

# Rare Diseases of the Orbit




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## ABSTRACT

This article provides an overview of rare orbital diseases. Congenital malformations, inflammatory diseases, and benign and malignant neoplasms are described. Although the orbit represents a relatively small area of the body, it encompasses multiple different tissues, and a great variety of diseases can arise within the orbital space. For this reason, the completeness and level of detail in the description of particular diseases must be somewhat limited in this overview. Nevertheless, clinical manifestations, important aspects of diagnosis, treatment strategies, and prognosis (if possible) are described. In a series of brief subsections, the authors highlight the most characteristic and relevant aspects of these different diseases.

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## 1 General Introductory Remarks

Oto-rhino-laryngologists and ophthalmologists regularly have to deal with diseases of the orbit. The complex anatomy of this small region of the body and the multitude of different tissues it encompasses entail a high heterogeneity of pathologies. In addition to numerous systemic diseases associated with the orbit, various malformations can arise from a complex embryology, and treatment of orbital diseases must be considered a prime example for interdisciplinary cooperation. The central facial position and close topographic association with the nose and paranasal sinuses, skull base, cranial skull, and temporal region can even require interdisciplinary surgical care.

The orbit serves as protection for the eye and its adnexae. The relatively stable bony frame with the corpus adiposum orbitae provides protection, but because of the confined space, volume expansion can rapidly lead to problems. These features are responsible for the fact that most pathological processes of the orbit primarily manifest ophthalmologically. Exophthalmos, diplopia, and

loss of vision are the most frequent clinical signs, and ophthalmologists play a crucial role in detecting and managing these conditions.

Many orbital diseases, such as endocrine orbitopathy, are well known yet still can follow atypical and rare courses. Other conditions are truly rare and so numerous that a complete overview of them all is beyond the scope of this manuscript. Most clinicians likely will never encounter many of the diseases described here yet will still find this comprehensive series of synopses useful. Our intention for this article is to sharpen the clinical perspective and provide preparation for first encounters with possibly unfamiliar manifestations.

In addition, this article does not deal with periorbital (preseptal) diseases. Thus, it does not cover pathologies of the eyelids and the draining lacrimal ducts or traumatology of the orbit. Furthermore, solely ocular diseases are not within the scope of this overview, as these conditions expand beyond the ocular border structures (e. g., to the sclera) or cause concomitant orbital reactions.

## 2. Interdisciplinarity and “What is rare, What is frequent?” – A Dilemma?

Different disciplines vary in perspective on the orbit and perception of the incidence of related conditions, as is also reflected in the literature. Because pathogenic processes related to the orbit are not common, precise incidences are difficult to pinpoint in the different patient populations treated or co-treated within different disciplines. Furthermore, large randomized trials are lacking, and most published studies are comparative with small case numbers or are non-comparative analyses or case reports.

The orbit is a quite limited region of the human body, encompassing numerous tissues that fall under the care of clinicians in the head and neck disciplines. When surgery is indicated, neurosurgeons, maxillofacial surgeons, oto-rhino-laryngologists, and ophthalmologists can be crucially involved. Furthermore, numerous other disciplines also have a role in good management of these diseases, including internal medicine, pediatrics, radiology, and hemato-oncology. Finally, pathologists make essential contributions to diagnosis by means of modern methods (e. g., molecular pathology).

### Note

**Orbital surgery is a field involving several disciplines according to the anatomically adjacent structures. This body region thus must be treated in an interdisciplinary context.**

## 3. History-taking and Diagnostics

### 3.1 History-taking

For conditions involving the area of the orbit, structured history-taking must always precede targeted diagnostics and therapy. It is useful to identify and assess key symptoms, quantify manifestations, and prioritize pathological changes in accordance with symptoms.

After the patient interview, leading symptoms must be retrieved and classified (by duration, intensity, or progression) (**infobox 1**).

#### INFOBOX 1

##### Leading orbital symptoms

- Exophthalmos/enophthalmos
- Ptosis/eyelid retraction
- Disorders of the eye motility/diplopia
- Periocular/ocular reddening and swelling
- Periocular congestion/chemosis
- Periorbital/orbital pain
- Foreign body sensation/epiphora
- Retrobulbar pressure sensation
- Bulbar movement pain
- Bulbar repulsion pain/difficult repulsion
- Elevated intraocular pressure
- Choroid folds/papilledema
- Visual field loss
- Loss of vision

The history-taking also should include the patient's background regarding general diseases as well as social and family history. In these cases, the focus must be placed on autoimmune diseases (e. g., autoimmune thyroid disease), other chronic inflammatory diseases (e. g., granulomatosis with polyangiitis), malignancies (e. g., prostate, breast, or bronchial cancer including existing genetic predisposition), and current medications (especially anticoagulants, among others). Known previous diseases of the orbit and neighboring structures (nose, paranasal sinuses, neurocranium) may give hints about recurrent conditions.

Because diseases of the orbit may lead to vision loss and frequently manifest primarily ophthalmologically, taking an eye-related history is of highest importance. Also important is an examination to determine if both eyes are functionally equal and to identify any amblyopia, to establish whether previous surgeries have been performed in the area of the eyes, and to try to determine how visual acuity and refraction (refractive power rates) have developed in the context of possible orbital disease. The leading symptom of “exophthalmos” might be confused with pseudo-exophthalmos (e. g., upper eyelid retraction) or enophthalmos of the contralateral side.

### 3.2 Ophthalmological diagnostics [1]

The diagnostic approach to assessing for orbit-related conditions includes the following:

- Inspection, palpation, and measurement of the palpebral fissure, determination of the repositioning of the eyeballs, testing of corneal sensitivity and intraocular pressure;
- Determination of vision, including refraction;
- Perimetry assessments, including visual field examination with determination of the stimulus threshold and measurement of the visual field limits and the blind spot;
- Exophthalmometry and orthoptics; and
- Split lamp examination and ophthalmoscopy with assessment of the papilla.

For detailed descriptions regarding ophthalmological history-taking and examination techniques, a recent continuing medical education article covers the specific information [2].

### 3.3 Radiological diagnostics (MRI, CT, ultrasound)

Radiological procedures allow for:

- Differential diagnostic classification,
- Determination of extent,
- Display of possible infiltration of surrounding structures,
- Surgery planning (CT scan/MRI for navigation), and
- Radiation planning.

Ultrasound can give initial hints about the type of tumoral mass but is limited regarding measurement of depth. MRI is superior to CT scan in cases of unclear inflammatory lesions and tumors. T1- and T2-weighted and T2 fat-saturated sequences (which afford excellent visualization of the optic nerve and the eye muscles) are performed. The additional application of contrast agents is suitable for examinations associated with tumors and inflammatory processes.

ACT scan allows for the best identification of calcified and bony structures with sufficient significance for soft tissue structures. Thus, this modality plays an important role in surgery planning. In cases of unclear masses and inflammation, the application of contrast agents may give additional information concerning the tissue type and vascularization. One disadvantage is radiation exposure, which can damage the eye lens and therefore should be applied sparingly in young patients.

Angiography, scintigraphy, PET, and SPECT are reserved for exceptional cases. For documentation and planning of reconstructions, photography, 3D photography, and perhaps surface scans also may be relevant [3].

### 3.4 Histopathological diagnostics

If a clinical diagnosis cannot be made based on the above-mentioned examination techniques, biopsy with histopathological examination is important and suitable, in particular in the context of unclear or advanced findings, recurrence, or therapy failure. In these cases, the risks of iatrogenic damage should not outweigh the benefit. For targeted planning of biopsy, adequate clinical examination and imaging with subsequent interdisciplinary discussion are advised. The following recommendations should be considered regarding biopsies:

- Intake of systemic corticosteroids and other immunosuppressants should be avoided in the weeks before biopsy, if possible.
- Incisional or excisional biopsies can be taken for formalin fixation or examinations of fresh material.
- The biopsy should afford sufficiently large specimens, as morphological examination of fine needle aspirates is not always possible (and may be sufficient only in cases of lymphoma or metastasis).
- Biopsy samples should be taken from different areas of a lesion.
- Damage to the examination material should be avoided.
- Material should be compared to previous biopsy samples of other organs, if available, for better identification of systemic diseases.

### 3.5 Laboratory diagnostics

For a multitude of rare orbital diseases, further examinations are useful, in particular adequate laboratory diagnostics. Readers interested in specific details can refer to [4].

In the following sections, we systematically illustrate the various rarely occurring structural, inflammatory, degenerative, and neoplastic changes involving the orbit.

## 4. Structural Lesions of the Orbit

Structural lesions of the orbit include congenital and acquired changes. The first category comprises hamartomas, choristomas, teratomas, and tissue ectopy and the large group of bone anomalies. Acquired alterations largely involve post-inflammatory and post-traumatic conditions.

### 4.1 Cysts and cystic lesions

Cystic lesions may occur as isolated or multiple findings. They are usually more or less spherical and can have different consistencies (e. g., serous, sebaceous, solid, mixed). In general, these lesions are painless masses that grow quite slowly. In the context of secondary inflammatory reactions, a local granulomatous tissue reaction may occur, leading to severe reactive changes and to osteolysis in the area of bone structures.

Below are some aspects that contribute to classification:

- Timing of manifestation (congenital or acquired)
- Number (isolated or multiple)
- Tissue type (epithelial or non-epithelial)
- Location
  - subperiosteal
  - extraconal
  - conal
  - intraconal
- Etiology
  - vascular/hematogenous
  - neurogenic
  - infectious
  - metastatic

#### 4.1.1 Congenital cysts and cystic lesions of epithelial origin: dermoids [5–8]

- Epidemiology
  - 3–9% of the orbital masses
- Etiology
  - congenital as choristoma
- Location
  - mostly extraorbital (preseptal) in a temporal-superior location, along the frontozygomatic suture (70–90%) (**► Fig. 1**)
  - less frequently in the area of the medial upper eyelid
  - rarely as intraorbital dermoids
- Clinical
  - well-delimited cystic lesion with slow progression
  - displacement of adjacent structures
  - sonographically well-defined, anechoic, oval/round lesion with hyperreflective echoes as an indication of epidermal differentiation (adnexa structures, sebum, cellular detritus), or secondary calcifications
  - fibrous capsula
  - **Cave:** ruptured dermoid cysts induce granulomatous inflammation; acute and chronic courses are known; And transsutural growth is possible (sandglass configuration)
- Therapy
  - complete excision with preservation of the cystic wall; proliferation-active areas (mostly near the bone) especially have to be removed
  - marsupialization
  - **Cave:** incomplete excisions may – although rarely – lead to recurrences; more rare are malignant transformations in the sense of squamous cell carcinomas
- Important differential diagnoses
  - temporal
    - primary and secondary lacrimal gland tumors

- medial
  - retention cysts and mucoceles (history regarding bone lesions)
  - meningoceles; encephaloceles
  - choristomas of the nasal mucosa
- general
  - each solid, non-infiltrative mass with cystic shape
- further cystic lesions are conjunctival cysts, epidermoids, and cysts originating from tissue ectopy (e. g., ectopic tissue of Rathke's pouch), cholesterol granulomas, and cholesteatomas

#### Note

If a cystic structure is found within the tissue (e. g., the external eye muscle), a secondary process (infection, metastasis) may be suspected.

### 4.1.2 Acquired cysts and cystic lesions

#### 4.1.2.1 Mucoceles [9–11]

- Epidemiology
  - 3–4% of orbital masses
  - age peak in the 4<sup>th</sup> to 6<sup>th</sup> decades of life
- Etiology
  - missing ventilation of the affected paranasal sinus
  - previous trauma/surgery in 50%
  - common in children with cystic fibrosis
- Location
  - medial to medial-superior in the orbit, accordingly originating from the ethmoid or frontal sinus
  - rarely originating from the sphenoid sinus

- subperiosteal to diffusely intraorbital as a complication of, e. g., orbital phlegmons
- Clinical
  - exophthalmos/bulbar displacement, diplopia (► Fig. 2)
  - pain only in the context of secondary inflammatory changes of the orbit; otherwise, often initially painless
  - displacing growth and secondarily compression of the optic nerve, the ocular bulb, or the draining lacrimal pathways
  - **Cave:** enophthalmos is a possible rare complication; possible osteolysis of the orbital floor in the context of “silent sinus syndrome” of the maxillary sinus; optic atrophy possible with chronic course
- Therapy
  - restoration of adequate ventilation of the affected sinus
  - excision of the cystic mass
  - complication management (incision, drainage, intravenous antibiotics)

#### Note

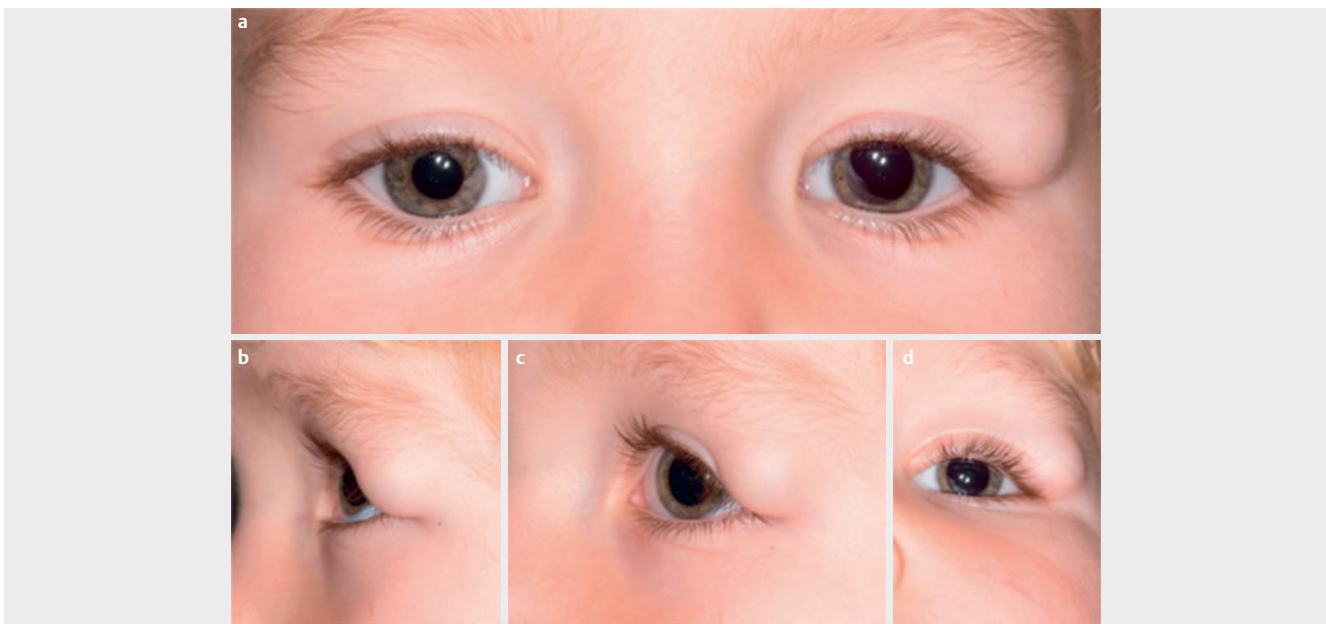
In cases of fronto-ethmoid location, meningocele/encephalocele must be considered. Hypertelorism and increased size during Valsalva maneuver are additional indicators.

#### Cave

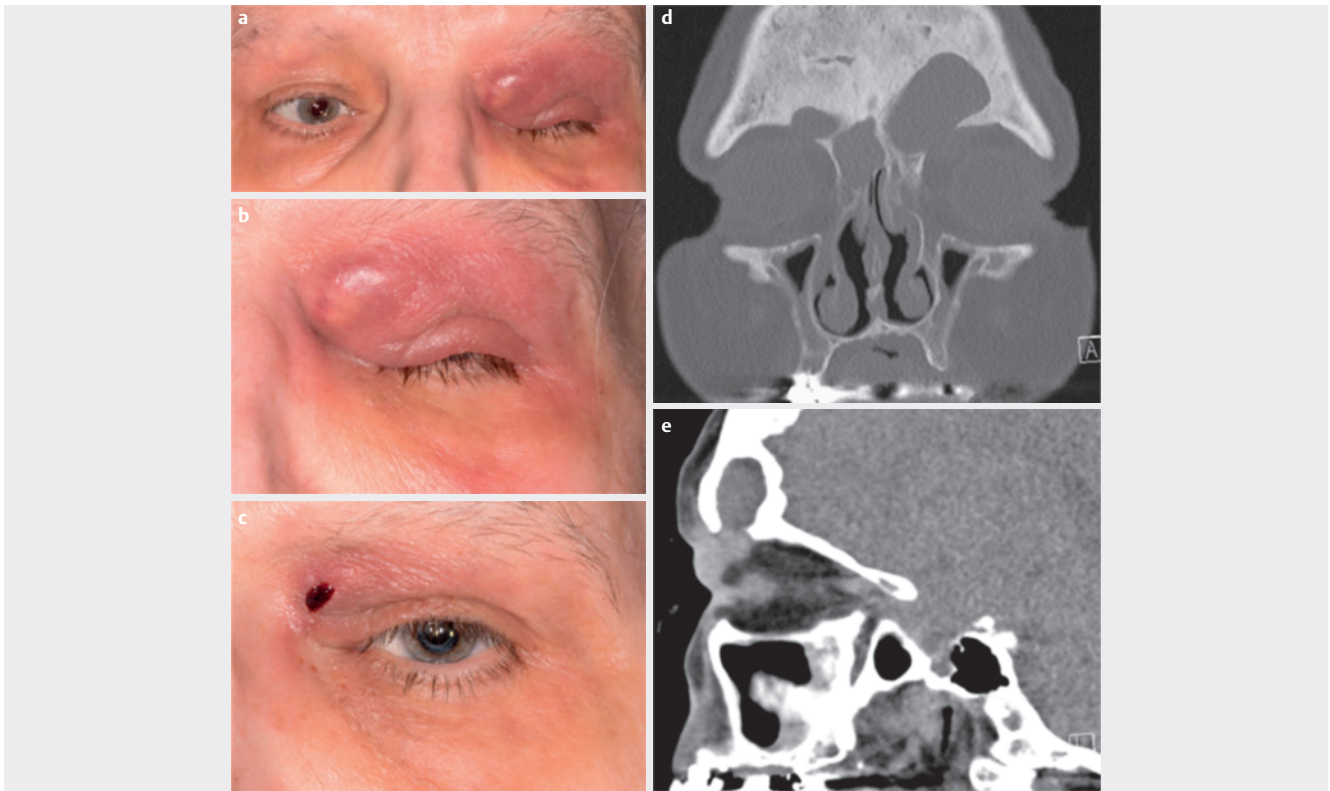
Bilateral fronto-ethmoid mucoceles also induce Hypertelorism.

