution + 20 mL 2% lidocaine + 1 mL 1:1000 epinephrine + 5 mL 8.4% sodium bicarbonate
Stab incision with a 11 blade. Inject local with 20 mL syringe and 2 mm diameter cannula
20 mL in deep fat, 20 mL in superficial fat. Wait 15 min for vasoconstriction
2- Harvesting:
Fat is suctioned with blunt cannulas using 10 mL syringes, adding 1 mL of Ringer solution to complete 10 mL
Do not exceed 2 cc of negative pressure to aspirate
The volume of fat harvested is twice the amount needed for injection
Donor site does not need suturing
3- Centrifugation:
Each syringe is placed on a sterile tube in the centrifuge
Fat is centrifuged 3 min at 3000 rpm
4- Processing:
The infranatant (blood + local) is discarded, same as supernatant (oil) that is also discarded
5- Platelet Rich Plasma (PRP)
20 mL of blood is withdrawn in 2 citrated tubes and centrifuged 2 min at 1000 rpm
PRP is mixed with the processed fat in a volume of 20% of the volume of the fat
6- Injection:
Fat + PRP is transfered to 5 mL syringes
The technique of injection will depend on the area to be filled
7- Donor Site Care
A small patch is applied to the entry poing
Compressive bandages are applied if you decide to harvest from the knee/thigh region

Adapted with permission from Riesco B, et al. Autologous fat transfer with SEFFI (superficial enhanced fluid, fat injection) technique in periocular reconstruction. Orbit. 2018;37:191–5.18

3. COMPLICATIONS

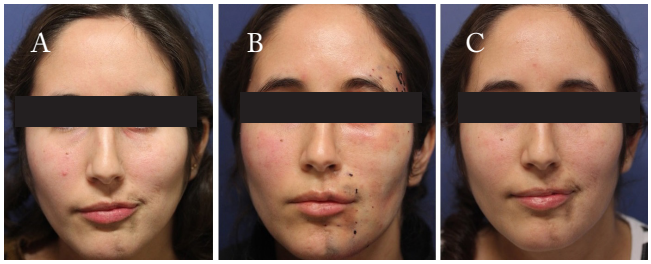
Being a surgical procedure, complications from lipotransfer may occur. As we have previously stated, there is a lack of strong evidence to support clinical recommendations. A recent meta-analysis[3] reported a 7.2% total complication rate, with a 5.2% prevalence of cysts. Other complications included nodules, calcification, and fibrosis. Infection or fat necrosis were extremely rare, with only one case reported.

A systematic review including 52 studies and 1568 patients[7] also assessed complications related to lipotransfer. Sixty-five complications were described along 1755 procedures. Among them there were 2 infections, 2 cases of fat necrosis and 10 hematomas. The remainder consisted of facial asymmetries post-lipotransfer, mainly in HIV-patients.

Using SEFFI,[5] only 4 of the 98 patients presented complications associated with the procedure. In three of them oil cysts that responded favorably to syringe aspiration, and in the remaining one a visible nodule persisted.

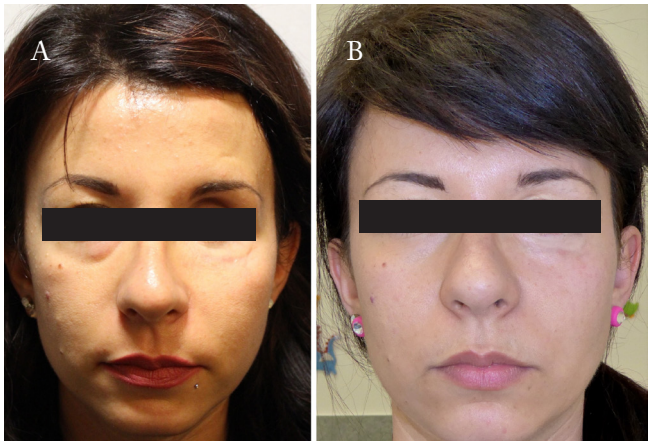
4. CLINICAL CASES

Case 1. In a 29-year-old female patient with Parry Romberg syndrome (Fig. 5A) a total of 24 mL of autologous fat were transfered into the left superior, temporal, and inferior periorbital areas, and 6 mL were used to treat the eyelids (Fig. 5B). A satisfactory improvement was obtained at 1 year of follow-up (Fig. 5C).



Adapted with permission from Riesco B, et al. Autologous fat transfer with SEFFI (superficial enhanced fluid, fat injection) technique in periocular reconstruction. Orbit. 2018;37:191–5.[18]

Case 2. A 36-year-old female patient with previous left-eye evisceration and left orbital floor and medial wall fractures was evaluated due to enophthalmos (Fig. 6A). Socket reconstruction was performed using a buccal mucosal graft on the lower fornix, and 4 mL of autologous fat were transfered into the upper lid, 3 mL to the lower lid, and 5 mL into the intraorbital space using an inferotemporal transpalpebral approach. After 1 year of follow-up, a good improvement was noticed (Fig. 6B).



Adapted with permission from Riesco B, et al. Autologous fat transfer with SEFFI (superficial enhanced fluid, fat injection) technique in periocular reconstruction. Orbit. 2018;37:191–5.18

CONCLUSION

In conclusion, lipotransfer may be considered a safe method. However, serious functional or aesthetic complications may still occur. Patient selection is a key element and, together with a good anatomical knowledge and training, ensures a safer practice and better results.