#### 4.1.2.2 Dacryops [12–13]

- Epidemiology
  - 0.5–2% of orbital masses
  - usually in the 2<sup>nd</sup> to 5<sup>th</sup> decades of life
- Etiology

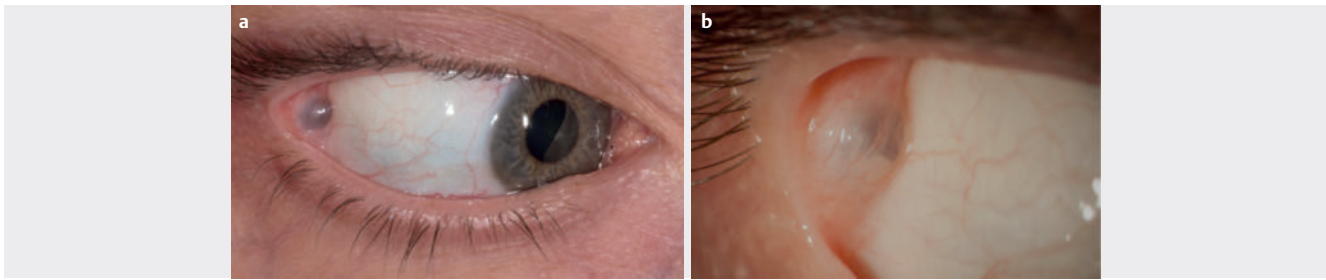


► **Fig. 1** 3-year-old patient with dermoid of the left orbit (reaching the lacrimal fossa). **a** Overview of the eyes. **b** Lateral view with clearly visible protrusion of the orbital contour. **c** The diagonal view shows the partial covering of the lid margin. **d** View from an inferior position shows the relation of the tumor to the eyebrow and the lacrimal fossa. The photos are from the archive of the University Hospital of Halle, Department of Ophthalmology.



► **Fig. 2** Frontal mucocele with invasion into the left orbit in a 73-year-old female patient. **a** Overview of the eyes shows the initial clinical findings comparing both sides. **b** The amplified picture shows the abscess formation at the medial eyelid with severe pseudoptosis and accompanying phlegmons (preseptal). **c** Clinical appearance after incision and subsequent drainage as well as intravenous antibiotic therapy. **d** Pictures of the initially performed CT (bone window, coronary plane) showing the opacity of the frontal sinus. **e** Soft tissue window of the initially performed CT (sagittal plane) showing an opacity reaching into the orbit originating from the frontal sinus. The clinical photos (**a–e**) are from the archive of University Hospital of Halle, Department of Ophthalmology (courtesy of the Department of Diagnostic Radiology, University Hospital of Halle. Professor and Chair: Prof. Wohlgemuth).

- occlusion of the glandular excretory duct (after inflammation/trauma)
  - multifactorial
  - idiopathic
  - Location
    - mostly palpebral part of the lacrimal gland (less frequently: orbital part, accessory lacrimal glands, cysts in the ectopic lacrimal gland tissue, or cysts of glandular tissue of the caruncle; ► **Fig. 3**)
    - isolated, rarely multiple and bilateral occurrence
  - Clinical
    - more or less pronounced paragraph shape of the upper eyelid (temporal pseudoptosis)
    - foreign body sensation
    - rapidly increasing size possible in the context of emotional reflex secretion or following bleeding (color change)
    - depending on the size, astigmatism and/or diplopia
    - **Cave:** rarely, secondary bacterial colonization
  - Therapy
    - complete excision of cyst(s)
    - marsupialization, laser photocoagulation
    - wait-and-see, tear substitute, avoiding cold wind/water
  - Important differential diagnoses
    - rarely dacryops as sequela of trachoma, pemphigoid, or dacryolith
- 4.1.2.3 Orbital implantation cysts [14–15]**
- Epidemiology
    - heterogeneous data depending on the etiology (most frequently after enucleation with an incidence of 2–7% of cases)
  - Etiology
    - posttraumatic (e. g., strabismus surgery, peri- and intraocular surgery, penetrating orbital trauma, enucleation, orbital fracture) because of dissemination of (conjunctival) epithelium
  - Clinical
    - slowly growing cystic tumor
    - **Cave:** rupture leading to granulomatous inflammation
  - Therapy
    - complete surgical excision
- 4.2 Neurogenic cysts**
- These rare anomalies are associated with congenital disorders of the eye, optic nerve, or meninges.



► **Fig. 3** Dacryops of the palpebral part of the right lacrimal gland in a 45-year-old female patient. She presented with a disturbing foreign body sensation. The cyst was resected via a transconjunctival access. **a** Clinical appearance of the cyst, picture taken while the patient looked to the left. **b** Amplified picture of the cyst (split lamp microscopy). The photos are from the archive of the University Hospital of Halle, Department of Ophthalmology.

#### 4.2.1 Congenital cystic eye [16–18]

- Synonym
    - anophthalmos with orbital cyst
  - Epidemiology
    - quite rare
  - Etiology
    - consequence of non-invagination of the primary optic vesicle
    - multifactorial
  - Location
    - central to superior in the orbit (protruded upper eyelid)
  - Clinical
    - mostly isolated, rarely syndromic (Orbeli syndrome)
    - cyst, sometimes lined by neuroglia
    - missing ocular bulb
    - possible contralateral occurrence of microphthalmos
    - mostly associated with systemic pathologies
      - agenesis of corpus callosum, basal encephaloceles, heterotopia of the gray matter
      - facial clefts, saddle nose, choanal atresia, sphenoid anomalies
      - genital malformations
      - finger malformations
      - **Cave:** possible connection to the arachnoid space
  - Therapy
    - depending on cyst size, indication for surgical excision
    - in cases of small, constant cysts, wait-and-see is justified
    - in cases of high surgical risk, cyst puncture should be considered
  - Important differential diagnoses
    - teratomas with a solid component in addition to the cystic part and showing (sometimes rapid) growth
- sequela of incomplete invagination of the primary optic vesicle
  - multifactorial
  - SOX2 gene on chromosome 3 with anophthalmos; additional associated genes (e. g., PAX6, OTX2, CHS10, FOXE3, and RAX)
  - microphthalmos/anophthalmos, isolated or in the context of syndromic malformations (> 30% syndromic; > 57% multiple congenital malformations)
  - predisposing factors
    - pregnancy-related (vitamin A deficiency, radiation exposure)
    - infections (e. g., rubella)
    - diabetes mellitus
    - substance abuse
    - medications
    - consanguinity
  - Location
    - unilateral: bilateral ratio, 2:1 for anophthalmos
    - mostly unilateral microphthalmos
    - microphthalmos with inferior cyst and protruding lower eyelid (compare delimitation of cystic eye)
  - Classification of microphthalmos/anophthalmos (► **Table 1, infobox 2**)
    - unilateral vs. bilateral
    - with or without other ocular pathologies
    - with or without systemic manifestation
    - syndromic or non-syndromic
  - Clinical
    - severe malformations and functional blindness of the contralateral eye in 12.5% of unilateral microphthalmos cases and 34.0% of unilateral anophthalmos cases
    - cerebral pathologies, mainly malformations in the area of the corpus callosum, occurring in cases of bilateral anophthalmos (70%), unilateral anophthalmos (20%), and unilateral microphthalmos (12.5%)
    - association with clefts
    - possible association with different internal diseases (cardiovascular, pulmonary, renal, gastrointestinal)
    - rare associations
      - Waardenburg syndrome (inner ear hearing loss)

#### 4.2.2 Microphthalmos, microphthalmos with cyst, and anophthalmos [16–24]

- Epidemiology
  - anophthalmos: 1–4:100 000
  - microphthalmos: 2–20:100,000; among them 2–5% with additional cysts
  - microphthalmos with cyst in 2% of cystic orbital lesions
- Etiology



► **Table 1** Different types of microphthalmos

Term	Characteristics
Simple microphthalmos (synonym, nanophthalmos)	<ul style="list-style-type: none"> <li>▪ Eyeballs symmetrically small, sagittal axis predominantly affected</li> <li>▪ Extreme hyperopia (up to + 25 dpt) and flat cornea (radius of 5.9 mm); rarely, myopic long structure</li> <li>▪ Severely reduced visual acuity</li> <li>▪ Amblyopia, nystagmus, concomitant esotropia, ptosis, enophthalmos, microcornea</li> <li>▪ Cognitive developmental delay</li> <li>▪ Secondary complications: angle-closure glaucoma, cataract, amotio choroideae et retinae</li> </ul>
Microphthalmos with coloboma, possibly with cyst	<ul style="list-style-type: none"> <li>▪ Combined with primary (deformities) and secondary (degenerative) changes</li> <li>▪ Severe microphthalmos with important coloboma formation up to anophthalmos</li> <li>▪ Cyst formation in the bulbus or orbit</li> <li>▪ Cataract</li> <li>▪ Pseudoglioma from retinal folds and mesodermal proliferation (bulbus septatus)</li> <li>▪ Persisting hyaloid vascular system and tunica vasculosa lentis</li> <li>▪ Severe malformations of the optic nerve (hypo- to aplasia, atrophy to a thin gliosis strain)</li> <li>▪ Further changes: sclerocornea, large lens (displaced in posterior direction), partly aphakia, aniridia, hypo- to aplasia of the ciliary body</li> <li>▪ Secondary changes: pseudogliomatosis, orbital cyst, inflammation sequelae</li> </ul>
Microphthalmos without confirmed coloboma	<ul style="list-style-type: none"> <li>▪ With other changes in the shape and structure of the eye</li> <li>▪ Corresponds otherwise to changes such as microphthalmos with coloboma</li> </ul>
Microphthalmos with systemic manifestation	<ul style="list-style-type: none"> <li>▪ Oculo-dento-digital dysplasia <ul style="list-style-type: none"> <li>– Dental changes, missing 2<sup>nd</sup> to 5<sup>th</sup> toes on both sides</li> <li>– Uni- or bilateral as complex or simple microphthalmos</li> </ul> </li> <li>▪ Dyscrania-pygo-phalangia <ul style="list-style-type: none"> <li>– Severe malformations of the skull, malformations of the spine, cephalocele, testicular hyperplasia</li> <li>– Coloboma microphthalmos to anophthalmos</li> <li>– Often lethal</li> </ul> </li> </ul>

Further occurrence of microphthalmos: dyscephalia oculo-mandibulofacial Ullrich-Fremery-Dohna, type Francois, dyscephalia according the Hallermann-Streiff, dysplasia oculo-vertebralis van der Hoeve syndrome, Potter syndrome, Fanconi syndrome.

- congenital ectodermal dysplasia
- Therapy
  - indication for surgical excision depending on cyst size
  - in cases of small, stable cysts, wait-and-see is justified
  - in cases of high surgical risk, cyst puncture possible
  - enlargement of the hypoplastic orbit with volume expanders
- Important differential diagnoses
  - teratomas, cryptophthalmos (**infobox 3**) and bulbar phthisis as degenerative (post-inflammatory) alteration (bulbus quadratus)

#### Note

A continuum has been described, from sighted, severely hyperopic microphthalmos to anophthalmos. The orbit with adnexa structures (eyelids and extraocular muscles) may show near-normal development. Bulbar rudiments that are in part microscopically small can be present so that true anophthalmos can be extremely difficult to define. Some authors diagnose (true, complete) anophthalmos only when histological examination of the orbital contents confirms the absence of ocular tissue. This gray area is why the term 'clinical anophthalmos' or 'incomplete anophthalmos' was coined.

#### INFOBOX 2

##### Anophthalmos

- Complete absence of ocular tissue
  - primary anophthalmos – development of neither eye nor orbit
  - secondary anophthalmos – non-viable malformations in combination with cranial malformations
  - degenerative anophthalmos – ocular primordium present but degenerated
- Frequently hypoplastic and thus size-reduced orbit but with enormous self-differentiation capacity
  - agenesis
  - complete anophthalmos, also secondarily possible
  - presence of mesodermal tissue
  - presence of ectodermal tissue
  - presence of meso- and ectodermal tissue
- Possibly involving malformations of the visual pathway and agenesis of the corpus callosum
- Malformations of the skull, meningoceles, orbital dermoids, deafness

## INFOBOX 3

## Cryptophthalmos

- Absence of eyelids in combination with microphthalmos/anophthalmos
- Hypoplastic orbit
- Eyebrow hairiness incomplete or completely missing
- Mostly bilateral
- In cases of unilateral occurrence, severe malformations of the orbit and of the contralateral eye
- Orbital roof absent, malformation of the sphenoid bone, auricular anomalies, syndactyly, facial clefts, laryngeal atresia, anal atresia, genital malformations, meningo-encephaloceles, hydrocephalus, persistent craniopharyngeal duct (orbital cyst formation from residues of Rathke's pouch), pituitary gland disorders, adrenal aplasia

## 4.2.3 Orbital cephaloceles [16, 25–26]

- Epidemiology
  - cephaloceles: overall 0.8–5:10,000; occipital in > 70% of cases
  - overall < 1% of orbital masses in children
- Etiology
  - deficient separations of neuroectoderm and ectoderm
  - persisting connections between the neurocranium and the orbit
- Classification
  - anterior (frontal bone, ethmoid bone, lacrimal bone, maxilla)
  - posterior (sphenoid bone)
- Clinical
  - hypertelorism, pulsatile exophthalmos
  - painless (pulsatile) tumor
  - frontal sinus aplasia
  - rarely bilateral, but if so, then associated with hypertelorism
  - differentiation between meningoceles (meninges) and meningoencephaloceles (meninges and brain tissue) depending on contents
  - further skull anomalies possible (sphenoid), hydrocephalus
  - association with neurofibromatosis
  - **Cave:** possible secondary ulceration and infection of the cephaloceles
- Therapy
  - excision and closure of the bone defect
  - duraplasty

## Note

Generally, these lesions are present at birth but sometimes will manifest only later in life (especially when located dorsally).

## 4.2.4 Other neurogenic cysts [27]

Primary arachnoid cysts may be found in combination with ipsilateral ocular colobomas. Nerve sheath cysts as a further entity are associated with other anomalies of the central nervous system (CNS).

## 4.3 Congenital tumors and tissue ectopy

## 4.3.1 Dermolipoma [28]

- Epidemiology
  - about 2% of orbital tumors in children
- Etiology
  - choristoma
  - ectopic ectoderm disseminated as epidermal tissue of the eyelids in the area of the conjunctiva and frequently in an intraorbital direction
- Location
  - temporal palpebral area
  - rarely along the inferior and superior conjunctival fornix
- Clinical
  - often asymptomatic
  - possibly keratinizing
  - partly bearing hair follicles
  - foreign body sensation
- Therapy
  - surgical excision with preservation of the conjunctiva, lacrimal gland, and exterior ocular muscles (lateral rectus muscle) if desired (esthetic) or in cases of irritation of the ocular surface
  - superficial removal without preparation into the depth of the orbit is sufficient in most cases
- Important differential diagnoses
  - lymphoma
  - orbital fat hernia (► Fig. 4)

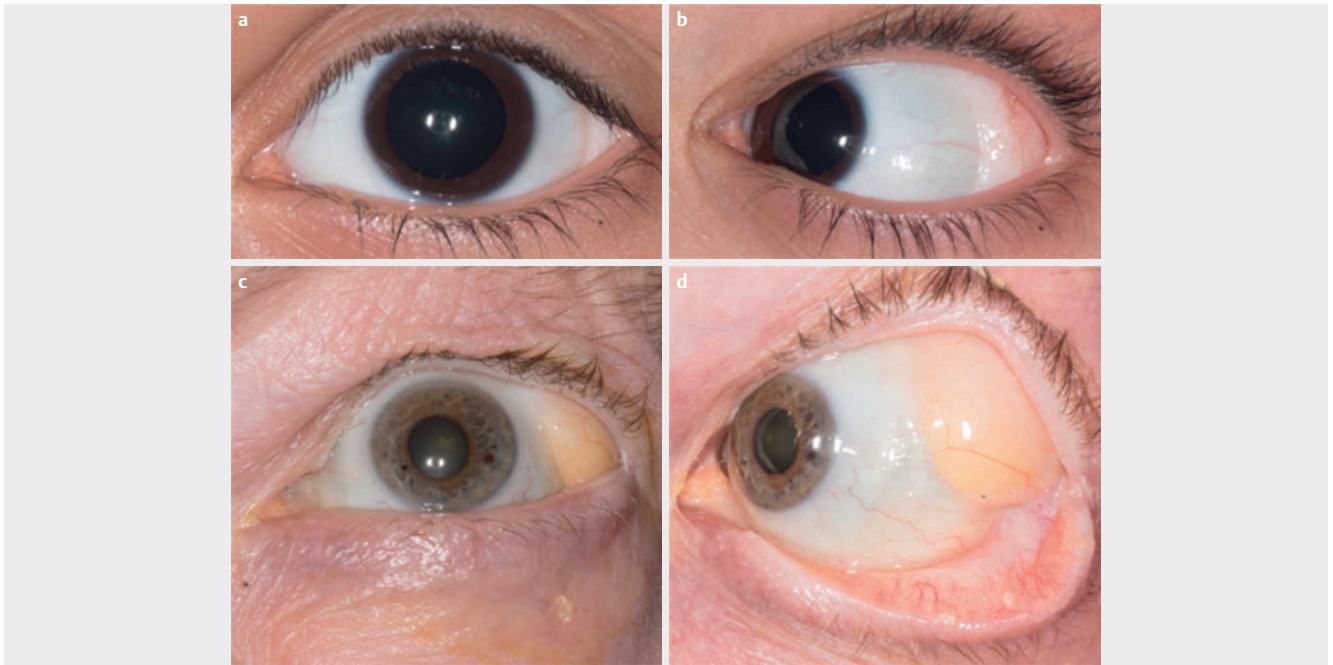
## 4.3.2 Ectopic lacrimal gland tissue and other tissue ectopy [29–30]

Accessory lacrimal gland tissue is regularly found in the area of the conjunctival fornices (Wolfring's and Krause's glands). In the posterior areas of the orbit, this tissue is rarely found. However, it may induce chronic scarring inflammation where it occurs that requires surgical intervention.

In addition, heterotopic cranial tissue and cartilage structures have been described in the orbit.

## 4.3.3 Orbital teratoma [31–33]

- Epidemiology
  - 6.6% of pediatric tumors, mostly located outside the orbit
  - quite rare orbital occurrence
- Etiology
  - neoplasm of two or all three germ layers (pluri- to totipotent embryonic stem cells)
- Clinical
  - progressive, unilateral, mostly cystic tumor
  - proptosis
  - possible enlargement of the bony orbit by a factor 2 or 3
  - strongly heterogeneous tissue



► **Fig. 4** Comparison of a dermolipoma (upper row) and orbital fat herniation (lower row). **a** Dermolipoma in a 12-year-old child, photo taken with patient looking straight ahead. **b** Dermolipoma, picture taken in maximal adduction, the pigmentation and hairs are visible. **c** Orbital fat herniation in a 55-year-old patient, picture taken with the patient looking straight ahead. **d** Picture of the orbital fat herniation in maximal adduction. Additional findings revealed a floppy eyelid (with obstructive sleep apnea syndrome). The photos are from the archive of the University Hospital of Halle, Department of Ophthalmology.

- complete teratoma as orbital fetus-in-fetu (orbitopagus parasiticus)
- incomplete second fetus with parts of a spinal cord
- teratoma with evidence of all three germ layers
- dermoid tumor with evidence of two germ layers
- Therapy
  - surgical excision
- Important differential diagnoses
  - dermoid, rhabdomyosarcomas, or vascular anomalies
  - **cave:**
    - malignant teratoma of the orbit (in 2% of cases)
    - intracranial extension

#### 4.4 Bone anomalies and mesodermal defects

##### 4.4.1 Accessory bones and sutures, osseous variations, aberrant foramina [34–36]

- Epidemiology
  - some types are frequent (duplication of the fronto-zygomatic suture in 7 of 400 skulls)
  - significant regional differences
  - found in about 1–2% of the orbits
- Etiology
  - disturbed ossification
  - classification into variations and congenital deformities
  - orbit mostly self-determined regarding development (independently from the eye)
  - anatomical pathways are only secondarily surrounded by bone; nerve and vessel duplications precede bone variations

- Clinical
  - partly clinically completely unapparent
  - association with dysostoses of the skull
  - exophthalmos
  - facial asymmetry
  - hyper- or hypotelorism

##### 4.4.1.1 Examples of bone variations [34]

- Accessory sutures and bone fragments (e.g., duplication of the fronto-zygomatic suture, fragmented zygomatic bone with ossiculum infraorbital marginale)
- Missing involvement of the maxilla in the development of the inferior orbital margin (incidence of 1:2250)
- Malformations of the ethmoid bone where the frontal bone forms the medial orbital wall
- Frequent dehiscence of the lamina papyracea
- Incomplete presence up to complete absence of the lacrimal bone; variations of the lacrimal hamulus and thus variations of the lacrimal sac and nasolacrimal duct
- Accessory ossicles in the area of the frontal maxillary process
- Maxillary hypoplasia
- Duplication of the anterior lacrimal crest

##### 4.4.1.2 Examples of foramina variations [34]

- Supra- and infraorbital foramina in form of channels, incisions/sulcus, multiple primordia
- Duplication of the optic canal/missing optic foramen in cases of anophthalmos
- Up to four-fold primordium of the zygomatico-facial foramen

- Up to five-fold primordium of the infraorbital foramen (double primordium in > 10%)
- Trochlear spine (simple, double, or as ring)
- Bony separation of the inferior orbital fissure by an accessory bone bridge

#### 4.4.1.3 Examples of wall defects [34]

- Unilaterally missing development of the frontal bone and the maxilla (frontal lobe covered only by meninges and skin; clinically also without presence of cephaloceles with downward displacement of the eyeball and divergence)
- **Cave:** association with cyclopia and arhinencephaly, rare coincidence with phacomatoses, e. g., in cases of neurofibromatosis (malformations in the area of the sphenoid bone)

#### 4.4.1.4 Examples of wall dehiscence [34]

- Infantile and sometimes senile physiological occurrence
- Especially in the area of the maxilla and the ethmoid bone
- More rarely in the area of the lacrimal bone, palatine bone, or sphenoid bone
- **Cave:**
  - optic canal variation because of absent parts of bone surrounding the optic nerve and the resulting direct communication between the dural sheath and sphenoid mucosa
  - association of orbital varices with bone dehiscence or misinterpretation of phleboliths

#### 4.4.2 Cribra orbitalia [34–35]

Thinning of the orbital roof with exposed diploe and contained venous plexus because of a bone development disorder (differential diagnosis of vitamin D deficiency, anemia).

#### 4.4.3 Familial hypoplasia of the orbital margin (Urrets-Zavalía syndrome) [34]

- Epidemiology
  - extremely rare (< 1:1 000 000; described in two families to date)
- Etiology
  - genetic agenesis of the orbital margin and parts of the ocular adnexa structures
  - dominant inheritance (high penetration, constant expression)
  - involves tissue of the paraxial and visceral mesoderm
- Clinical
  - missing bony orbital frame
  - hypoplasia of the eyelid skin and palpebral tarsus
  - variable defects with disorders of the draining nasolacrimal pathways, eyelid coloboma, vertical strabismus

#### Note

Accessory bones and sutures or aberrant foramina often have no pathological significance but sometimes must be considered in the context of sinus, orbital, and lacrimal duct surgery.

#### 4.4.4 Facial clefts, facial dystrophy, craniofacial dysostoses, and malformations of the skull [34, 37–38]

Complex facial deformities originating from a disorder of embryogenesis in the area of the first and second pharyngeal arches.

##### 4.4.4.1 Rare facial clefts (including Tessier clefts) [37–39]

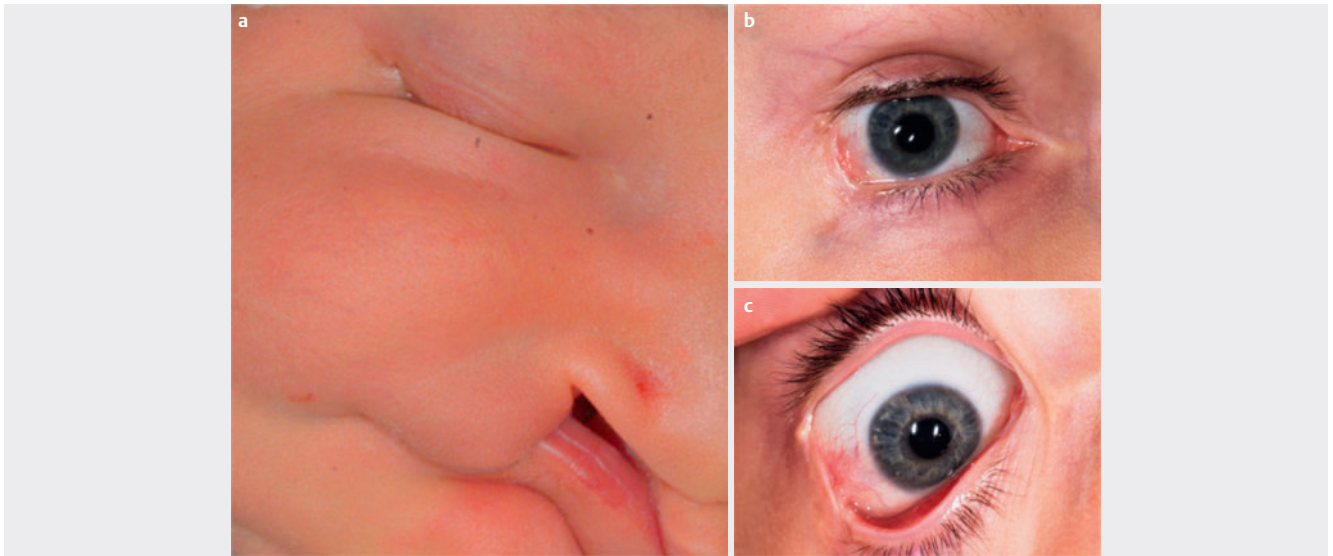
- Epidemiology
  - 1–5:100 000
- Etiology
  - lack of fusion of embryonic tissues of the first pharyngeal arch (association with malleus and incus malformations)
  - early developmental stage (embryonic weeks 5–8)
  - in later stages because of umbilical cord trauma (atypical cleft, amniotic band syndrome)
- Typical type
  - oro-ocular or oro-orbital facial cleft
  - transverse and diagonal clefts
  - clinical
    - numerous manifestations
    - partly medial eyelid colobomas
- Atypical type
  - oro-temporal facial cleft
  - clinical
    - temporal eyelid colobomas
    - association with dermoids, ear adnexae, other facial deformities (cleft lip and palate)
    - anophthalmos, microphthalmos, uveal coloboma

Tessier clefts [38, 40]

- 15 types (0–14), possible course from the maxilla via the orbit to the frontal bone
- Groups
  - midline clefts
  - paramedian clefts
  - orbital clefts
  - lateral clefts (► Fig. 5)
- Therapy
  - plastic reconstruction by maxillofacial surgeons to close the soft tissue and bone defect, orthodontic treatment
  - phoniatrics/pedaudiological involvement
  - if needed, oculoplastic intervention for eyelid correction or coloboma closure

##### 4.4.4.2 Facial dystrophy, craniofacial microsomia [37, 41]

- Epidemiology
  - 1:3000 to 1:5000
- Etiology
  - disturbed embryogenesis (concerning the first pharyngeal arch)
- Clinical
  - jaw bones
    - asymmetric midfacial hypoplasia
    - ankyloses
    - micrognathia
  - eye
    - dermoid (epibulbar)
    - upward or downward displacement of the globe
    - anophthalmos/microphthalmos



► **Fig. 5** Tessier orofacial cleft 6. **a** Postnatal photo with an untreated cleft lip and palate and coloboma at the temporal lower lid of the right eye. **b** Picture taken at the age of 8 years with patient looking straight ahead; the misinsertion of the lateral eyelid support structures of the lower eyelid to the temporal-inferior orbital edge is seen. **c** Picture taken with patient looking downward; symblepharon must be considered. The photos are from the archive of the University Hospital of Halle, Department of Ophthalmology.

- eyelid coloboma
  - mouth
    - macrostomy (clefts)
    - facial clefts
  - skeletal system
    - changes in the spine
  - cranial nerves
    - facial nerve palsy
    - sensory hearing loss
    - palatal lift disorder
    - ocular muscle paresis
  - ear
    - ear adnexae
    - microtia/anotia
    - auricular canal atresia
    - conductive hearing loss
  - **Cave:** rare association with tetralogy of Fallot, ventricular septum defect, transposition of the major vessels, aortic arch anomalies, kidney malformations (absence of one kidney, duplicate ureter, renal ectopy), hydronephrosis, hydroureter, anomalies of the extremities (ulna, radius), microcephaly, encephalocele, hydrocephaly, corpus callosum hypoplasia, Arnold-Chiari malformation, holocencephaly
  - present as syndromes: VA(C)TER(L) – **v**ertebral **a**nomalies, **a**nal atresia, **c**ardiac anomalies, **t**racheoesophageal atresia, **r**enal anomalies, and **l**imb anomalies; or CHARGE – **c**oloboma, **h**eart, **a**tresia choanae, **r**etardation of growth and development and **g**enitourinary and **e**ar anomalies
  - Types (► **Table 2**)
    - otocephaly
    - mandibulo-facial dysostosis
    - oto-mandibular dysostosis
    - oculo-auricular dysplasia
    - mandibulo-oculo-facial dyscephaly
    - oculo-vertebral dysplasia
    - microgenia and glossoptosis
- #### 4.4.4.3 Facial (hemi)atrophy (Parry-Romberg) [42–43]
- Synonym
    - progressive facial trophoneurosis
  - Epidemiology
    - 1:700 000
    - females more frequently affected than males
  - Etiology
    - uni- or rarely bilateral disorder of the soft tissue and bone because of missing/insufficient innervation (cranial nerves V and VII)
  - Clinical
    - slowly progressive, generally unilateral atrophy of the facial soft tissue including muscles as well as some of the bony-cartilaginous structures
    - facial asymmetry
    - highly variable disease activity over 2 to 20 years until self-limiting stagnation
    - malformation of the external auricle (misplaced ear, auditory canal atresia, adnexae, reduced ossicles, small tympanum)
    - unilateral micrognathia
    - hypoplastic mastoid
    - atrophic facial muscles, yellowish skin (possible hypo- and hyperpigmentation), lanugo hairiness with otherwise alopecia
    - temporally sloping axis of the eyelid, enophthalmos, lagophthalmos, pseudoptosis (differential diagnosis of associated Horner's syndrome)

► **Table 2** Types of facial dystrophy

Term	Described by	Laterality	Characteristics
Otocephaly	St. Hilaire	Bilateral	<ul style="list-style-type: none"> <li>▪ Aplasia or severe hypoplasia of the mandible</li> <li>▪ Deformity of the tongue, nose, and ears</li> <li>▪ Transversal facial cleft</li> <li>▪ Anophthalmos</li> </ul>
Mandibulo-facial dysostosis	Franceschetti, Zwahlen, Klein, Treacher-Collins	Bilateral	<ul style="list-style-type: none"> <li>▪ Eyelid coloboma (after temporally declining lid axis)</li> <li>▪ Hypoplastic facial bones (maxilla/mandible)</li> <li>▪ Deformities of the external ear and partly of the middle ear</li> <li>▪ Macrostomia, high palate</li> <li>▪ Fistula between ear and mouth</li> <li>▪ Hairline displaced to the cheek</li> <li>▪ Facial clefts, skeletal deformities</li> <li>▪ Rarely: incomplete and unilateral cases</li> </ul>
Oto-mandibular dysostosis	Francois and Haustrate	Unilateral	<ul style="list-style-type: none"> <li>▪ Agenesis/aplasia of the mandible</li> <li>▪ Malformation of the mandibular joint</li> <li>▪ Malformation of the external ear</li> <li>▪ Atresia of the external auditory canal</li> <li>▪ Ear adnexa</li> <li>▪ Fistula between mouth and tragus</li> <li>▪ Transversal facial cleft</li> <li>▪ Cleft lip and palate</li> <li>▪ Dental malalignment</li> </ul>
Oculo-auricular dysplasia	Goldenhar	Unilateral	<ul style="list-style-type: none"> <li>▪ Epibulbar dermoids</li> <li>▪ Ear adnexa</li> <li>▪ Ear fistula</li> <li>▪ (mainly) mandibular hypoplasia</li> <li>▪ Coloboma of the upper eyelid</li> <li>▪ Macrostomia</li> <li>▪ Microphthalmos</li> <li>▪ Neural, muscular, and skeletal anomalies</li> </ul>
Mandibulo-oculo-facial dyscephaly	Hallermann and Streiff, Ullrich and Fremerey-Dohna	Unilateral	<ul style="list-style-type: none"> <li>▪ Mandibular hypoplasia (mainly)</li> <li>▪ Nasal anomaly</li> <li>▪ Congenital cataract, microphthalmos, microcornea</li> <li>▪ Microsomia</li> <li>▪ Dental anomalies</li> <li>▪ Hypotrichosis (eyebrows)</li> <li>▪ Skin atrophy</li> </ul>
Oculo-vertebral dysplasia	Weyers and Thier	Unilateral	<ul style="list-style-type: none"> <li>▪ Maxillary dysplasia</li> <li>▪ Facial asymmetry</li> <li>▪ Deformity of the maxillary alveolar process</li> <li>▪ Occlusion disorders</li> <li>▪ Anophthalmos, cryptophthalmos</li> </ul>
Microgenia and glossoptosis	Pierre Robin		<ul style="list-style-type: none"> <li>▪ Mandibular hypoplasia</li> <li>▪ Glossoptosis</li> <li>▪ Cleft palate</li> <li>▪ Retinal detachment</li> <li>▪ Cataract</li> <li>▪ Microphthalmos</li> <li>▪ Glaucoma</li> <li>▪ High myopia</li> </ul>

- exposed facial nerve in the middle ear
- atrophy of soft palate and tongue (speaking and swallowing disorders)
- saber-like scleroderma along the medial orbital skin
- heterochromia, blepharophimosis, coloboma, oculo-motor paresis, partly nystagmus
- **Cave:**
  - rare hemiatrophy of the entire body
  - frequent occurrence of orbital tumors (among others neurinomas)
- Therapy

- systemic medication (including glucocorticoids, cyclophosphamides, methotrexate) and local therapies (among others PUVA, botulinum toxin, phototherapy)
- surgical therapy options for stabilization or reconstruction in cases of periocular changes
- Important differential diagnoses
  - facial hemihypertrophy
    - unilateral hypertrophy of one side of the body
    - exophthalmos with megalophthalmos
  - congenital facial nerve palsy (Möbius syndrome)

#### 4.4.4.4 Craniofacial dysostoses [44–48]

Extreme heterogeneity of diseases with different nomenclature

- Epidemiology
  - syndromic and non-syndromic
  - 3–10:10,000
  - syndromic types occur 10–50 times more rarely; extremely rare types < 1:1,000,000 (e. g., Boston syndrome)
  - most frequent syndromes
    - Crouzon syndrome
    - Pfeiffer syndrome
    - Saethre-Chotzen syndrome
  - rare syndromes
    - Boston syndrome
    - Cole-Carpenter syndrome
    - Herrmann-Opitz craniosynostosis
    - craniosynostosis, Philadelphia type
    - cardio-cranial syndrome, Pfeiffer type
    - Jackson-Weiss syndrome
    - Hunter-McAlpine craniosynostosis
    - Lopez-Hernandez syndrome
    - Baller-Gerold syndrome
- Etiology
  - primordial disorder of the bone, premature closure of affected sutures
  - increased volume expansion in one direction because of expansive cranial growth and blockage in the other direction (Virchow's rule: blockage perpendicular to the synostosis and compensatory growth along the synostosis)
  - metopic suture (physiologically open up to the 8th month of life), sagittal suture, lambdoid suture, coronal suture not open until adulthood
  - manifestation of the disease typically in the 1<sup>st</sup> to 4<sup>th</sup> years of life
- Clinical
  - skull deformity with or without orbital involvement
  - exophthalmos, hyper- and hypotelorism, strabismus
  - increased intracranial pressure (headaches, papillary edema, optic atrophy)
  - encephalocele
  - syndactyly
  - ear malformations (auricle, external auditory canal, middle ear)
  - association with metabolic disorders (hyperthyroidism, vitamin D-resistant hypophosphatemia, mucopolysaccharidosis [associated with dysmorphia of the head, formerly

called gargoylism], and mucopolidosis), chondro- and osteodystrophies (e. g., achondroplasia)