Ethical Disclosures
Confidentiality of Data: Patient consent obtained.
Conflicts of Interest: The authors have no financial interest in the products or procedures mentioned in this chapter

Corresponding author
Benjamin Riesco
benjaminriesco@gmail.com

REFERENCES

1. Bucky L, Percec I. The science of autologous fat grafting: views on current and future approaches to neoadipogenesis. Aesthet Surg J. 2008;28:313–21.
2. Tiryaki T, Findikli N, Tiryaki D. Staged Stem cell-enriched tissue (set) injections for soft tissue augmentation in hostile recipient areas: a preliminary report. Aesthetic Plast Surg. 2011;35:965–71.
3. Zhou Y, Wang J, Li H, Liang X, Bae J, Huang X, et al. Efficacy and safety of cell-assisted lipotransfer: a systematic review and meta-analysis. Plast Reconstr Surg. 2016 ;137:44e-57e.
4. Oh DS, Cheon YW, Jeon YR, Lew DH. Activated platelet-rich plasma improves fat graft survival in nude mice: a pilot study. Dermatol Surg. 2011;37:619–25.
5. Bernardini FP, Gennai A, Izzo L, Zambelli A, Repaci E, Baldelli I, et al. Superficial enhanced fluid fat injection (SEFFI) to correct volume defects and skin aging of the face and periocular region. Aesthet Surg J. 2015;35:504–15.
6. Sezgin B, Ozmen S, Bulam H, Omeroglu S, Yuksel S, Cayci B, et al. Improving fat graft survival through preconditioning of the recipient site with microneedling. J Plast Reconstr Aesthet Surg. 2014;67:712–20.
7. Krastev TK, Beugels J, Hommes J, Piatkowski A, Mathijssen I, van der Hulst R. Efficacy and safety of autologous fat transfer in facial reconstructive surgery: a systematic review and meta-analysis. JAMA Facial Plast Surg. 2018;20:351-60.
8. Guibert M, Franchi G, Ansari E, Billotet B, Diner PA, Cassier S, et al. Fat graft transfer in children's facial malformations: A prospective three-dimensional evaluation. J Plast Reconstr Aesthet Surg. 2013;66:799–804.
9. Tanikawa DYS, Aguena M, Bueno DF, Passos-Bueno MR, Alonso N. Fat grafts supplemented with adipose-derived stromal cells in the rehabilitation of patients with craniofacial microsomia. Plast Reconstr Surg. 2013;132:141–52.
10. Gu Z, Li Y, Li H. Use of condensed nanofat combined with fat grafts to treat atrophic scars. JAMA Facial Plast Surg. 2018;20:128-35.
11. Jianhui Z, Chenggang Y, Binglun L, Yan H, Li Y, Xianjie M, et al. Autologous fat graft and bone marrow–derived mesenchymal stem cells assisted fat graft for treatment of parry-romberg syndrome. Ann Plast Surg. 2014;73: S99–103.
12. Agrawal K, Bachhav M, Naik C, Tanwar H, Sankhe S. Autologous fat transfer for esthetic contouring of face in posttraumatic nonfunctional maxillofacial deformities. Craniomaxillofacial Trauma Reconstr. 2015 5;09:113–20.
13. Agostini T, Perello R, Arcuri F, Spinelli G. Retroseptal lipotransfer to correct enophthalmos in the posttraumatic amaurotic eye. Plast Reconstr Surg. 2014 ;134:989e-90e.
14. Van Gemert JV, Leone CR. Correction of a deep superior sulcus with dermis-fat implantation. Arch Ophthalmol. 1986;104:604–7.
15. Cetinkaya A. Management of unilateral superior sulcus deformity with dermis-fat graft. In: 37th Annual Meeting of the European Society of Ophthalmic Plastic and Reconstructive Surgery (ESOPRS) Bucharest, 2018.
16. Aryasit O, Preechawai P. Indications and results in anophthalmic socket reconstruction using dermis-fat graft. Clin Ophthalmol. 2015;9:795-9.
17. Kuzmanović Elabjer B, Bušić M, Bosnar D, Elabjer E, Miletić D. Our Experience with dermofat graft in reconstruction of anophthalmic socket. Orbit. 2010;29:209–12.
18. Riesco B, Abascal C, Duarte A, Flores RM, Rouaux G, Sampayo R, et al. Autologous fat transfer with SEFFI (superficial enhanced fluid, fat injection) technique in periocular reconstruction. Orbit. 2018;37:191–5.
19. Godse K, Abhyankar S, Patil S, Nadkarni N, Marwah M, Kulkarni A. Fat fulfillment: A review of autologous fat grafting. J Cutan Aesthetic Surg. 2013;6:132-8.
20. Sinno S, Wilson S, Brownstone BS, Levine SM. Current Thoughts on fat grafting using the evidence to determine fact or fiction. Plast Reconstr Surg. 2016;137:818-24.

20. Post-Surgical Strabismus: Treatment Options

OPHTHALMOLOGY
Alcina Toscano MD, Diogo Hipólito Fernandes MD

Summary

Any orbital surgery, especially orbital fracture repair, decompressive orbitotomy for thyroid eye disease, endoscopic sinus surgery and deep orbital tumors biopsy/excision, can result in postoperative diplopia and strabismus. Strabismus may have restrictive, paralytic or mixed causes. Motor and sensory evaluations such as forced duction test, force generation test, Hess screen test and imaging are useful for diagnosis. Strabismus surgery should be delayed until the patient's condition is stable, which usually occurs at least six months after surgery. In small deviations, non-surgical management with prisms may be used. Botulinum toxin injection may also be helpful in minimizing diplopia during the acute phase. The goal of strabismus surgery is to reduce the restriction from fibrous muscles, with weakening procedures such as recession being preferred over resection techniques. In cases of severe palsy, muscle transposition should be considered.

Keywords: *Diplopia/etiology; Strabismus/etiology; Strabismus/surgery ; Surgical Procedures, Orbital surgery/complications*

INTRODUCTION

The occurrence of strabismus after orbital surgery is not an uncommon complication despite improvements in surgical techniques. Postoperative, clinically significant diplopia and extra-ocular movement restriction is the most frequent presentation[1], and may occur following any type of periocular surgery.[2]
Orbital fracture repair, orbital decompression for thyroid eye disease (TED) and endoscopic sinus surgery are the most frequent procedures related to postoperative diplopia. Orbital tumor resection has also been associated with this complication. Surgical intervention following orbital trauma poses the highest risk of postoperative diplopia.[2,3]

1. ETIOLOGY

Distinct or combined etiologies may be responsible for strabismus after orbital surgery (Table 1). Each etiology requires its own treatment approach, which can be complex.[4]
The main causes of strabismus are:

- **Restrictive**
- **Paralytic**
- **Mixed**

Restrictive

The mechanism of ocular movements restriction may be at the extraocular muscles (EOM), conjunctiva, Tenon's capsule, soft tissues surrounding EOM or other orbital structures.
In the acute phase, localized changes such as edema and hemorrhage may cause restriction with motility impairment and diplopia. In these cases, spontaneous improvement occurs during the first weeks with the resolution of the inflammation.[1,2,4,5]
Chronic restriction may be related to persistent muscle or orbital tissue entrapment, postoperative scarring of the muscles, and/or damage and scarring of the surrounding tissues, with adhesions.[1,4,6]

Paralytic

- Direct EOM trauma
- Nerve injury

Direct muscle injuries, like laceration or disinsertion, can cause partial or complete loss of function. Nerve injury may also cause paralysis.[4]

Mixed

A combination of restrictive and paretic strabismus may be present with multiple possible presentations. In most cases, the pattern of eye movement impairment will evolve over time. It is important to recognize and distinguish complex mechanical strabismus from multiple cranial nerve palsies.[7]

Table 1. Main causes of strabismus

RESTRICTIVE	PARALYTIC
Acute phase (edema, hemorrhage)	Direct muscle trauma
Muscle entrapment/scarring	Cranial nerve palsy
Incarcerated/scarring surrounding tissues	

2. EVALUATION

Clinical history

Clinical findings vary considerably, depending on the time elapsed after the injury.[4,8] Careful history, clinical evaluation and orbital imaging usually provides enough information for an accurate diagnosis.[9] Before any surgical intervention, it is important to document the presence or absence of pre-existing strabismus. A preoperative orthoptic examination, including a sensory and motor examinations, is recommended and should be routinely performed.[2]

Observation

Evaluate facial symmetry from both a direct frontal and superior view. Exophthalmometry will reveal relative

enophthalmos and/or exophthalmos. Crepitus when palpating around the orbit implies a communication with the sinuses.
Any abnormal head position (AHP) may suggest that the patient can fuse.[8] AHP is adopted to minimize diplopia or to obtain a more comfortable binocular vision. The head can be turned to the right or left, suggesting that horizontal muscles are involved, with exotropia/esotropia; tilted to the left or right, meaning a probable involvement of oblique muscles with cyclotropia; or the chin angled up or down, suggesting that vertical muscles are involved with hypo/hypertropia. A combination of these positions may also be seen.[10]

Sensory examination
The sensory exam is critical to decide which motor tests should be used to investigate the strabismus. In addition to diplopia, other sensory deficits resulting from the injury (such as visual field defects, poor visual acuity and central loss of fusion) or preexisting conditions (such as amblyopia and strabismus) may confound evaluation results.[4] Stereopsis and the amount and location of the field of binocular single vision (BSV) have a significant impact on patient´s quality of life.
Fusional capacity and BSV field tests may be helpful before and after surgery/treatment to assess diplopia-free visual field and the degree of disability.[8,11]

Motor examination
Ocular motility is often impaired after orbital surgery. It is important to distinguish between deviations caused by a restriction and those caused by a paresis or palsy.[8] Ocular ductions (one eye) and versions (both eyes) should be carefully evaluated to determine the presence of restrictions or motility defects.[9]
To detect grades of under and overaction, a full orthoptic evaluation should include the study of ductions and versions in diagnostic positions of gaze. When versions are limited, we suspect paralytic or restrictive strabismus.[10] The evaluation is completed with the measurement of misalignment with the prism and alternating prism-cover test in both primary and other directions of gaze. When performing the cover test, it is important to occlude one eye at a time long enough to allow the patient to take up fixation. Strabismus may be underestimated in patients with decreased vision, visual field defects or a painful eye, which may limit the capacity to take up fixation.[4]

Forced duction test (FDT)
FDT provides valuable information about a possible mechanical restriction of eye movements. FDT is performed with local anesthesia in a cooperative patient, by moving the eye passively in the opposite direction of the suspected injured muscle, with the help of a forceps or a cotton-tip applicator. If the globe cannot be rotated passively beyond what the patient is capable of, a restriction is present.[4] In its early stages, edema and hemorrhage produce restrictions that improve over time.[4,5] In uncooperative patients, the test may be performed before surgery in the operating room.[4]

Force generation test (FGT)
The FGT informs the examiner about the muscle forces available to move the globe. Under local anesthesia, the eye is grasped and the patient is instructed to look maximally into the field of action of the suspected paretic muscle. If a diminished pull from the muscle is felt, a paresis is present.[4,9,12]
FDT can be used in conjunction with FGT. If paralytic strabismus is present, the FDT will be negative and the FGT will be diminished.[5] If FDT is positive and the FGT shows poor muscle function, then the diagnosis is a combination of restriction and paralysis.[12]

Hess-Weiss screen test
The Hess-Weiss test may also be used for incomitant deviations, when the angle of deviation differs between distinct fields of gaze. It is an important test for the diagnosis of EOM underaction or overation, distinguishing mechanical from neurogenic palsy. It is also valuable in treatment planning, condition monitoring and postoperative evaluation of alignment (Fig. 1).[8]

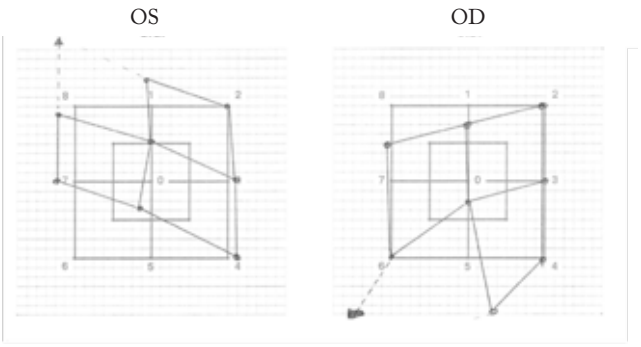


Figure 1. Hess-Weiss screen test: patient after orbital surgery with left eye downgaze limitation and inferior rectus underaction