#### 4.4.4.4.1 Cleidocranial dysostosis [44, 49]

- Hypoplastic dysostosis of the skull with brachy- or platycephaly (► Fig. 6)
- Dental anomalies
- Pseudoarthrosis, hypoplasia or aplasia of one or both clavicles
- Hypoplasia of the nasal bone and maxilla
- Elevated palate
- Possible deformities of thorax, pelvis, and extremities
- Spina bifida

#### 4.4.4.4.2 Oxycephaly (acrocephaly, tower skull) [44–48]

- Male:female ratio, 4:1
- Vertical elongation of the skull
- Transverse and sagittal shortening
- Coronary and facial synostoses
- Reduction of the skull base
- Prominent nose, hypoplastic maxilla, narrow palate
- Flat orbits with small volume
- Supraorbital pronounced exophthalmos, strabismus, motility disorders, nystagmus, exposition keratopathy, mild hyper-telorism
- Papillary edema, optic atrophy
- Retinal vascular stasis, tortuosis vasorum
- Eyelid edema
- Rare associations: cataract, corneal dystrophy, eyelid coloboma, orbital encephaloceles
- Often minor impairment of intelligence (**Cave:** apparent intellectual disability often possibly a consequence of psychosocial stigmatization and not biological)
- Classic syndrome: Apert syndrome (acrocephalo-syndactyly)
- Oxycephaly with exophthalmos, exposition keratopathy, ophthalmoplegia, papillary edema, optic atrophy
- Syndactyly (second to fourth fingers/toes); synarthroses (shoulder, elbow)

#### 4.4.4.4.3 Scaphocephaly (sphenocephaly) [44–48]

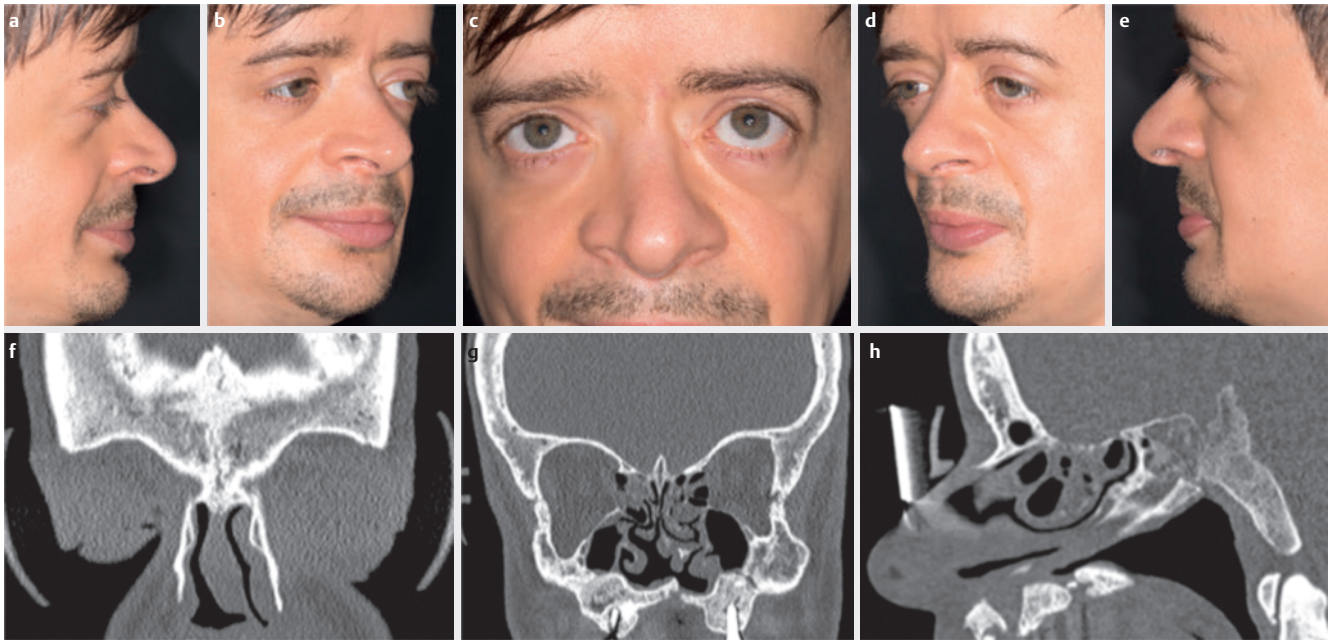
- Synostosis of the sagittal suture
- Long small shape of the head
- Low width of the skull with hypotelorism
- Sagittal synostosis

#### 4.4.4.4.4 Brachycephaly [44–48]

- Synostosis of the coronal or lambdoid sutures
- Short, broad skull
- Intermediate between scaphocephaly and oxycephaly

#### 4.4.4.4.5 Dolichocephaly [44–48]

- Prominent frontal skull
- Coronal, sagittal, and/or lambdoid synostoses
- Coronal representative: Crouzon syndrome
  - prominent front, typical shape of the nose (parrot beak)
  - hypoplastic maxilla, prognathism, malpositioned teeth, elevated palate, partly with cleft formation



**▶ Fig. 6** Dysotosis cleidocranialis in a 32-year-old male patient. **a–c** Clinical pictures of the midface in frontal view (**c**), 45° (**b** and **d**) as well as lateral view (**a** and **e**), hypoplastic midface (caved glabella region), temporally declining lid axes with mild exophthalmos and hypertelorism. **f–h** CT images (soft tissue window, coronary and sagittal planes); bilaterally hypoplastic frontal (**f**) and maxillary sinuses (**g**) as well as a multiply operated hard palate and changes in the area of the frontal base (**h**). The clinical photos (**a–h**) are from the archive of University Hospital of Halle, Department of Otolaryngology (courtesy of the Department of Diagnostic Radiology, University Hospital of Halle, Professor and Chair: Prof. Wohlgemuth).

- diverging strabismus, lacrimal duct stenosis, papillary edema, opticus atrophy, exposition keratopathy, ocular coloboma, glaucoma, ectopia lentis
- ear anomaly (auditory canal atresia, auricular anomaly)

#### 4.4.4.4.6 Plagiocephaly [44–48]

- Sagittal asymmetry
- Unilateral synostosis of different sutures
- Classified into:
  - anterior type
    - unilateral synostosis of the coronal suture
    - hypoplastic ipsilateral orbit
    - orbital roof with declining axis in temporal direction
  - posterior type
    - closure of the lambdoid suture
    - to be delimited against acquired positional plagiocephalus by differential diagnosis

#### 4.4.4.4.7 Hemicraniosis [44–48]

- Prominent frontal bone, parietal bone, and zygomatic bone
- Significant asymmetry
- Exophthalmos and opticus atrophy

#### 4.4.4.4.8 Trionocephaly [44–48]

- Frontal cranial dysplasia (synostosis of the metopic suture) with occipital compensation
- Also with coronary synostosis
- Hypotelorism
- Opticus atrophy
- Narrow anterior cranial fossa

- Hypoplastic ethmoid sinus

#### 4.4.4.4.9 Platycephaly (clinocephaly) [44–48]

- Increased posterior cranial fossa with overriding of the cervical spine
- Synostosis of the superior sutures
- Therapy:
  - conservative by changing the skull position, i. e., through physiotherapy or helmet wearing
  - correction or prevention of increased intracranial pressure
  - treatment of the head deformity (functional/psychosocial indication)
  - surgery techniques:
    - open or minimally invasive suturotomy
    - suturotomy and removal or remodeling of single bone fragments, if needed as fronto-orbital advancement
    - cranial distraction

#### 4.4.4.5 Hypertelorism [37, 44–45]

- Interorbital distance of > 30 mm
- Association with craniosynostosis or cleft formation in the maxillary and facial area, but also isolated
- Rare occurrence of frontal or frontobasal encephaloceles
- Classification
  - primary
    - morphogenetic (habitual) because of disproportional growth
    - embryonic because of developmental disorders (e. g., Apert and Crouzon syndrome) with nasal cleft (rarely duplicate nasal septum, dermoid)



- secondary
  - developmental disorder attributable to environmental factors (trauma, encephaloceles, diseases of the cartilage or bone)

#### 4.4.4.6 Median cleft face syndrome [50]

- Synonym/manifestation
  - cyclopia, holoprosencephaly, arhinencephaly, otocephalic anomalies
- Epidemiology
  - 1:16 000 live births
- Etiology
  - complex cerebral malformation with missing hemisphere separation
  - cyclopia from disturbed balance of excitation and inhibition processes of development and concerning the entire cranial position
- Clinical
  - sometimes presence of proboscis as rudiment of the nasal apparatus
  - malformations such as completely missing eyes (anophthalmos) or face (aprosoposus, i. e., missing eyes and olfactory and gustatory organs) as well as presence of one (cyclopia or synophthalmia) via three (diprosopus triophthalmus, cephalotheracopagus) or four separated eyes (tetrophthalmus) possible
  - starting at the optic nerve, possible separated presentation of both eyes and orbits from posterior in anterior direction (for example, a single cornea with otherwise duplicated tissues)
  - many clinical variations with fluent transition, e. g., median facial clefts, microphthalmos, anophthalmos, cyclopia, hypotelorism (facial dysmorphism correlating with cerebral anomaly)
  - isolated or in the context of syndromes (including CHARGE, Smith-Lemli-Opitz syndrome, Rubinstein-Taybi syndrome, Meckel syndrome, Lambotte syndrome, Steinfeld syndrome)
  - complications
    - neurological: epilepsy, hydrocephalus, developmental intellectual disability, hypotonia, spasms
    - craniofacial: microcephaly, hypo- or hypertelorism, median and lateral clefts (concerning lips, maxilla, and palate), arhinia, hypoplasia of the piriform aperture
    - endocrinological: diabetes insipidus, growth hormone deficiency, hypoplasia of the adrenal cortex, hypogonadism
    - otomotor dysfunction: speaking and swallowing disorders, gastroesophageal reflux, necessity for gastrostomy
    - vegetative dysfunctions: temperature regulation, heart and respiratory rate control
  - life expectancy
    - unfavorable prognosis, lethal in early childhood (mean mortality at age 4 years; 15 % between ages 10 and 19 years)
- Therapy

- symptom-based

### 4.4.5 Developmental disorders of the bones

#### 4.4.5.1 Fibrous dysplasia [51]

- Etiology
  - mesenchymal defect of the bone spongiosa and the bone marrow and replacement by fibrous tissue
- Clinical
  - subtypes:
    - affecting only one bone (monostotic)
    - affecting several bones (polyostotic)
    - McCune-Albright syndrome (severest type of microsomia, endocrine and pigment disorders of the skin)
  - possibly affecting skull
  - in cases of cranial location, orbital involvement in >40 %
  - atypical facial pain and headache
  - sinusitis
  - hearing disorders
  - exophthalmos
  - facial asymmetry
- Therapy
  - surgical decompression (optic channel, orbit) in cases of clinical complaints such as optic neuropathy
  - surgical excision of involved areas with consideration of functional aspects (curative surgery is not possible; basically, a benign disease)
  - **Caution:** radiation therapy contraindicated because of the high risk of malignant transformation

#### 4.4.5.2 Osteopetrosis [52]

- Epidemiology
  - 1:250 000 to 5:100 000 (dominant inheritance)
- Etiology
  - disturbed differentiation of osteoclasts
  - increasing bone substance with reduced stability
- Clinical
  - macrocephaly, craniofacial dysmorphism
  - fractures, microsomnia
  - nerve compressions (blindness, deafness, facial palsy)
  - osteomyelitis
  - hydrocephalus, pituitary hypoplasia, cerebral demyelination
  - choanal atresia
  - dental anomalies, double tooth series, palatal cleft, caries
  - disturbed calcium balance, secondary hyperparathyroidism
  - retinal atrophy, cataract
  - disorder of the hematopoiesis with risk of pancytopenia, hepatosplenomegaly
  - manifestations; types:
    - autosomal recessive osteopetrosis (ARO) (malignant type)
    - neuropathic type of ARO
    - association with renal tubular acidosis (i. e., RTA)
    - X-linked osteopetrosis with lymph edema, anhidrotic ectodermal dystrophy, and immune deficiency (i. e., OLE-DAID)

- common variable immune deficiency (i. e., CVID)
- leukocyte adhesion deficiency syndrome (i. e., LAD-III)
- autosomal dominant type (Albers-Schönberg disease)
- pyknodysostosis
- dysosteosclerosis
- osteopoikilosis (with occurrence of connective tissue naevi as Buschke-Ollendorff syndrome)
- osteopathia striata (with or without cranial sclerosis)
- Therapy
  - symptomatic, depending on the manifestation of the functional disorder or complication (e. g., surgical decompression of the optic nerve)
  - multi- and interdisciplinary approach
  - vitamin D substitution
  - transfusion if needed

#### 4.4.5.3 Cherubism [53]

- Etiology
  - different inheritance pathways, probably mainly dominant with high penetration
  - cystic proliferation of the mandible and maxilla
- Clinical
  - disease onset in early childhood (2nd to 5th years of life)
  - various courses, sometimes clinically almost undetectable
  - prominent chin and cheeks, irregular tooth position
  - eyes displaced in upward direction, proptosis, diplopia
  - coarse bone swellings
  - occasional association with regional lymphadenopathy
  - spontaneous involution after bone growth (at about age 30 years)
  - **Cave:** dysarthria, dysphagia, and dyspnea possible
  - association with Ramon syndrome, neurofibromatosis type 1, and fragile X syndrome
- Therapy
  - surgical resection of the affected region under functional aspects
  - **Cave:**
    - possible activation of disease by surgery
    - radiotherapy contraindicated (osteoradionecrosis, malignancy induction)

#### Note

**Cleft formation and other craniofacial malformations show a broad variation. They may appear as isolated or as syndromic findings. Clinically, the courses are sometimes highly complex with vital risks. The early detection and treatment of these complication-associated conditions are the major challenge in this group of diseases. The interdisciplinary approach is multimodal; often several surgical interventions are necessary.**

## 4.5 Conclusion

In cases of structural anomalies of the orbit, orbital bone malformations have to be delimited from ocular pathologies. The first category encompasses mainly craniosynostoses that may occur as isolated findings or in the context of syndromes. Ocular malformations may be associated with orbital lesions (e. g., Goldenhar syndrome) or lead to them. The development of the orbit can occur

completely independently from ocular organogenesis. Dermoids are the most frequently observed congenital lesions of the orbit. The major challenges are complications that require the attention of members of the neurological and/or neurosurgical disciplines (e. g., encephaloceles, hydrocephalus).

The acquired structural anomalies include mainly posttraumatic changes or sequelae of surgeries and/or radiation. These changes are highly variable and occur rather frequently.

Knowledge of possible structural changes is essential for successful therapy. The observation of the close neighborhood of the orbit to the skull is extremely important. Regarding diagnostics, appropriate imaging procedures for further topographic assessment are essential. For therapy, often an interdisciplinary exchange with neuro- and ophthalmic surgeons is necessary, initiated by the primarily treating discipline (usually ENT/maxillofacial surgery).

## 5. Inflammatory Diseases of the Orbit

There are many inflammatory lesions of the orbit. Below, an overview is given with classification into infectious and non-infectious types.

### 5.1 Infectious orbital inflammation

Infectious cellulitis is the most frequent cause of orbital inflammation. It develops mainly from inflammatory processes of the paranasal sinuses, face, oropharynx, and ocular adnexa structures, but sometimes can arise because of foreign bodies or septic dissemination. The causes are a large spectrum of bacterial and viral pathogens, fungi, and parasites.

#### 5.1.1 Bacterial inflammation (orbital cellulitis)

The most frequent origins of infectious orbital inflammation are orbital complications of purulent sinusitis, which will not be dealt with in this article on rare orbital diseases. For reviews of their classification, pathogenesis, diagnostics, and management, see [54–67].

The identification of rare pathogens may be a challenge but is crucial for affected patients because the diseases can entail a high local and systemic morbidity, independent of their rarity. Opportunistic infections must be considered especially in immunocompromised and previously affected patients [58]. The keys to successful management are a high index of suspicion, prompt diagnosis, and adequate therapy of the underlying disease.

##### 5.1.1.1 Tuberculosis

In recent years, the incidence of tuberculosis has increased because of resistant strains and the distribution of immunosuppressant agents.

- Pathogenesis: in cases of tuberculosis, the involvement of the orbit may occur via two different pathways:
  - hematogenic dissemination with two manifestation types in the orbit:
    - periostitis (more frequent): slow course with cold abscess, sequestrs, and fistulas; mainly young patients affected; mostly located in the zygomatic bone
    - tuberculoma (rarer): infiltrative orbital mass, sometimes associated with neurosensory deficit

- direct spread from contagious neighboring structures (paranasal sinuses or lacrimal gland); causes necrotizing infiltrative lesions, partly with cutaneous fistulas [60]
- Clinical
  - painful movement impairment, no intraocular lesions, rather non-specific symptoms leading to late diagnosis
  - very rarely also atypical mycobacteria (mycobacterium hominis; mycobacterium avium)
  - **Cave:** especially in cases of cold abscess, wet cavities or (very rarely) complicated sphenoid osteomyelitis because of optic neuropathy, clinical suspicion often more important than blood culture for diagnosis [58]
- Diagnostics
  - biopsy with caseating granulomas, culture of acid-proof rods (gold standard) is difficult [61]
  - additional diagnostics: skin test (tuberculin test) and serology (interferon- $\gamma$  release assay [IGRA] as well as molecular pathological PCR diagnostics from biopsies) [60]
- Therapy
  - timely tuberculostatic triple therapy (isoniazid, rifampicin, ethambutol) by specialists (not only after evidence of positive culture; the associated constellation of clinical and molecular pathological findings is crucial)
  - indication of surgical intervention for symptom relief, e. g., in cases of vision loss [58]
  - in cases of interaction between HIV and tuberculosis, sometimes complex management [60]

### 5.1.1.2 Syphilis

This venereal disease, which currently affects mainly immunosuppressed patients and men who have sex with men, is caused by *Treponema pallidum* and can involve the orbit because of post-primary hematogenous dissemination. In the orbit, it manifests as painful periostitis or a soft tissue lesion after latency [61].

- Clinical
  - in cases of posterior manifestation, painful apex orbitae syndrome
  - focal or diffuse syphilitic periostitis into the orbital bone
  - occurrence of intraconal soft tissue lesions, in the extraocular muscles, or the lacrimal gland
- Diagnostics
  - serological confirmation of the diagnosis by means of a fluorescence *Treponema* antibody absorption test
- Therapy
  - complete healing with antibiotic therapy with penicillin G [61]

### 5.1.1.3 Necrotizing fasciitis

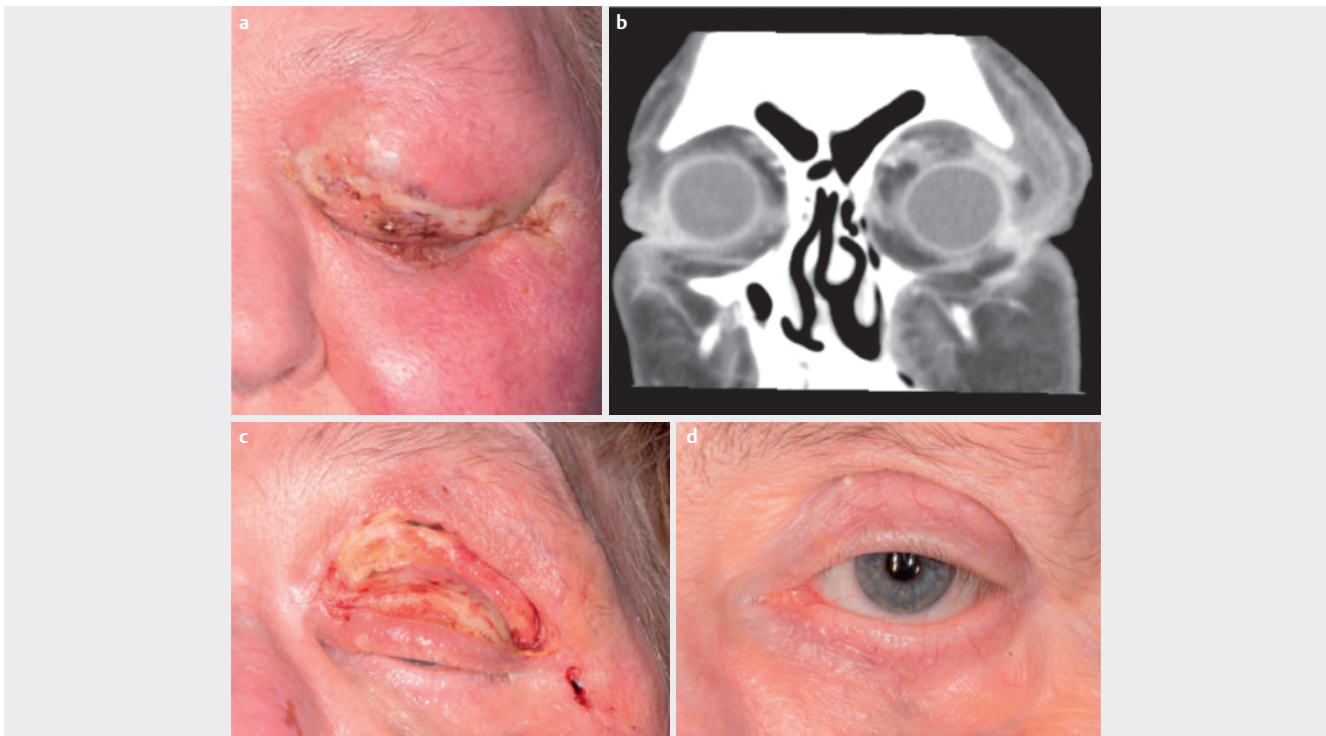
Necrotizing fasciitis of the orbit is an ophthalmological emergency but quite rare because of the good blood supply. Because of rapid progression, it can lead to death when the diagnosis is made too late [58].

- Epidemiology
  - incidence of 0.24:100 000 [62]
- Classification [63]

- type I: polymicrobial, e. g., aerobic and anaerobic bacteria (especially in patients with multiple morbidities) (► **Fig. 7a–d**)
- type II: at about 80%, the most frequent type [64] (single bacterial pathogens, mostly beta-hemolyzing streptococci of group A; superantigens and exotoxins as most important virulent factors)
- type III: mainly vibrio bacteria; rarely occurring in Europe
- type IV: fungi
- Etiology
  - penetrating traumas are the most frequent triggers (35%), along with surgeries as well as acute infections of the paranasal sinuses, efferent lacrimal ducts, or skin, and pharmaceutical immune suppression or malignancies
  - unknown trigger in 25% of cases [64]
- Risk factors
  - greater age, alcohol and drug abuse, diabetes mellitus, collagenosis, and cardiovascular disease
  - in 50% of cases, no risk factors present [64]
- Clinical
  - early detection possible because of thin skin near the eye
  - severe pain possible even prior to skin changes (“pain out of proportion”) [62]
  - fever and intensive sweating
  - gangrene development within a few hours with livid, blistering skin discoloration
  - risk of blindness in cases of central artery closure [58]
  - toxic shock syndrome in 30% of cases
- Diagnostics
  - based on clinical symptoms
  - scores, e. g., LRINEC [65], imaging for rapid diagnosis and delimitation of other infections such as mucormycosis possibly helpful
- Therapy
  - intensive debridement (mainly subcutaneous near the eye, sometimes repeatedly performed [66] up to exenteration as ultima ratio [67]) in combination with broad spectrum antibiotics (mostly broad-spectrum penicillin or cephalosporins plus clindamycin/vancomycin; see 2009 DGHNO consensus paper [68])
  - exclusively additive effect of hyperbaric oxygen therapy and immunoglobulins [63]
- Prognosis
  - mortality varies between 8 and 14%, especially high in cases of systemic complications such as toxic shock syndrome with multi-organ involvement, periorbital necrotizing fasciitis with blindness, or involvement of facial soft tissue [64, 66]
  - reduction in mortality possible through high index of suspicion and immediate therapy [58]

### 5.1.1.4 Non-infectious (non-bacterial) osteomyelitis in childhood

- Epidemiology
  - very rare, non-infectious inflammation with multifocal bony lesions and periodic exacerbations of painful swellings



► **Fig. 7** Necrotizing fasciitis of the left orbit in an 83-year-old female patient; no risk factors, mixed infection with *Streptococcus pyogenes*, MRSA, *Aspergillus fumigatus*. **a** Clinical findings at presentation. **b** Coronal CT scan of the paranasal sinuses (soft tissue window) with inhibition of the orbital fatty tissue, inflammatorily changed superior obliquus muscle, pre- and postseptal cellulitis (courtesy of the Department of Diagnostic Radiology, University Hospital of Halle. Professor and Chair: Prof. Wohlgemuth). **c** Intraoperative site after debridement. **d** Because of repeated debridement and antibiotic/antimycotic therapy, uncomplicated wound healing per secundam intentionem. ► **Figures 7a, c, and d** are from the archive of the University Hospital of Halle, Department of Ophthalmology.

- synonym: chronic recurrent multifocal osteomyelitis (CRMO)
- pediatric equivalent of SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis)
- prevalence: 1–2:1,000,000
- age peak around 10 years [69]
- Etiology
  - multifocal bony lesions
  - frequent association with other chronic inflammatory diseases, e. g., rheumatoid arthritis (RA), Crohn's disease, sacroiliitis, psoriasis, or gangrenous pyoderma [70]
- Clinical findings in cases of orbital involvement
  - cephalgia
  - hyperemic swelling
- Diagnostics
  - CT scan: osteolytic findings
  - scintigraphy: focus with increased uptake
  - histology: lesions with osteoblastic/osteoclastic remodeling, granulomatous infection infiltrates with giant cells
  - biopsy of involved bone needed for confirmation of diagnosis and exclusion of differential diagnoses (e. g., Langerhans cell histiocytosis, osteoblastoma, osteosarcoma)
- Therapy
  - first choice: NSAIDs (e. g., naproxen)
  - alternative: bisphosphonate or biologicals such as TNF antagonists (etanercept) or IL-1 inhibitors (anakinra)
- Prognosis
  - unfavorable course of CRMO is possible (in contrast to earlier opinions) with persistent chronic pain and physical impairment in up to 50 % of cases [71]
- Important differential diagnosis:
  - **infectious osteomyelitis of the orbit**
    - another rare disease in the area of the orbit
    - etiology: mostly after previous trauma, inflammation (paranasal sinuses, dentogenic, or secondary after bacteremia in the context of intravenous drug abuse or leukemia) [72]
    - Clinical: in acute stages, fever and swelling; in chronic courses, sequestrs and fistulas
    - many other possible differential diagnoses, including bacterial cellulitis, atypical pathogens (tuberculosis), neoplasms as in Ewing sarcoma

### 5.1.2 Orbital fungal infections

Fungal infections as the origin of orbital inflammation are quite rare; however, this aspect should always be considered in immunocompromised patients. The most frequent infections are caused by Phytomyces (*Mucor* spp.) and Ascomycetes (*Aspergillus* spp.).

### 5.1.2.1 Rhino-orbital mucormycosis

Mucormycosis is a rare infectious disease with high mortality. There often is a delay to diagnosis, and the disease is characterized by quick deterioration. Rapid surgical and medical treatment may be lifesaving [73].

- Pathogenesis
  - ubiquitously occurring pathogen that leads to endothelial damage, ischemia, and the typical necrotic eschar (missing in early stages) because of angioinvasion
  - affecting the lung, skin, and gastrointestinal tract, but most frequently the paranasal sinuses with involvement of the orbit and finally also intracranial involvement via the orbital apex/lamina cribrosa
- Etiology
  - almost always associated with another factor, e. g., uncontrolled diabetes mellitus (especially in cases of ketoacidosis), malignancies, burn injuries, hemochromatosis, post kidney or stem cell transplantation, intake of the chelating agent deferoxamine, AIDS
- Clinical
  - general symptoms: fever, fatigue, pharyngitis
  - rhino-orbital symptoms: acute pansinusitis with purulent rhinorrhea, pain, and massive crust formation (black crusts at the nose and palate), subsequent apex-orbital syndrome with sudden loss of vision and ophthalmoplegia, stupor with intracranial extension with cavernous sinus thrombosis [58]
- Diagnostics
  - suspected mucormycosis and rapid biopsy examination in cases of unclear facial complaints, paresthesia, swellings, and rapidly progressive sinusitis in patients with relevant comorbidities [74]
- Therapy
  - pharmacotherapy of first choice: liposomal amphotericin B
  - other pharmacotherapy: isavuconazole and posaconazole, especially for salvage therapy [73, 75]
  - repeated and extensive debridement almost always required
  - exenteration necessary when the orbital apex is affected, but not mandatory in cases of affected anterior orbital parts [76]
- Prognosis
  - formerly almost always lethal, but survival rate of ~70% with the introduction of amphotericin B [58]
  - in recent years, lethal courses observed in immune-healthy patients – especially after injuries or insect bites in warm climates – because of mucor infections caused by a new pathogen strain (*Apophysomyces elegans*) [58]

### 5.1.2.2 Aspergillosis of the orbit

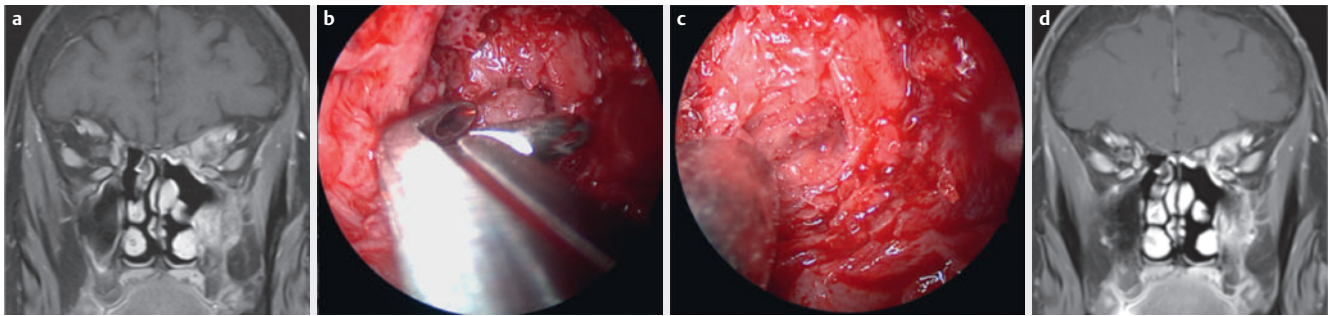
*Aspergillus* spp. are ubiquitous and generally colonize the mucosa of the upper airways as harmless saprophytes. As opportunistic pathogens, they play a major role in immunocompromised patients (e. g., after kidney transplantation).

- Classification: two types of courses are differentiated regarding infections of the head and neck:
  - non-invasive

- because of a pre-existing lesion of the mucosa (mostly in the context of chronic sinusitis), colonization with formation of so-called fungus balls or chronic allergic rhinosinusitis
- occurrence also in healthy patients
- rarely affecting the orbit [77]
- invasive
  - in cases of impaired immune competence (e. g., because of leukemia or AIDS), rapid distribution by vascular invasion with tissue necrosis, via ethmoid and sphenoid sinus into the orbital apex, the cavernous sinus, and in the intracerebral direction; development of thromboses and aneurysms with high mortality [78–80]
  - possible hematogenous dissemination from pulmonary infection foci or because of contaminated needles with heroin abuse [61]
- Clinical
  - invasive type: similarly fulminant manifestation as for mucormycosis
  - non-invasive type: mostly slowly progressive indolent mass developing in the paranasal sinuses with extension in direction of the orbit, often pre-existing sinusitis
  - isolated involvement of the sphenoid sinus with optic neuritis without involvement of the orbit is possible [81–82]
- Diagnostics
  - rather low sensitivity and specificity of the single test procedures, warranting identification by a combination of imaging (CT scan, MRI), microbiological examinations (direct microscopy, culture, PCR, biomarker), and histopathology (branch-like septated hyphae, chronic-fibrous granulomatous inflammation) [83]
  - because of non-specific symptoms (minor sinusitis, retrobulbar, partly neuropathic pain, apical orbital inflammation difficult to identify by imaging), particular attention is needed in the context of diagnostic procedures [59]
- Important differential diagnoses
  - bacterial cellulitis, cavernous sinus thrombosis, Tolosa-Hunt syndrome
  - tumors of the orbital apex or the sphenoid sinus
- Therapy
  - antifungal therapy with liposomal amphotericin B until exclusion of mucormycosis, followed by a shift to the more effective voriconazole [84]
  - extensive debridement of the infected tissue, especially in the context of the invasive type
- Prognosis
  - good in immunocompetent people and localized, non-invasive type with adequate therapy [85] (► Fig. 8a-d)
  - poor in invasive type
  - almost always lethal in cases of intracranial extension in immunocompromised patients [86]

### 5.1.2.3 Other mycoses

Outside of Europe, other pathogens may be responsible for fungal infections of the orbit [58, 59], including:



► **Fig. 8** Aspergillosis of the orbital apex and the pterygopalatine fossa: 60-year-old female patient suffering from severe pain on the left side of the face for months with dysesthesia of the palate and trigeminal nerve, anamnestically chronic sinusitis with maxillary sinus surgery twice, immunosuppression because of chronic fatigue syndrome, presentation for increasing external oculomotor paresis with ptosis, diplopia, and visual impairment (to <0.05 on the left side). Several rounds of systemic prednisolone therapy and left-sided orbital decompression achieved only short-term improvement of vision and other complaints. **a** MRI (T1 TSE+CA) signal enhancement in the area of the orbital apex and the pterygopalatine fossa (courtesy of the Department of Diagnostic Radiology, University Hospital of Halle. Professor and Chair: Prof. Wohlgemuth). After molecular pathological examination of the biopsy of the left pterygopalatine fossa (see ► **Fig. 8b, c**), evidence of infection with *Aspergillus fumigatus*. After oral therapy with voriconazole for 6 weeks and sufficient pain therapy with gabapentin and amitriptyline, there was subjectively complete regression of the pain; on the MRI performed 6 months later, only limited regression was found (see ► **Fig. 8d**). ► **Figs. 8a and d** courtesy of the Department of the Diagnostic Radiology, University Hospital of Halle (Professor and Chair: Prof. Wohlgemuth). ► **Figs. 8b, c** are from the archive of the University Hospital of Halle, Department of otolaryngology.

- North American blastomycosis
- Fusariosis
- African histoplasmosis
- Sporotrichosis
- Rhinosporidiosis
- Coccidioidomycosis
- Candidiasis
- *Bipolaris hawaiiensis*

### 5.1.3 Viral infections

Orbital effects from viruses are rare; however, these microbes may cause diseases based on infection or secondary immune phenomena, including:

- Varicella zoster virus (VZV): acute myositis, optic neuritis
- Mumps virus: acute dacryoadenitis
- Epstein-Barr virus (i. e., EBV): acute dacryoadenitis, some cases associated with T cell lymphomas of the orbit and the paranasal sinuses [61]

### 5.1.4 Parasitoses

Infestation of the orbit is also possible by larvae of different parasitic worms. In Germany, echinococcosis ranks among these rare diseases of the orbit.