Imaging
In most cases, high resolution computed tomography (CT) scans and/or dynamic magnetic resonance imaging (MRI) are required to determine the extent and nature of suspected EOM injury, as well as muscle contractility.[4] High-resolution CT scans provide the best image of the relationship between the muscle and the fracture while MRI provides a better image of the structural integrity of the muscle and soft tissue.[9] Dynamic scanning gives information about the contractility of the muscle.[4]

3. TREATMENT OPTIONS
Promptly after diagnosis establishement, appropriate measures should be taken in order to obtain the best postoperative results.[9] Patients and families should understand that motility may never return to normal and diplopia may persist.[2]

3.1 NON-SURGICAL MANAGEMENT
Due to inflammation or muscle contusion, observation is advised in the acute phase. Many early problems will spontaneously resolve with a complete recovery of the extraocular movements.
In the presence of significant swelling, anti-inflammatory agents, such as corticosteroids, might be indicated to accelerate recovery time.
Botulinum toxin injection in the ipsilateral muscle antagonist may be helpful to avoid diplopia and prevent

secondary contracture.[4-7,13]
For small deviations. (<10 DP), prisms may be used in both acute and chronic phases.

3.2 SURGICAL MANAGEMENT

When necessary, strabismus surgery should be postponed until the condition is stable, typically at least six months after the initial orbital surgery.[3,4]
The goal of the treatment is to control diplopia in primary position and during lecture, as well as to eliminate AHP.[5]

Early surgery

In cases where traumatic disinsertion of the muscle is suspected, early surgery is recommended to avoid muscle contraction and a more difficult recovery. An initial attempt should be made to recover and repair the damaged EOM. However, as initial tissue disruption and hemorrhage may compromise both imaging studies and surgical visualization of tissue plans, consider re-imaging and exploration after edema and hemorrhage resolve.[5]

Delayed surgery

Perform repeated FDT before and during surgical procedures to confirm muscle restriction and assess surgical efficacy.[4,9]
When present, the principles used to repair restrictive strabismus are similar to those in other restrictive problems and often involves a combination of recession (retroplacement of the muscle from its original insertion) of the affected muscle and recession of the contralateral yoke (synergist) muscle.[5,7]
A paralytic strabismus is diagnosed when FDT is negative, FGT is diminished and muscle integrity is confirmed intraoperatively. Surgical techniques are identical to other paralytic strabismus.
Attempt surgical reconstruction when direct muscle injury is confirmed. If deviation persists, a recession of the ipsilateral antagonist muscle or the yoke contralateral may be performed in a second surgery.[5,9]
Consider muscle transposition when a damaged muscle is not found, recovered or repaired.
When multiple muscle damage is present, a tether procedure may be indicated.[4]
Before surgery, the patient should be advised that the surgical plan may be adjusted intraoperatively.[5]

4. SPECIFIC CLINICAL CONDITIONS

Orbital fracture repair (Fig.s 2 to 4)

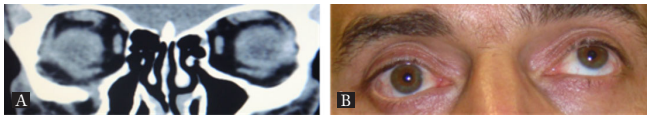


Figure 2. A 40-year-old male patient with hypotropia after right orbital floor fracture repair; a. CT scan revealing orbital floor fracture; b. Left eye hypertropia when fixating with the right eye (restricted inferior rectus on the right side after fracture repair).

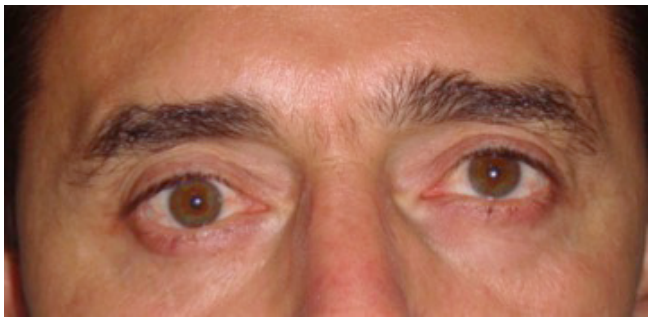


Figure 4. Same patient six years after strabismus surgery with recession of both the right inferior rectus and left superior rectus. A small left hypertropia persists and can be corrected with prisms.

The most common presentations of orbital wall fractures with or without previous surgical repair usually involve the thinnest, inferior and/or medial, bony walls.[7,9]
Following orbital fracture repair, diplopia may be caused by persistent entrapment of extraocular muscles and/or associated orbital tissue; scaring of the tissue surrounding an implant (orbital adherence syndrome), and/or neuromuscular trauma.[1,2]
The most commonly affected muscles are the inferior rectus, the medial rectus, the inferior oblique and the superior oblique.
Orbital surgery may worsen a previous motility compromise, and special care is needed to avoid EOM damage and to ensure that all incarcerated tissue is removed. Typically, orbital floor fractures may be present with a restrictive hypotropia combined with a limitation of elevation on the affected side and a positive FDT.[2,8] Prefer small, non-adherent implants to reduce fibrosis of the surrounding tissues and to prevent mechanical restriction of EOM movements.[2]
Inferior rectus palsy can also occur from direct injury to the EOM or cranial nerve. In these cases, a hypertropia in the primary position will be noted.[8]