#### 5.1.4.1 Cystic echinococcosis

- Epidemiology
  - occurring worldwide, especially when humans and animals live in close proximity
  - mainly patients between the 1<sup>st</sup> and 4<sup>th</sup> decades of life [59]
  - endemic distribution in Central and South America, Middle East, North Africa, China, and Russia
- Pathogenesis
  - excretion with feces of eggs of adult tapeworms from the gut of carnivores (e. g., dogs)

- intake of eggs by herbivores (e. g., sheep, cattle) as intermediate hosts or humans via the consumption of contaminated vegetables
- distribution of the eggs in intermediate host via the blood circulation into the tissue and intake by the final host with food
- growing in the final host until the final larval stage
- effects in the lung and liver are most frequent, with orbital involvement in 1 % of cases [88–89]

#### ▪ Clinical

- slowly progressive, indolent, intraconal mass
- increasing proptosis and motility disorder [88–89]
- possible thinning of the orbital wall with intracranial extension
- rupture of the cystic wall (spontaneous or in the context of surgical excision) may lead to fulminant inflammatory or anaphylactic reaction [61]

#### ▪ Diagnostics

- well-defined cystic structure by ultrasound and CT scan with contrast-enhancing margin [90]
- hemagglutination and enzyme-linked immunosorbent assays for antibodies available but with sensitivity of only 50 % in cases of isolated orbital involvement [61]

#### ▪ Therapy

- classic: surgical excision
- alternative: different recommendations [91, 92], e. g.:
  - monotherapy with albendazole over 3 months; in cases of concomitant inflammation additionally systemic corticosteroids
  - combination of albendazole, praziquantel, and surgical excision
- in cases of unclear diagnosis or compression-induced loss of vision, surgical excision required [61], fine needle aspiration may be applied for diagnostics and therapy (albendazole injection) [59]

#### 5.1.4.2 Cysticercosis

- Epidemiology
  - endemic occurrence in countries with poor sanitary conditions (Latin America, parts of Asia, and in South Sahara)
- Pathogenesis
  - caused by the parasite *Taenia solium* (pork tapeworm)
  - intake of eggs via underdone pork and hematogenous distribution
  - formation of encapsulated larvae with preferential colonization in the eye and brain (neurocysticercosis, life-threatening) [61]
- Clinical
  - at the eye, often subconjunctival, intravitreal, and retinal involvement
  - in the area of the orbit, mainly extraocular muscles affected [93–94]
- Therapy
  - surgical excision and pharmacotherapy with albendazole or praziquantel
  - reduction of the concomitant inflammation by steroids [95]

#### 5.1.4.3 Trichinosis

- Pathogenesis
  - intake of encapsulated larvae by ingestion of underdone pork
  - in the gut, development of larvae into roundworms, development of new larvae, and hematogenous distribution
  - development of cysts in the striated muscles
- Clinical
  - first manifestation often in the extraocular muscles
  - preseptal edema, chemosis, and painful myopathy
- Therapy
  - pharmacotherapy with thiabendazole [59, 61]

#### 5.1.4.4 Ophthalmomyiasis

- Etiology
  - caused by botfly larvae in tropical regions
- Clinical
  - the symptoms vary from mild conjunctivitis to destruction of the entire orbit
- Therapy
  - removal of the larvae
  - disinfection up to exenteration in cases of severe disease

#### 5.1.4.5 Other parasitoses and fly larvae with possible eye involvement [96]

- Cestodes
- *Dirofilaria*
- *Loa loa*
- *Onchocerca volvulus*
- *Oxyuris*
- *Plasmodia*
- *Porocephalus armillatus*
- *Schistosoma*
- *Thelazia*

- *Wuchereria bancrofti*

## 5.2 Non-infectious orbital inflammation

### 5.2.1 Introduction

In the proper sense of the word, orbital inflammation is not a diagnosis [97]. The inflammation corresponds to the adaptive response of the immune system to a cause, e. g., an infection or injury, and to autoimmune disease. In 20% of tumoral lesions of the orbit, an association with inflammation is found [98]. The detection of the underlying disease is often a major challenge. Common characteristics are signs of clinical inflammation as well as the histological manifestation of a polymorphic inflammatory cell infiltration [59]. With regard to occurrence and intensity, a significant variability is observed [99]. Endocrine orbitopathy as the most frequent non-infectious inflammatory change in the orbit will not be discussed because it falls outside the scope of this article covering rare diseases of the orbit.

### 5.2.2 Idiopathic orbit inflammation

Idiopathic orbit inflammation (IOE) was formerly known as ‘pseudotumor orbitae’. encompasses a heterogeneous group of diseases characterized by orbital inflammation without an identifiable local or systemic cause. It is a rare entity as well as an exclusion diagnosis [100], characterized by an increase in mass of orbital structures, which may be caused by non-specific inflammatory, sometimes fibrotic, and rarely even destructive lesions [61]. The pathophysiology is not fully clarified; an autoimmune genesis that might be triggered by infections has been proposed [99]. Several classifications have been suggested, but none are generally acknowledged because of the highly variable clinical and pathologic properties [101–103].

IOE may affect every orbital structure, and the first manifestation varies from acute onset to a slowly progressive course.

Depending on the location, the following differentiations can be made [61]:

- Idiopathic dacryoadenitis: isolated and affecting the lacrimal gland (most frequent variant)
- Idiopathic orbital myositis: limited to one or more extraocular muscles
- Diffuse IOE affecting different orbital structures (rare)
- Idiopathic perineuritis of the optic nerve (very rare): involvement of the optic nerve sheath
- Anterior IOE: listed as an independent entity by some authors [103]

The list of differential diagnoses is long and encompasses almost all types of infectious and non-infectious orbital inflammation as well as a multitude of neoplastic and vascular lesions [99]. The diagnosis can be made only based on histology so that biopsies play a major role, especially in cases of advanced disease and recurrences, to exclude relevant differential diagnoses. Exceptions are idiopathic myositis with its characteristic clinical and radiological appearance as well as lesions in the area of the orbital apex where the risks of iatrogenic injuries are higher than the expected benefit. Good response to corticosteroids is observed in numerous different orbital lesions including endocrine orbitopathy and malignan-

cies, so that this response should not be used for confirming the diagnosis.

- Histological characteristics [100, 102]
  - classic orbital pseudotumor
    - broad inflammatory substrate of lymphocytic, granulocytic, and sometimes histiocytic infiltrates, organized into lymph follicles with germinal centers
    - increased connective tissue with edema and fibrosis
    - early visible destruction of the lacrimal gland acini or muscle fibers
    - delimitation to lymphoproliferative diseases is important
  - idiopathic sclerotic type
    - tissue sclerosis and hyalinization dominant
    - poor inflammatory infiltrate, similarity to retroperitoneal fibrosis
    - diagnostics based on IgG4-associated diseases recommended [104]
  - rarely granulomatous (histiocytic giant cell infiltration) and vasculitic (vasculitis of the minor vessels) inflammatory reactions
  - possible transition of classic orbital pseudotumors to the sclerotic subtype [100]
- Clinical
  - highly variable, typically unilateral occurrence with disease history of several days to weeks, ranging from mild signs of inflammation to severe pain and increased orbital pressure with the risk of optic nerve compression; often recurrences in cases of classic pseudotumors as well as the sclerotic type [100]
  - depending on the location, painful (swelling-related) pseudoptosis, chemosis, exophthalmos, and (mostly pain-related) impaired ocular motility
  - sclerotic type: pain frequent, rather notable swelling of the eyelid, impaired ocular mobility, loss of vision (► Fig. 9a, b)
- Imaging and serologic diagnostics
  - idiopathic dacryoadenitis/idiopathic myositis: increase in affected structures with unchanged differentiation
  - sclerotic type: homogeneously enhancing, poorly delimited infiltrates of different orbital structures (initially mostly lateral with involvement of the lacrimal gland), in the further course, possible extension in the direction of the cavernous sinus and pterygopalatine fossa; in addition, possible multifocal fibrosclerosis (in particular retroperitoneal) (► Fig. 9c, d)
  - broad laboratory and serological diagnostics for differential diagnosis and assessment of the inflammatory activity possibly useful (among others, kidney and thyroid values, ANCA, ACE, rheumatoid factors, IgG4 serum level)
- Therapy
  - in cases of a high level of suffering, immediate therapy is required
  - different levels of anti-inflammatory therapy, from antibiotic therapy, NSAIDs, or steroids to application of immunosuppressants [100]
  - mostly good response to systemic high-dose therapy with corticosteroids, although response can be poor to corticosteroids and irradiation in cases of sclerotic type

- with rapid diagnosis and onset of combination therapy consisting of corticosteroids and immunosuppressants (in cooperation with rheumatologists), delayed progression at least possible in cases of the sclerotic subtype [59]
- in cases of refractory and chronic courses, systemic application of immunosuppressants (e. g., methotrexate and azathioprine), biologicals such as rituximab, and a combination with radiation of the orbit
- surgery such as debulking in the lacrimal type, decompression of the orbit in cases of optic nerve compression, orbital exenteration as ultima ratio in persistent severe pain [99]

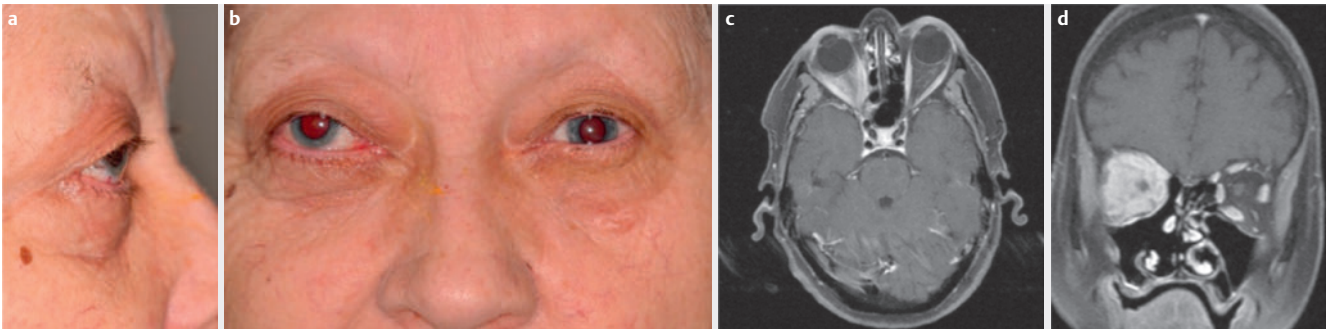
### 5.2.2.1 Tolosa-Hunt syndrome

- Epidemiology
  - rare idiopathic granulomatous inflammation of the cavernous sinus and the orbital apex with compression of the neighboring cranial nerves (III–VI)
  - incidence of 1:1,000,000 per year [105]
- Clinical
  - unilateral ophthalmoplegia and (partly migrating) pareses of the cranial nerves running along the cavernous sinus and the superior orbital fissure (the oculomotor nerve most frequently affected)
  - often associated with constant retrobulbar facial pain
- Diagnostics
  - confirmation of the diagnosis by means of MRI or biopsy to exclude differential diagnosis (sarcoidosis, malignancies, cavernous sinus thrombosis, cavernous carotid fistula) [106]
- Therapy
  - initially high-dose glucocorticoid boost therapy, then slowly reducing over at least 4–6 weeks (even longer if needed)
  - further options: radiotherapy and immunosuppressants (e. g., infliximab) [107–108]
- Prognosis
  - rapid pain relief from corticosteroids
  - **Cave:** even in cases of malignancies, high-dose corticosteroid application may lead to temporary improvement of the complaints; see case report in ► Fig. 10a–f
  - regression of neuropathies often only after several months, sometimes persisting
  - recurrence possible [109–110]

### Case report 1

- History
  - 79-year-old male patient with right-sided periorbital headaches progressing for months: intermitting neuralgic character in the area of the ophthalmic nerve, touch-sensitive
  - trochlear and abducent paresis on the right side for weeks (diplopia)
- Diagnostics
  - MRI of the orbit: contrast-enhancing structure in the extraconal space at the orbital roof (most likely thickened supraorbital nerve) reaching into the superior orbital





► **Fig. 9** Sclerosing type of idiopathic orbital inflammation. **a, b** 62-year-old female patient, initially foudroyant course with massive pain, diplopia, and exophthalmos. **c, d** Orbital MRI (courtesy of the Department of Diagnostic Radiology, University Hospital of Halle. Professor and Chair: Prof. Wohlgemuth): diffuse, not well-delimited tissue proliferation infiltrating almost the entire intraconal space; extraocular muscles could be differentiated. Rapid loss of vision and finally blindness despite multiple rounds of maximal systemic corticosteroid therapy and surgical orbit decompression on the right side, biopsy without hint of malignancy, clinically and serologically no hint of other autoimmune disease, in particular no granulomatosis with polyangiitis or IgG4-associated disease; maintenance therapy for 5 years with methotrexate, nonetheless with repeated exacerbations of the pain symptoms. ► **Figures 9a, b** are from the archive of the Department of Ophthalmology, University Hospital of Halle.

fissure, focal contrast enhancement in the orbital apex and into the cavernous sinus (► **Fig. 10a–c**)

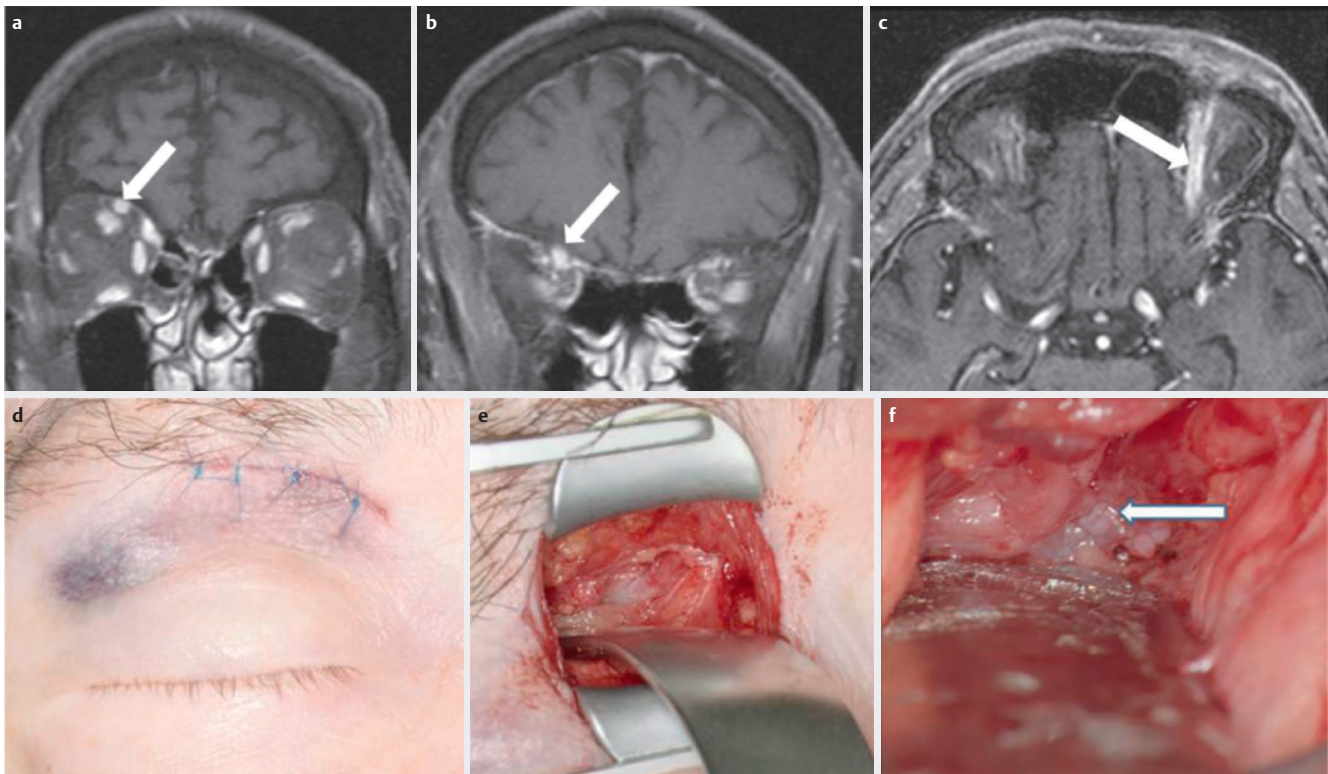
- PET-CT: no glucose consumption typical for malignancy, in particular in the area of the orbit
- lumbar puncture: no hint of a florid inflammatory reaction of the CNS, no local immunoglobulin synthesis, no oligoclonal bands, no hint on serology of acute infection with neurotropic pathogens
- Further course
  - working diagnosis: suspected Tolosa-Hunt syndrome; differential diagnostics in direction of infectious genesis, systemic granulomatous inflammation, or neoplasm
  - interdisciplinary board: therapy attempt with systemic glucocorticoid application (also because of the significant periprocedural risk in case of biopsy), and analgesics
  - initial improvement (in particular of the bulbar motility) and regressive MRI findings; differential diagnosis of autoimmune genesis, malignancy could not be excluded with certainty
  - continuation of glucocorticoid therapy
  - because of pre-damaged lung (fibrosis) with immunosuppressive therapy, repeated pneumonia and/or influenza pneumonitis
  - after 3 months, indication for biopsy because of persistent complaints despite regressive MRI findings
  - histological diagnosis: poorly differentiated adenocarcinoma
  - further staging diagnostics without clear findings, thus most likely primary tumor location
- Therapy
  - radiotherapy (with consideration of the comorbidities and patient's wishes)

#### Note

**Even in cases of inflammatory processes of the orbit, malignant disease must be considered. Improvement with glucocorticoid therapy does not exclude malignancy.**

### 5.2.2.2 IgG4-associated orbitopathy

- Definition
  - subacute to chronic courses of immunological systemic disease with coarse lymphocytic infiltrates and fibrotic lesions [111]
- Locations and clinical
  - most frequent manifestations are autoimmune pancreatitis, sclerotic cholangitis, nephritis and renal fibrosis, and involvement of the lacrimal glands, salivary glands, and lymph nodes [111]
  - manifestations in the area of the orbit are typical, each structure may be affected, but in particular:
    - lacrimal gland: IgG4-associated dacryoadenitis with mostly painless swelling, mostly bilateral manifestation and with sicca symptoms [112]
    - orbital nerves and muscles: mainly infraorbital nerve; mostly painless with diplopia
    - orbital fatty tissue: associated with increased lacrimal glands [112–113]
    - rarely, destructive lesion with enophthalmos [113, 114], affecting ocular structures or the bony limits
    - in more than 70% of patients extraocular manifestations [111]
    - visual disorders as leading symptom [111]
- Diagnostics
  - imaging
    - diffusely increased lacrimal gland, muscles (mainly lateral), infraorbital nerve, partly with swelling of the bone channel (► **Fig. 11a, b**)
    - often ipsilateral effect on the paranasal sinuses [112]
  - histology
    - lymphoplasmacellular infiltration with obliterating phlebitis and eosinophilic inflammation
    - percentage of IgG4-positive plasma cells >40% (triggering stimulus for differentiation of B lymphocytes in IgG4-producing plasma cells still unknown)
    - fibrosis in the further course



► **Fig. 10** Case report 1: wrong diagnosis of a Tolosa-Hunt syndrome. **a–c** MRI of the orbit (T1 sequences) in coronary section (**a**: at the level of the bulbous, **b**: retrobulbar) or axial section (**c**). The arrow marks the strand-shaped, contrast-enhancing structure in the extraconal space at the orbital roof (most likely a thick-ended supraorbital nerve) visible until the superior orbital fissure where a focal contrast enhancement also can be observed reaching into the orbital apex and the cavernous sinus; finally no satisfactory assessment was possible. **d–f** Incision (anterior orbitotomy) (**d**), intraoperative site (**e**), with a tumorous mass at the orbital roof (**f**, arrow) infiltrating the superior obliquus muscle and growing along the supraorbital nerve. ► **Figures 10d–f** courtesy of Prof. S.K. Plontke, Department of Otolaryngology, University Hospital of Halle.

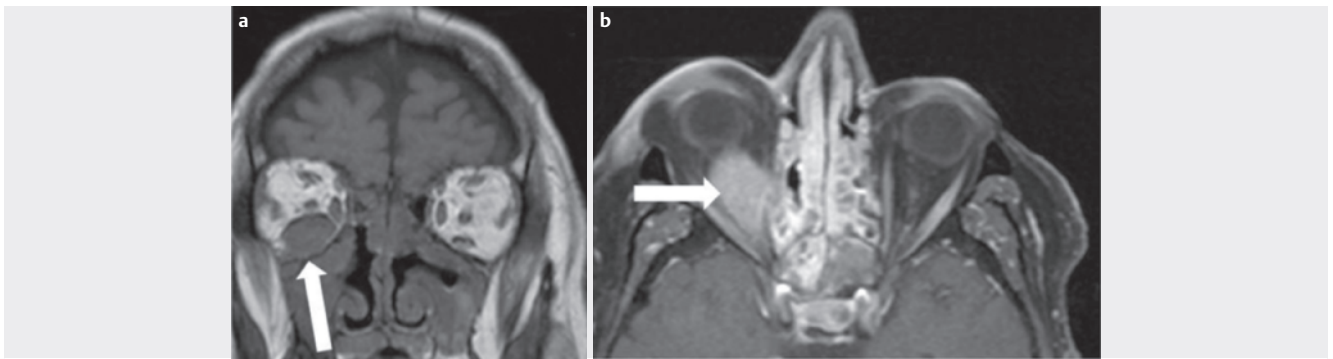
- histologic diagnostic criteria: IgG4/IgG ratio > 50 % as well as > 30 % IgG4-positive cells per high-power field [115]
- laboratory
  - increased IgG4 serum level, although non-specific (increased also in Churg-Strauss syndrome, sarcoidosis, allergic diseases) and not identifiable in particular in limited orbital involvement
  - otherwise, no signs of systemic inflammation [99]
- Therapy
  - first choice: traditionally oral glucocorticoid application (30–40 mg/d) as induction therapy, low-dose maintenance therapy over years, regression of complaints often observed
  - recommendation from recent studies: application of rituximab not only in recurrences but also in first-line therapy, leading to significantly better outcome rates than other disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, mycophenolate, and azathioprine [116]
  - surgical debulking and radiotherapy only rarely indicated [116–117]

### Case report 2

- History
  - 75-year-old patient, condition after functional endoscopic sinus surgery (FESS) in 2007
  - 6 months prior, right eye swelling and diplopia for 6 months, re-FESS in a new location with a clinical finding of “orbital abscess”
  - 3 months later, re-FESS with polypous pansinusitis with orbital involvement, also performed alio loco
  - at first *in domo* presentation, persistent diplopia, loss of vision, eyelid edema, hypoesthesia
- Diagnostics
  - MRI: extraconal mass at the orbital floor not delimited from the inferior rectus muscle with contrast enhancement (► **Fig. 11a, b**)
  - after biopsy via a transconjunctival access, diagnosis of IgG4-associated orbital inflammation
- Therapy (in cooperation with rheumatologists)
  - glucocorticoids and methotrexate, leading to full recovery

### 5.2.3 Vasculitis of the orbit

Orbital inflammation is often part of a systemic disease that cannot always be identified initially, even though it can have far-reaching consequences. Vasculitis plays a particular role. Vasculitic



► **Fig. 11** Case report 2: IgG4-associated orbitopathy. **a, b** MRI in coronary section (T1 sequence): extraconal mass at the floor of the orbit that cannot be clearly delimited from the inferior rectus muscle (**a**) and enhancement with contrast agent (**b**, axial section [T1 sequence] with contrast agent) (courtesy of the Department of Diagnostic Radiology, University Hospital of Halle. Professor and Chair: Prof. Wohlgemuth).

diseases encompass numerous pathologies; for the orbit, these are mainly orbital granulomatosis with polyangiitis (GPA, formerly called Wegener's disease) as well as polyarteritis nodosa. These and other related diseases are listed below with their main characteristics.

### 5.2.3.1 Small and medium-sized vessel diseases

#### 5.2.3.1.1 Orbital granulomatosis with polyangiitis (GPA)

- Definition
  - necrotizing granulomatous inflammation of the respiratory tract and necrotic vasculitis of small and medium-sized vessels of the airways and kidneys
- Epidemiology
  - rare disease, incidence of 3:100 000 [118]
  - orbital involvement in about 50 % of cases [111] (almost every structure may be affected)
- Classification into two clinical types [119]
  - limited form
    - mostly affecting the upper airways
    - mostly no identification of ANCA
  - systemic form
    - affecting the airways, kidneys, other organs
    - often associated with c-ANCA (90 %) and p-ANCA increase (20 %) [111]
    - formerly high mortality: currently up to 90 % remissions because of early combination therapy [120]
- Symptoms [111]
  - proptosis as a key characteristic (in combination with pulmonary and renal symptoms, groundbreaking for correct diagnosis)
  - painful ophthalmoplegia because of extension of the orbital mass into neighboring structures (e. g., cavernous sinus)
  - epiphora from obstruction of the efferent lacrimal ducts in cases of sinus involvement, diplopia caused by vasculitis of the extraocular muscle vessels, inflammation of the lacrimal gland, bulb perforation caused by necrotic scleritis, xanthelasma-like staining of the eyelids (“yellow lid sign”)
- vision-threatening compression of the optic nerve in cases of infiltration of the neighboring structures
- mostly subacute onset, mostly bilateral in the further course, episodes with significant progression of findings in the context of chronic disease
- possibly dramatic deterioration during the disease course because of fibrosis and orbital atrophy with enophthalmos, motility disorders, and chronic pain [118, 121]
- Diagnostic imaging (CT and MRI) [122]
  - extraconal infiltrates, mainly infero-medial in close proximity to the affected sinuses with bone destruction and septum perforation
  - possible isolated effect on the orbital apex (partly with intracranial extension) or isolated effect on the lacrimal gland (diffuse enlargement)
  - diffuse extension in intra- and extraconal direction (“wall-to-wall” tumor) as a pathognomonic sign of advanced stage
  - MRI suitable for identification of granulomatous inflammatory reaction
- Pathology
  - classic histological triad of vasculitis, necrosis, and granulomatous inflammation in the orbit in 50 % of patients
  - other characteristics: polymorphic inflammatory infiltrates, degeneratively changed granules/collagen as well as increased number of IgG4-positive plasma cells in many cases [123]
  - also in ANCA-negative GPA: additional immunohistochemical examination of IL-17 and IL-23 for differentiation of sarcoidosis [111]
- Therapy
  - management of orbital GPA similar to that for systemic GPA
  - current standard: combination of corticosteroids with cyclophosphamide, methotrexate, or azathioprine; early therapy start may avoid fatal local or systemic courses [118]
  - in refractory cases: rituximab [124] (more favorable side-effect profile with comparable effect)

- surgical debulking in cases of persistent proptosis, uncontrollable pain, or compressive neuropathy of the optic nerve [121]

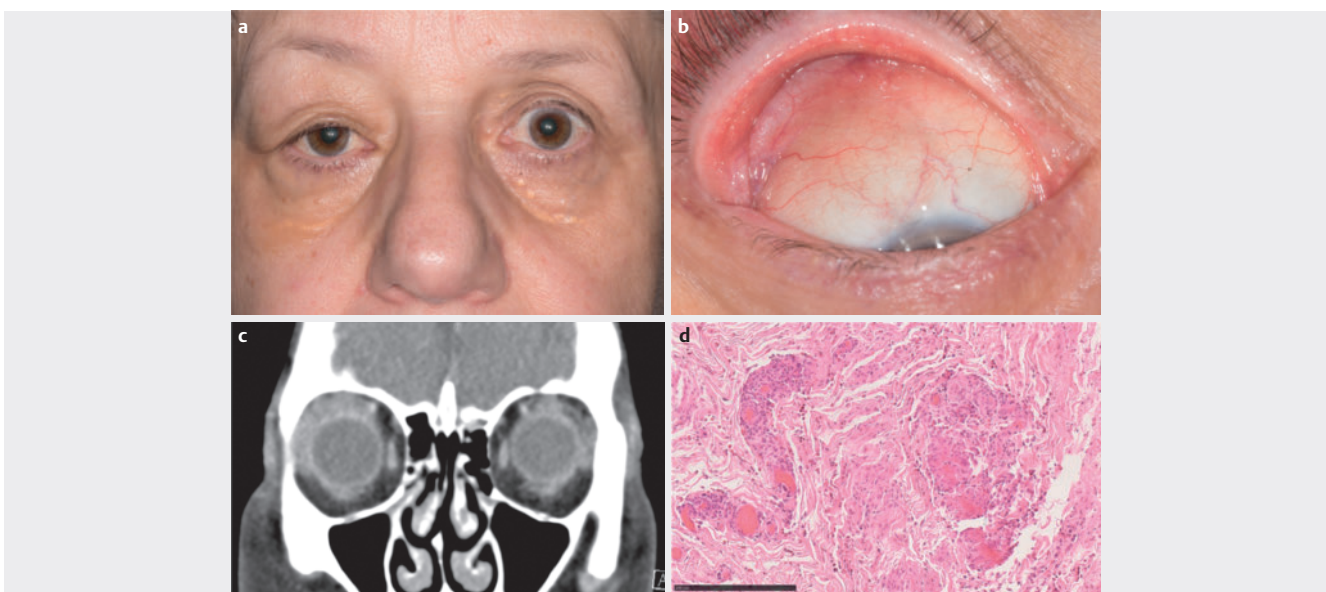
### 5.2.3.1.2 Allergic granulomatosis (Churg-Strauss syndrome)

- Definition
  - allergic systemic disease; initial manifestation with asthma and rhinosinusitis, and in the course, necrotic vasculitis of small and medium-sized vessels and eosinophilic granulomatous inflammation [118]
  - orbit rarely affected
- Location
  - predominantly involving the lung, paranasal sinuses, and peripheral nerve system
- Clinical
  - ischemic vasculitis or orbital inflammatory pseudotumor with dacryoadenitis, myositis, periscleritis, perineuritis
  - may be a first manifestation of the syndrome [125] (► Fig. 12a–c)
  - in the course, proptosis, diplopia, ophthalmoplegia, loss of vision from optic nerve compression
  - in the stage of vasculitis, life-threatening complications possible (peritonitis from gut perforation, eosinophilic myocarditis with myocardial infarction [127])
- Diagnostics
  - biopsy of affected structures
  - main histological features: necrotizing vasculitis with extravascular infiltrates (► Fig. 12d)
  - seropositive pANCA in 70 % of patients [126]

- imaging (CT, MRI): non-specific changes with increased retrobulbar space, swelling of lacrimal gland and extraocular muscles (EOM)
- diagnostic criteria of American College of Rheumatology (1990; 4 of 6 must be applicable): asthma, paranasal sinus abnormalities, pulmonary infiltrates, eosinophilia greater than 10 % of white blood cell differential, extravascular eosinophils, presence of a mononeuropathy or polyneuropathy [127]
- Therapy
  - first-line therapy: systemic corticosteroids (oral, intravenously applied), additional methotrexate and cyclophosphamide as steroid-saving measure in cases of critical organ involvement
  - biologicals in case of recurrence or refractory disease: rituximab, infliximab, mepolizumab, or omalizumab [118, 128]; in general, permanent pharmacotherapy needed
- Prognosis
  - before the era of biologicals: mortality in up to 50 % of cases if two or more organs affected [129]

### 5.2.3.1.3 Polyarteritis nodosa

- Definition
  - necrotic vasculitis of small and medium-sized arteries and sometimes of the accompanying veins
  - segmental effects characteristic (typically bifurcations)
  - typically thromboses and nodular aneurysms [59]
  - histological characteristics: fibrinoid necrosis of the media and simultaneous occurrence of different inflammatory stages



► **Fig. 12** Churg-Strauss syndrome; 68-year-old female patient with bronchial asthma known for many years, chronic rhinosinusitis, blood eosinophilia, and otherwise no hint of systemic vasculitis; complete regression of the complaints with prednisolone and azathioprine. **a, b** Inflammation imposing mass in the area of the right anterior orbit (pictures from the archive of the Department of Ophthalmology). **c** Hyperdense laterocranial signal enhancement as a correlate of the inflammatory infiltrate (courtesy of the Department of Diagnostic Radiology, University Hospital of Halle. Professor and Chair: Prof. Wohlgemuth). **d** Biopsy with evidence of an eosinophilic granulomatous infiltrate (courtesy of the Institute of Pathology, University Hospital of Halle. Professor and Chair: Prof. Wickenhauser).

- Epidemiology
  - mostly male patients in the 4<sup>th</sup> and 5<sup>th</sup> decades of life
  - association with hepatitis B
  - orbit involved in about 10% of patients [118], sometimes as the first manifestation of the disease
- Location
  - predilection for kidney, heart, liver, gastrointestinal tract, peripheral nerves, and CNS, and also bones and joints
- Clinical
  - typical ophthalmological lesions: retinal vasculitis, choroidal infarction with exudations, ischemic optic neuropathy
  - secondary phenomena of vasculitis: ischemia of the EOM with ophthalmoplegia, diffuse orbital inflammation with exophthalmos, impaired motility, chemosis
- Diagnosis based on the combination of orbital inflammation with other disease symptoms, non-specific inflammation signs on labs, biopsy, and imaging (sometimes angiographic confirmation of aneurysms)
- Therapy
  - systemic corticosteroids and cyclophosphamide
  - application of other DMARDs such as methotrexate, azathioprine, and rituximab also reported [118]
- Prognosis
  - 5-year survival rate of about 80% [118]

### 5.2.3.2 Vasculitis of the major vessels

#### 5.2.3.2.1 Giant cell arteritis (temporal arteritis)

- Definition
  - idiopathic vasculitis of the middle and major arteries of the head and neck
  - histologically segmental inflammation with giant cells, lymphocytes, plasma cells, and eosinophils [118]
- Epidemiology
  - age peak in the 7<sup>th</sup> to 8<sup>th</sup> decades of life
  - mostly female patients [111]
  - orbital involvement rarely observed
- Etiology
  - combination of genetic predisposition (European ancestry) and environmental factors (association with virus infection, e. g., VZV, CMV, parvovirus 19) [130]
- Clinical
  - general symptoms
    - headaches, jaw claudication
    - B symptoms such as fever, fatigue, weight loss
    - polymyalgia rheumatica, scalp tenderness [111]
  - ophthalmological symptoms
    - loss of vision because of ischemia of the optic nerve (anterior ischemic optic neuropathy [i. e., A-AION]: urgent treatment indicated)
    - further diplopia, choroidal and retinal ischemia signs [111]
  - orbital symptoms
    - ophthalmoplegia and diplopia (because of ischemia and inflammation) [131]
- Diagnostics
  - diagnosis by means of combination of typical symptoms (headache, scalp tenderness), laboratory parameters (increased erythrocyte sedimentation rate (ESR), radiological findings (contrast enhancement of the orbit in MRI), and biopsy of the temporal artery (biopsy of the orbital lesion is rarely necessary) [118]

- Therapy
  - first-line therapy: high-dose corticosteroids (**Cave:** undesired long-term effects)
  - current study results with tocilizumab (anti-IL-6) quite promising [132]

#### 5.2.3.2.2 Takayasu arteritis

- Definition
  - granulomatous panarteritis affecting the aorta and its main branches
- Epidemiology
  - first description in middle-aged female Japanese patients
  - current investigations: all ethnic groups affected with increasing prevalence [133]
- Clinical
  - vasculitic destruction of the carotid artery with collateral blood supply to the eye
  - possible loss of vision because of ischemic ocular complications
  - initially, amaurosis fugax or progressive permanent loss of vision possible [134]
- Diagnostics
  - fluorescence angiography to confirm critical perfusion of the retina
  - in recent years, replaced by MR angiography and FDG-PET
- Therapy
  - primary glucocorticoids
  - in steroid refractory cases: leflunomide and tocilizumab [135]

#### 5.2.3.3 Vasculitis of vessels with variable size

##### 5.2.3.3.1 Cogan's syndrome

- Definition
  - rare inflammatory systemic disease
  - main involvement of the visual and audiovestibular system as well as vessels of variable size [111]
- Epidemiology
  - affects mostly young adults
  - age peak at 29 years
  - to date, about 250 cases published [136]
  - orbital involvement extremely rare
- Etiology and pathogenesis
  - autoimmune genesis with origin in the inner ear
  - triggered by initial virus infection
  - identification of different autoantigens (CD 148, connexin 26) [137]
- Classification
  - typical type
    - non-infectious interstitial keratitis with Menière-like vestibulo-cochlear disorder within 2 years after first manifestation [111]