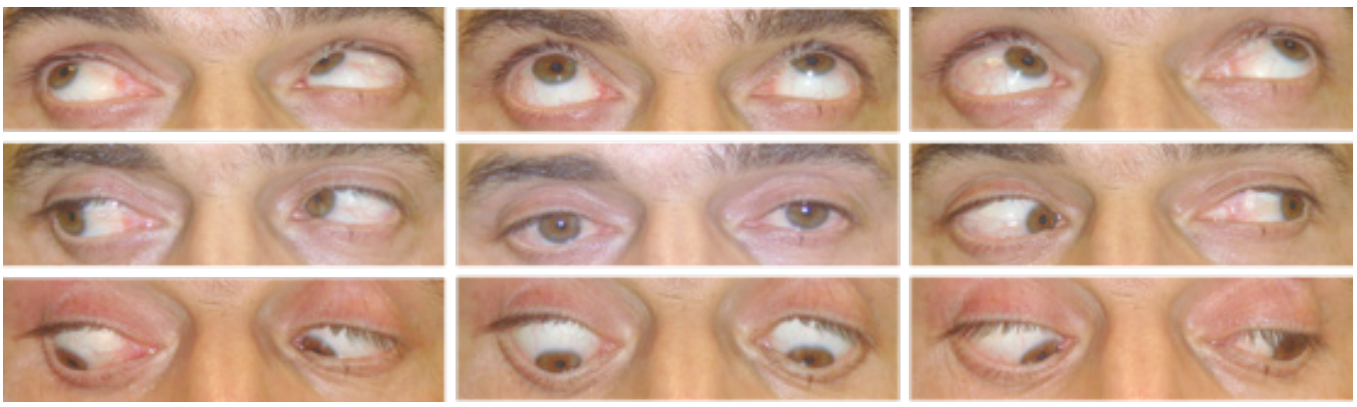


Figure 3. Same patient as Fig. 2 presenting a right eye motility limitation in abduction and upgaze due to a restriction of the inferior rectus.

Damage of more than one muscle is possible when the orbital floor and medial wall are involved, affecting both elevation and abduction in the same eye.[9]

Decompressive orbitotomy (Fig.s 5 and 6)

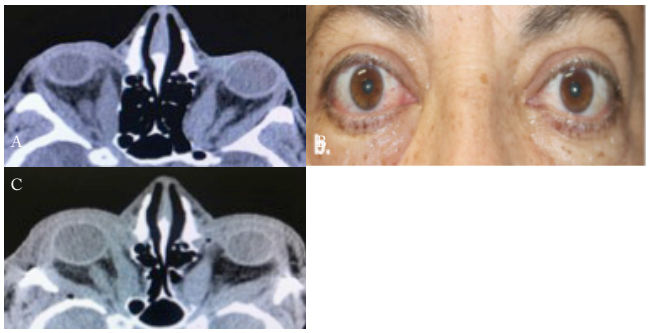


Figure 5. A 52-year-old female with TED and compressive optic neuropathy a. CT scan before decompressive orbitotomy; b. Exophthalmos before surgery; c. CT scan after decompressive orbitotomy.

Postoperative diplopia is one of the most common complications after orbital decompression. Patients with more severe TED and preoperative muscle enlargement are more likely to develop postoperative diplopia.
The mechanism of motility disturbance and diplopia is primarily restrictive. Muscles are often fibrotic before decompression as a result of TED. During surgery, the displacement of muscles alters their function and ocular alignment.[13,14]
The incidence of strabismus is higher after medial and inferior wall decompression, being the medial and the inferior rectus more frequently involved.[3,5,15]

The goal of EOM surgery is to reduce restriction of the fibrous muscles. Surgical management is similar to other causes, with weakening procedures, such as recession, being preferred over resection (where a portion of the muscle is removed).[11,13] After decompressive orbitotomy, patients may need more than one procedure on several muscles.

Endoscopic sinus and orbital surgery
In recent years, the introduction of endoscopic surgery has improved the outcomes of sinus disorders treatment and brought a new approach to orbital conditions. However, ophthalmologic complications can still occur, including optic nerve trauma and strabismus. During endoscopic surgery, extraocular muscles can be damaged. Although the medial rectus is particularly at risk, the inferior rectus and inferior oblique tendon may also be involved. Trauma can vary from a mild contusion to total EOM laceration, both causing permanent strabismus and diplopia.[4,5,8]
Surgical management may be complex, often including vertical muscle transpositions in cases of severe medial rectus damage.[7]

Orbital tumor resection (Fig.s 7 and 8)
Postoperative diplopia after orbital tumor excision may cause diplopia and strabismus.[2,3,7]
As previously described, based on the degree of muscle damage and recovery, treatment is similar to other conditions.

Ethical Disclosures
Confidentiality of Data: Patient consents obtained.
Conflicts of Interest: The authors have no financial interest

Corresponding author
Alcina Toscano
alcina.toscano@gmail.com

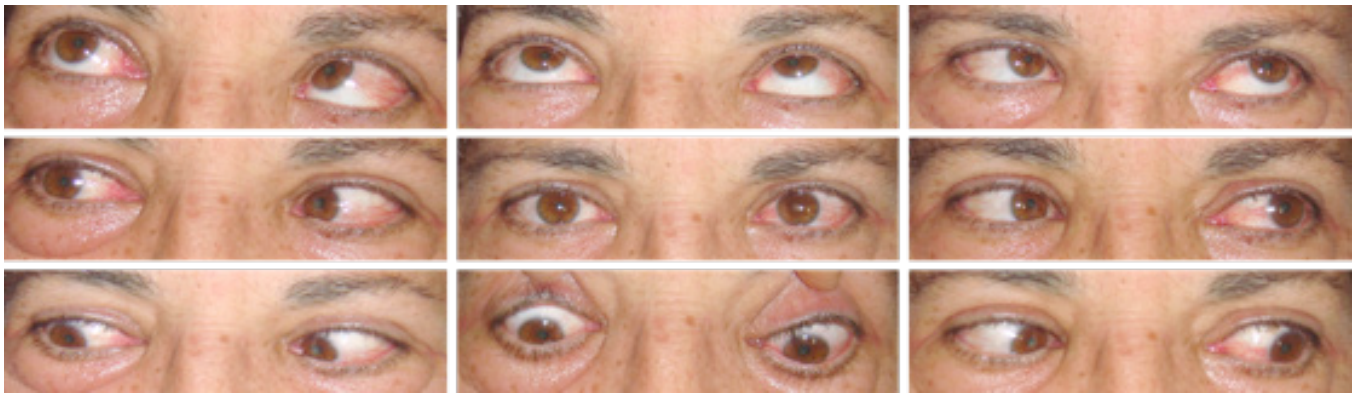


Figure 6. Same patient from Fig. 4 after bilateral three-wall orbital decompression (lateral, inferior and medial) presenting a left eye esotropia.

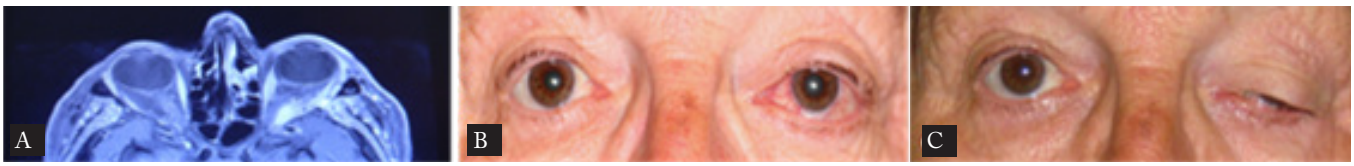


Figure 7 - A 73-year-old female patient with a lesion of the left orbit causing optic nerve compression. a. MRI showing the posterior location of the tumor; b. Left eye proptosis (before orbital surgery); c. Partial left III nerve palsy with ptosis (after orbital surgery)

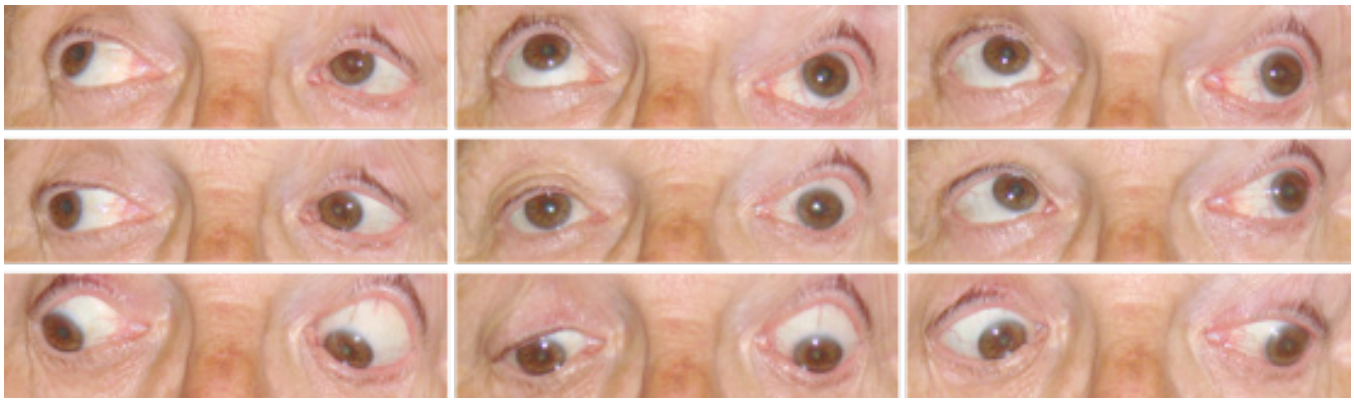


Figure 8. Same patient from Fig. 7. Partial left III nerve palsy with left eye hypotropia. Left eye upgaze limitation is observed.

REFERENCES

1. Shah HA, Shipchandler T, Vernon D, Baumanis M, Chan D, Nunery WR, et al. Extra-ocular movement restriction and diplopia following orbital fracture repair. Am J Otolaryngol. 2018;39:34–6.
2. Silbert DI, Matta NS, Singman EL. Diplopia secondary to orbital surgery. Am Orthopt J. 2012;62:22–8.
3. Zloto O, Ben Simon G, Didi Fabian I, Sagiv O, Huna-Baron R, Ben Zion I, et al. Association of orbital decompression and the characteristics of subsequent strabismus surgery in thyroid eye disease. Can J Ophthalmol. 2017;52:264–8.
4. Murray AN. An approach to some aspects of strabismus from ocular and orbital trauma. Middle East Afr J Ophthalmol. 2015;22:312.
5. Terraza AG, Nasarre JV. Estado actual del tratamiento del estrabismo. Madrid: Sociedad Española de Oftalmologia; 2010:
6. Özkan SB. Restrictive problems related to strabismus surgery. Taiwan J Ophthalmol. 2016;6:102–7.
7. Volpe NJ. Orbital and periorbital disease causing mechanical strabismus. Annu Meet Syllabus - North Am Neuro-Ophthalmology Soc. 2015;477–83.
8. Rosenbaum AL, Santiago AP. Clinical Strabismus Management: Principles and Surgical Techniques. Philadelphia: Saunders; 1999.
9. Molinari AD. Strabismus Following Extraocular Muscle Trauma. Network - Ophthalmic News Educ Netw. American Academy of Ophthalmology. 2018.[accessed May 2018]. Available from: https://www.aao.org/disease-review/strabismus-following-extraocular-muscle-trauma
10. Teodorescu L. Anomalous head postures in strabismus and nystagmus diagnosis and management. Rom J Ophthalmol. 59:137–40.
11. Eckstein A, Esser J, Oeverhaus M, Saeed P, Jellema HM. Surgical treatment of diplopia in Graves orbitopathy patients. Ophthal Plast Reconstr Surg. 2018; 34(4S Suppl 1): S75-S84.
12. Wright KW, Strube YN, editors. Pediatric Ophthalmology and Strabismus. 3rd ed. Oxford: Oxford University Press; 2012.
13. Sobol EK, Rosenberg JB. Strabismus after ocular surgery. J Pediatr Ophthalmol Strabismus. 2017;54:272–81.
14. Rootman DB, Golan S, Pavlovich P, Rootman J. Postoperative changes in strabismus, ductions, exophthalmometry, and eyelid retraction after orbital decompression for thyroid orbitopathy. Ophthal Plast Reconstr Surg. 2017;33:289–93.
15. Cestari DM, Freire M V, Chun BY. Vertical rectus muscle recession versus combined vertical and horizontal rectus muscle recession in patients with thyroid eye disease and hypotropia. J Am Assoc Pediatr Ophthalmol Strabismus. 2018;22:257–61.

Section 6

The future

21. New Trends in the Treatment of Orbital Diseases

OPHTHALMOLOGY
Rui Tavares, MD, Vera Soares, MD

Summary

Many challenges will appear in the future of orbital and oculofacial surgery. A better knowledge of orbital diseases, improved diagnostic skills and techniques, improved and individually targeted medical therapy, and better microincisional computer-assisted surgery will be new trends in the treatment of orbital diseases.

Keywords: *Antibodies, Monoclonal; Molecular Targeted Therapy; Ophthalmologic Surgical Procedures; Orbital Diseases/therapy; Orbit/surgery; Surgery, Computer-Assisted*

INTRODUCTION

Orbital surgery is a passionating field in Ophthalmology, Maxillofacial Surgery, Otorhinolaryngology and Neurosurgery, and has had recent advances that are changing the way we look at orbital diseases and also the way we treat them.

We are currently living in a growing world of technology, which is increasingly present in our lives. The same is expected to occur in the field of oculoplastic and orbital surgery in the next few years. Many challenges exist, and here we mention some of those that will emerge as these areas progress.

1. DIAGNOSIS

We still do not know much about some diseases and how they evolve or can be medically treated. For example, botulinum toxin is an excellent treatment in blepharospasm, but we do not know clearly what causes the disease. Nor how to handle it medically so that surgery or repeated botulinum toxin injections would no longer be needed. And neither how to deal with cases of associated eyelid apraxia, sometimes with poor surgical results. In the future, a better knowledge of this kind of diseases will unquestionably improve the way treatment is proposed to patients.[1]

2. MEDICAL THERAPY

We still see too many patients with thyroid eye disease (TED). Two centuries ago, Graves and von Basedow conjectured that thyroid disease and eye disease were somehow connected. Today, we believe that the thyroid and the orbit are immunologically linked; however, we still often treat TED surgically, even though there is now a common belief that using surgery to manage cytokines is to fight the wrong war.[2]

Significant advances have been made in oncology and rheumatology with the introduction of molecular targeting agents. The same is happening in the field of orbital diseases and oculoplastic surgery.[3] These agents, either monoclonal antibodies or small molecule inhibitors, allow the treatment of diseases more effectively with fewer adverse effects. Traditional chemotherapy and anti-inflammatory agents are relatively nonspecific in their action, affecting all cells that have a high mitotic rate. Although this therapy may be effective in halting or slowing inflammation or cancer growth, it also affects other healthy tissues in the body, leading to significant side effects.

We already have some examples of monoclonal antibodies use in the treatment of oculoplastic conditions, either oncologic or inflammatory. For instance, anti-VEGF monoclonal antibodies, now widely used to treat several retinal conditions, have successfully treated cases of vascular malformations in the orbital apex and periocular hemangiomas. The use of rituximab (anti-CD20) in the treatment of lymphoma is now common, either as monotherapy or in combination with chemotherapy, and good outcomes have been reported in primary ocular adnexal lymphoma. Treatment of inoperable squamous cell carcinoma, with or without orbital invasion, with cetuximab and panitumumab has also been described.

Being the most common cause of orbital inflammation, thyroid eye disease (TED) has been thoroughly investigated and treated with several monoclonal antibodies, either targeting B cells, tumor necrosis factor (TNF)-α, interleukin (IL)-6 receptor or the insulin-like growth factor (IGF)-1 receptor.

Rituximab is an anti-CD 20 molecule, a human B lymphocyte-specific antigen. Some studies proved its role as a therapeutic agent in moderate to severe TED. Furthermore, rituximab has been shown to have broad applications in other oculofacial inflammatory conditions, such as IgG4 disease, mucous membrane pemphigoid and granulomatosis with polyangiitis. The latter, in particular, has shown excellent outcomes with this therapy.

Several TNF-α inhibitors have also been used for TED, such as etanercept. Recent advances with the use of **tocilizumab** - an interleukin-6 receptor antagonist – gave also new insights into TED´s management, demonstrating to be able to avoid its sometimes devastating sequelae, even in patients previously treated with intravenous steroids and active disease.[4]

Recently, an IGF-1 receptor (IGF-IR) antagonist antibody is being studied in active, moderate-to-severe TED: patients who received **teprotumumab** had improvements in proptosis, Clinical Activity Score, Graves Orbitopathy Quality of Life questionnaire (GO-QOL), and subjective diplopia that were clinically significant. The marked reduction in proptosis was similar to that reported after decompression surgery. Altogether, these findings support the theory that the inhibition of IGF-IR in patients with ophthalmopathy may result in a disease-modifying reduction in the volume of

orbital fat, muscle, or both. However, as no orbital imaging was performed, it is still unclear which orbital tissues were primarily affected by teprotumumab therapy. Authors advise further studies, and a longer-term follow-up will be necessary for assessing the durability of the response.[5]

In addition, after the work of Lee BW *et al*, who studied RNA sequencing of orbital fat in patients with active TED compared to normal controls, we might say that the future lays on a personalized gene profiling and customized therapy. The authors conclude that "the identification of genes with altered levels of expression in active, severe TED may inform the molecular pathways central to this clinical phenotype and guide the development of novel therapeutic agents." [6]

Biomarker testing is nowadays already being used for conjunctival melanoma; a number of mutations have been previously described, and many of them can be used as a target for treatment (e.g., vemurafenib[7] and dabrafenib for BRAF mutations).[8]

The use of small molecule inhibitors has been described in the treatment of basal cell carcinoma, squamous cell carcinoma, and Erdheim–Chester disease, a rare form of histiocytosis. Immunotherapy with checkpoint inhibitors has also showed applications in orbital disease. These therapies can however lead to the development of ophthalmic side-effects, including edema, hypertrichosis, and orbital and eyelid inflammation, with which the oculoplastic surgeon should be familiar.

3. SURGICAL OPTIONS

When treating cancer we need to find ways to eliminate the enemy with greater success and less morbidity. Exenteration should be an end-stage option. Regrettably, so far, the use of more conservative approaches in advanced sebaceous gland carcinoma, Merkel cell carcinoma, lacrimal gland adenoid cystic carcinoma, and melanoma has been somehow disappointing. New therapies must be studied, and the focus should be on early diagnosis. An example is the traditional treatment of lacrimal gland carcinoma with orbital exenteration followed by radiation therapy. It has been shown that exenteration does not prevent distant relapse and death, and some patients may experience local recurrence. A fibroblast growth factor receptor (FGFR) inhibitor is currently being studied for colorectal cancer, as these cells may have FGFR deregulated signals, with encouraging results.[9] The potential use of AZD4547 fibroblast growth factor receptor-1 inhibitor in lacrimal gland adenoid cystic carcinoma is now under investigation and may open a new paradigm in the treatment of this aggressive tumor.[10]

Recently, eye-sparing surgery and adjuvant radiation therapy and chemotherapy have also gained popularity for the treatment of lacrimal gland carcinoma.[11]

Preliminary studies show that these approaches are associated with reasonable rates of local control and ocular safety profiles. One study showed oncogenic mutations in more than half of the cases of lacrimal gland adenoid cystic carcinoma, with KRAS mutations being identified in 10 of 24 patients, suggesting a potential benefit of targeted treatments.

In the last 20 years, we have witnessed a trend towards minimally invasive surgery with micro-incisions and often endoscopic visualization. Computer-assisted surgery (CAS) with neuronavigation is now an established adjunctive tool used by many surgeons operating in the head and neck region. Imaging during orbital surgery may offer excellent three-dimensional guidance for intraorbital lesions, allowing a safer and more controlled surgery.[11] Surgical targets in the orbit are fixed structures, thus no shifting occurs and high intraoperative navigation accuracy can be achieved. The use of the navigation clearly reduces the operative risk and increases the effectiveness of microsurgical orbital procedures. However, this technology is still seen by many as not cost-effective and time-consuming, although it may have an important role in teaching and shortening the learning curve of many orbital procedures. Increased safety and patient benefit, and the integration of refined and cost-effective CAS systems into operating room environments will surely and definitely influence its future role.[13]

4. MODULATION OF WOUND HEALING

Watching, for example, a socket heading to severe contraction emphasizes the fact that we need a better understanding of abnormal wound healing and how to modulate it. An article published in 2018 by Parra F *et al* highlights how autologous platelet-rich plasma treatment enhances some parameters associated with healing, suggesting a potential therapeutic value after blepharoplasty surgery.[14]

CONCLUSION

Oculoplastic and orbital surgery are unique in ophthalmology, crossing boundaries with different surgical areas or sub-specialties, and compelling us to work together as a team. Moreover, oculoplastic surgery has an interesting and broad spectrum of pathologies and surgical techniques: the repair of eyelid malpositions (ptosis, retraction, ectropion, and entropion, trichiasis); trauma; lacrimal disorders; evisceration, enucleation, exenteration and orbital, socket, and sinus surgery; oncology; trauma; and, of course, a whole new variety of cosmetic procedures, which makes our sub-specialty very interesting, fun and challenging at the same time.

Ethical Disclosures

Conflicts of Interest: The authors have no financial interest in the products or procedures mentioned in this chapter

Corresponding author

Rui Tavares

rui.tavares@jmellosaude.pt

REFERENCES

1. Yen MT. Developments in the treatment of benign essential blepharospasm. Curr Opin Ophthalmol. 2018;29:440-4.
2. Bartley, George B. Oculoplastic and Orbital Surgery. Ophthalmology, Volume 122 , Issue 2 , 224 - 226
3. Allen RC. Molecularly targeted agents in oculoplastic surgery. Curr Opin Ophthalmol. 2017;28:485-92.
4. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo-Lopez A, Rodríguez Alvarez FM, et al. Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant graves orbitopathy: a randomized clinical trial. Am J Ophthalmol. 2018; 195:181 – 90.

5. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. N Engl J Med. 2017;376:1748-1761.
6. Lee BW, Kumar VB, Biswas P, Ko AC, Alameddine RM, Granet DB, et al. Transcriptome analysis of orbital adipose tissue in active thyroid eye disease using next generation RNA sequencing technology. Open Ophthalmol J. 2018;12:41-52.
7. Maleka A, Åström G, Byström P, Ullenhag GJ. A case report of a patient with metastatic ocular melanoma who experienced a response to treatment with the BRAF inhibitor vemurafenib. BMC Cancer. 2016;16:634.
8. Dagi Glass LR, Lawrence DP, Jakobiec FA, Freitag SK. Conjunctival melanoma responsive to combined systemic BRAF/MEK inhibitors. Ophthalmic Plast Reconstr Surg. 2017;33:e114-e116.
9. Yao TJ, Zhu JH, Peng DF, Cui Z, Zhang C, Lu PH. AZD-4547 exerts potent cytostatic and cytotoxic activities against fibroblast growth factor receptor (FGFR)-expressing colorectal cancer cells. Tumour Biol. 2015;36:5641-8.
10. Ann Q. Tran The potential use of AZD4547 fibroblast growth factor receptor-1 inhibitor in lacrimal gland adenoid cystic carcinoma .Presented at the AAO 2018 meeting (Chicago, IL, USA)
11. Woo KI, Kim YD, Sa HS, Esmaeli B. Current treatment of lacrimal gland carcinoma. Curr Opin Ophthalmol. 2016 Sep;27(5):449-56.
12. Hejazi N1. Frameless image-guided neuronavigation in orbital surgery: practical applications. Neurosurg Rev. 2006 Apr;29(2):118-22. Epub 2005 Dec 23.
13. Hussain A, Nijhawan N, DeAngelis D, Oestreicher J. Perceptions and use of computer-assisted surgery (CAS) in the orbit. Orbit. 2018 Jul 11:1-4.
14. Parra F, Morales-Rome DE, Campos-Rodríguez R, Cruz-Hernández TR, Drago-Serrano ME. Effect of platelet-rich plasma on patients after blepharoplasty surgery. Orbit. 2018 Apr;37(2):81-86. doi: 10.1080/01676830.2017.1383453.

Orbital Disease and Surgery

A multidisciplinary approach

Orbital Disease and Surgery

A multidisciplinary approach

SCIENTIFIC SUPPORT

cuf
Academic and Research Medical Center

SPONSORED BY

LABORATOIRES Théa