- atypical type
  - different ocular symptoms such as conjunctivitis, episcleritis, glaucoma, uveitis; labyrinthine affection about two years after first manifestation
  - partly severe hearing loss, bilateral deafness in 60 % of the patients [138]
- Clinical
  - resulting from necrotic vasculitis in about 70 % of cases, systemic involvement with manifestation in the blood vessels (aorta, renal, and coronary vessels), neurological and gastrointestinal symptoms; severe, sometimes life-threatening course
  - in cases of orbital involvement (only case reports): hearing loss, vertigo, enophthalmos, and orbital inflammation (however, without biopsy confirmation of the genesis) [118]
- Diagnostics
  - neurotological, ophthalmological, and angiological diagnostics to exclude differential diagnoses
- Differential diagnoses
  - congenital syphilis, Susac's syndrome, Vogt-Koyanagi-Harada syndrome
  - other vasculitis diseases, e. g., granulomatosis with polyangiitis [136]
- Therapy
  - first-line therapy: systemic high-dose glucocorticosteroids, often leading to improvement in vestibulo-cochlear and ocular symptoms [139]
  - prophylaxis against recurrence: biologicals such as infliximab (application also as first-line pharmaceutical in combination with glucocorticoids at an early stage of the disease to avoid irreversible damage) [140]

#### 5.2.3.3.2 Behcet's disease

- Definition
  - idiopathic systemic vasculitis of blood vessels of variable size with episodic course [141]
- Epidemiology
  - highest prevalence in the Middle East and Asia
  - male:female ratio, 3.5:1
  - orbital involvement extremely rare
- Etiology and pathogenesis
  - strong association with HLA-B51
  - non-specific increase in CRP and BSG [118]
- Clinical
  - general symptoms
    - aphthous lesions of the oral mucosa and genitals
    - skin lesions and intraocular inflammation
    - further organ manifestations in the gastrointestinal tract, lung, muscles, joints, and CNS [111]
  - in cases of ocular involvement
    - mostly uveitis with hypopyon, retinal vasculitis
    - rarely, anterior ischemic optic neuropathy (i. e., AION)
    - **Cave:** ocular involvement requires particular attention because of the high morbidity
  - in cases of orbital involvement (single case reports)

- affecting EOM and/or lacrimal gland (however, without biopsy confirmation) [142]
- Diagnostics
  - definition of HLA-B51, CRP, and BSG [118]
  - diagnosis of orbital involvement based on the combination of clinical symptoms and lab parameters in accordance with Behcet's disease and orbital inflammation [118]
- Therapy
  - first-line therapy: corticosteroids
  - second-line therapy: azathioprine, ciclosporin, infliximab or adalimumab; in severe cases with vision-threatening retinitis, combination therapy also possible [143]
  - promising current study results with application of IL-1 inhibitors (anakinra, canakinumab) [144]

#### 5.2.3.3.3 Kawasaki syndrome

- Definition
  - systemic autoimmune vasculitis, preferentially affecting medium-sized vessels, in particular the coronary vessels
- Epidemiology
  - children younger than 5 years
  - incidence: in Japan 240:100 000; in those of European descent, 9:100 000 [145]
- Etiology and pathogenesis
  - histopathologically six typical lesions: endothelial degeneration, necrotic arteritis, granulomatous inflammation, media degeneration, scarring, development of aneurysms [118]
- Clinical
  - cardinal symptoms: fever (> 5 days), palmar and plantar erythema, polymorphic exanthema, bilateral conjunctival injection and chemosis, erythema of the oral mucosa, cervical lymphadenitis, aneurysms of the coronary vessels
  - ophthalmological symptoms
    - bilateral non-purulent conjunctivitis in 80 % of cases with conjunctival injection and chemosis
    - anterior uveitis [145]
  - orbital inflammation (single case reports) confirmed by biopsy; otherwise, by diagnosis in the context of further symptoms of the disease [146–148]
- Diagnostics
  - typical clinical constellation
  - important: cardiological diagnostics with heart echocardiogram, and coronary angiography if needed
  - lab: non-specific increase in ESR, CRP, alpha-1 antitrypsin, thrombocytes
- Therapy
  - standard: high-dose intravenous application of immunoglobulins plus aspirin for symptom reduction and prevention of aneurysms of the coronary arteries [118]
  - therapy-refractory cases: infliximab [149]
  - application of corticosteroids is controversially discussed (administration only in refractory cases) [147]

#### 5.2.3.3.4 Collagenosis-associated vasculitis: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), dermatomyositis (DM)

- Definition
  - vasculitis as typical sign in patients with collagenoses
  - mostly affecting minor vessels in form of leukocytoclastic vasculitis (perivascular infiltration with apoptotic degeneration of neutrophilic granulocytes) [59, 118]
- Epidemiology
  - occurrence in about 30–40 % of SLE patients and 5–15 % of RA patients [59, 118]
  - ocular involvement in 20 % of the patients with SLE
  - orbital involvement much rarer [150]
- Etiology and pathogenesis
  - immunocomplex-mediated pathogenesis
- Clinical
  - frequently: cutaneous lesions, involvement of the mesenteric, coronary, and pulmonary arteries, the arteries of the lower extremities, and the CNS
  - ocular involvement: mostly retinopathy, keratoconjunctivitis sicca, uveitis
  - single publications about symptoms of orbital inflammation (infarction, myositis, exophthalmos)
  - orbital inflammation symptoms together with according general symptoms and typical serological findings of SLE and RA (increased ANA and ds-DNA-AB) [151–153]
  - very rare orbital involvement in DM: case report of delayed bilateral orbital involvement with exophthalmos by increased EOM, associated with muscle weakness, and typical EMG changes (without confirmation by biopsy) [154]
- Therapy
  - SLE and RA: glucocorticoids intravenous or oral; alternatively, azathioprine and biologicals (rituximab, infliximab, belimumab)
  - DM: glucocorticoids intravenous; also immunoglobulins as first-line therapy as well as methotrexate and azathioprine have been described [118]

#### 5.2.4 Granulomatous inflammation of the orbit

##### 5.2.4.1 Sarcoidosis

Sarcoidosis is a chronic inflammatory systemic disease. The term ‘sarcoid’ was introduced by Caesar W. Boeck because these lesions are histologically similar to sarcomas without being malignant. Effects in the lung with bilateral lymphadenopathy as well as skin and eyelid lesions are typical findings [155–157].

- Etiology and pathogenesis
  - increased inflammatory reaction to some pathogens (not precisely identified) with increased cellular immune response and formation of non-caseating granulomas
  - genetic component (higher familial incidence)
- Epidemiology
  - peak between the 30<sup>th</sup> and 40<sup>th</sup> years of life
  - women more frequently affected
  - in about 30 % of cases, limited orbital sarcoidosis with isolated effects on orbital structures [102, 158]
- Location

- ocular involvement (including the most frequent extrapulmonary symptoms): conjunctivitis, uveitis, chorioretinal lesions, vitreous body changes
- orbital involvement possible as first manifestation: mostly lacrimal gland (often bilateral involvement); furthermore, orbital fatty tissue, optic nerve sheath (as part of neurosarcoïdosis), efferent lacrimal ducts, or eye muscles [155, 156, 159–161]
- Clinical
  - depending on the affected structure, palpable tumor mass, eyelid swelling, ptosis, diplopia, exophthalmos, epiphora, sicca symptoms, or painful ophthalmoplegia [156, 161]
  - depending on size and location, possible central artery obstruction and loss of vision [159, 161]
- Diagnostics
  - biopsy essential for confirmation of the diagnosis; because of the histological similarity with other lesions such as idiopathic orbital inflammation or lymphoproliferative diseases, diagnosis can be difficult
  - serology: angiotensin converting enzyme and liver values; possibly inconspicuous serological findings
  - imaging
    - MRI: if affected, the lacrimal gland is diffusely increased with homogeneous enhancement, with further manifestations as a poorly delimited mass, swelling of the optic nerve sheath, or diffusely increased muscles
    - thoracic X-ray for pulmonary assessment
- Therapy
  - intravenous corticosteroids to improve the functional prognosis (essential)
  - interdisciplinary care with rheumatologists is important
  - surgical excision or debulking if needed, but only in combination with previous systemic therapy [159, 161]
  - in refractory cases or recurrence: immunosuppressive combination therapy, e. g., with methotrexate or azathioprine, or with biologicals such as infliximab or adalimumab [156, 161]

##### 5.2.4.2 Melkersson-Rosenthal syndrome

- Definition
  - neuromucocutaneous granulomatous dermatosis
- Epidemiology
  - incidence of 0.08 % [162]
  - first manifestation mostly in young adults
- Etiology
  - autosomal dominant inheritance with variable expression [163]
- Clinical
  - classic symptom triad: lingua plicata, cheilitis granulomatosa, peripheral facial nerve palsy; mono- or oligosymptomatic appearance quite frequent
  - often diffuse edematous facial swellings, rarely isolated in the area of the eyelids (thus a difficult diagnosis, especially when other characteristics are missing; imaging and biopsy may facilitate the delineation)
  - rare involvement of other cranial nerves [162–165] (e. g., diplopia because of oculomotor paresis [162, 166])

- Therapy
  - intralesional and systemic glucocorticosteroids
  - excision and plastic-reconstructive facial surgery in cases of functional as well as cosmetic problems [59]
  - systemic therapy approaches with immunosuppressants (e. g., azathioprine), hydroxychloroquine, and thalidomide [162, 163, 167]
- Prognosis
  - variable chronic course with spontaneous remissions and recurrences

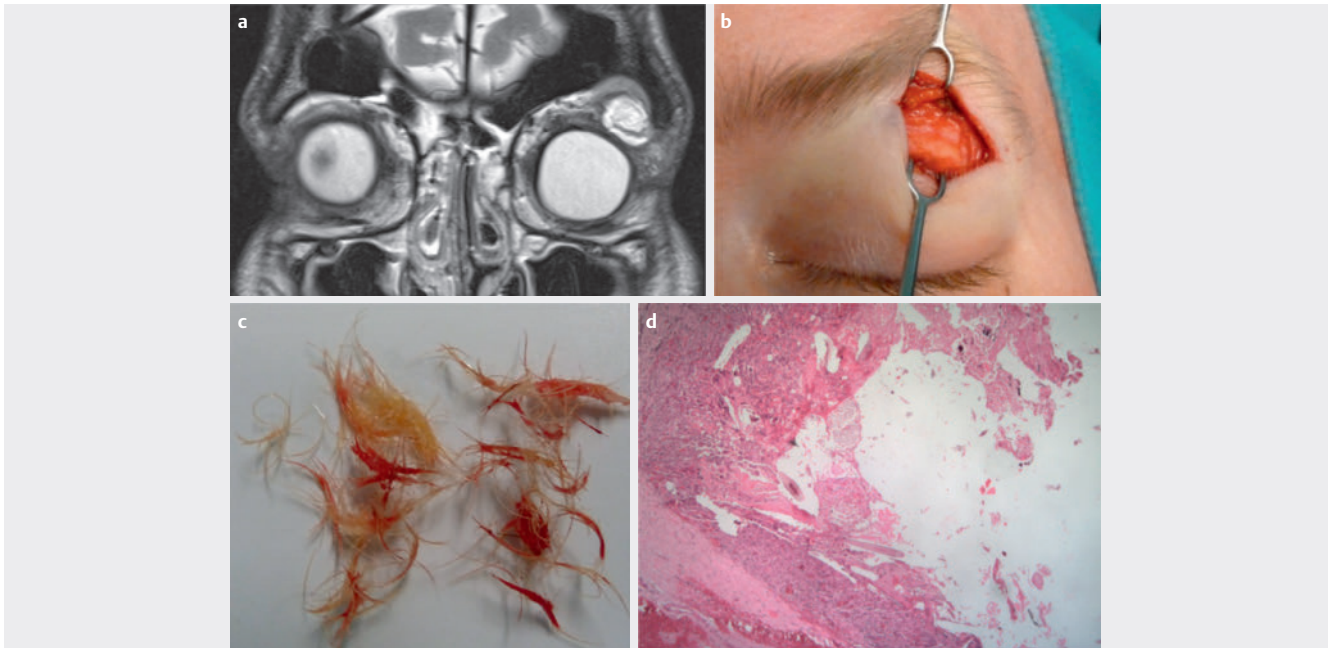
### 5.2.4.3 Foreign body granulomas and idiopathic lipogranulomas

- Definition
  - granulomatous inflammatory reaction caused by foreign bodies
- Classification according to the type of foreign body
  - ruptured dermoid cyst (► Fig. 13a–d)
    - most frequent intrinsic cause of foreign body granulomas (partly with inflammatory reaction)
    - mostly inhomogeneous lesion with irregular borders on CT scans
    - therapy: excision (possibly complete removal without damaging neighboring structures; if small fibrotic parts remain, treatment with intralesional corticosteroids)
  - herbal foreign bodies
    - further source of granulomatous inflammatory reaction, exact history-taking is important
    - slowly progressive course and fistulation possible
  - paraffin-induced sclerotic lipogranuloma
    - mostly as consequence of application of moisturizing nasal ointments after endoscopic sinus surgery (with intraoperative damage of the lamina papyracea) [168–169]
    - accidental leakage of intraocular silicone oil in the context of ophthalmological interventions
    - after autologous fat injection in plastic surgery
  - idiopathic lipogranuloma
    - in cases of missing trigger
    - only single case reports in the literature, unclear etiology
    - histologically orbital fatty tissue necrosis [170]
- Clinical
  - eyelid swelling
  - subcutaneously palpable nodes
  - in cases of tumoral lesions: exophthalmos, impaired oculomotor function, and bulb deviation are possible
- Diagnostics
  - classic inflammatory signs because of concomitant vasculitis [168, 171–172]
  - CT scan and/or MRI: partly poorly delimited, partly diffusely configured lesion [171]
- Therapy
  - complete surgical removal with subsequent systemic glucocorticoid application is most effective [170]
  - optionally: triamcinolone injection or debulking
- Prognosis
  - spontaneous remission as well as recurrences observed [171–174]

### 5.2.5 Sjögren's syndrome (SS)

- Definition
  - chronic autoimmune disease characterized by inflammation of the lacrimal and salivary glands as well as the epithelia
  - keratoconjunctivitis sicca as one of the leading diagnostic criteria (inflammation of the accessory conjunctival lacrimal glands) [61]
- Epidemiology
  - age peak in the 4<sup>th</sup> to 5<sup>th</sup> decades
  - affects mainly women
- Classification
  - primary SS: independent disease with ocular and oral symptoms (Sicca syndrome)
  - secondary SS (more frequently observed): in the context of other autoimmune diseases (RA, SLE, systemic sclerosis)
- Etiology and pathogenesis
  - environmental and hormonal factors as well as genetic predisposition
  - lymphocytic infiltration and sclerosis of the lacrimal and salivary glands by T cells and autoantibodies; B cells presumably also pathogenetically significant [175]
- Clinical
  - slowly progressing, painless swelling of the lacrimal gland (and sometimes of the salivary glands)
  - in the further course, glandular atrophy, often bilateral, xerostomia, xerophthalmia (rather in the atrophic stage)
  - other ocular and orbital symptoms: uveitis, episcleritis/scleritis, optic neuropathy [155, 176], myositis of the EOM [177]
  - extraglandular symptoms: fatigue, pain, polyneuropathy, vasculitic skin lesions, pulmonary changes, musculoskeletal, renal, and gastrointestinal manifestations [175]
- Diagnostics
  - CT/MRI: orbitally enlarged lacrimal glands with enhancement, difficult to delimit to lymphoproliferative diseases [178]
  - lab: increased specific antinuclear antibodies (SS-A and SS-B, the latter highly specific for SS)
  - biopsy: confirmation of the diagnosis and exclusion of lymphoma (SS patients have a 20-fold increased risk for lymphoma, in particular in the head and neck [175, 179, 180])
- Therapy
  - interdisciplinary therapy is necessary because SS is relatively resistant against pharmacotherapy with corticosteroids and other anti-rheumatics
  - symptomatic therapy of sicca symptoms by ophthalmologists and systemic rheumatological medication consisting of steroids and immunosuppressants, application of biologicals, e. g., rituximab, mostly recommended in SS with extraglandular manifestation [181]





► **Fig. 13** Ruptured dermoid cyst. **a** Swelling in the area of the left upper eyelid and progressive diplopia for 2 months. **b** Suspected ruptured dermoid cyst on MRI (courtesy of the Department of Diagnostic Radiology, University Hospital of Halle. Professor and Chair: Prof. Wohlgemuth). **b–d** Intraoperative and histological confirmation of the diagnosis, biopsy with evidence of an eosinophilic granulomatous infiltrate (figures b and c: courtesy of Prof. Plontke, Professor and Chair of the Department of Otolaryngology, Head and Neck Surgery, University Hospital of Halle; **d**: courtesy of the Institute of Pathology, University Hospital of Halle. Professor and Chair: Prof. Wickenhauser).

### 5.2.6 Kimura syndrome

- Definition
  - benign chronic inflammatory disease of the subcutaneous tissue, of unknown genesis, also called angiolymphoid hyperplasia with eosinophilia
  - first description by Kimura in 1948 [182]
- Epidemiology
  - mainly observed in males of Asian origin between the 20<sup>th</sup> and 30<sup>th</sup> years of life
  - orbit rarely affected
- Histopathology
  - circumscribed skin lesion with a mixture of blood vessels with coarse endothelial cells and areas of polymorphic inflammatory infiltrates with abundant eosinophils, regularly structured multiple lymph follicles and development of eosinophilic abscesses [182–185]
- Clinical
  - inflammatory angiomatous lesions of the head and neck with regional lymphadenitis
  - possible involvement of the salivary glands as well as oral and nasal mucosa
  - orbit (rarely): well-delimited mass of the eyelids, lacrimal glands, or anterior orbit [184, 186], exophthalmos, loss of vision, and diplopia
- Diagnostics
  - typical findings: increased serum IgE and blood eosinophilia
- Therapy

- systemic and topical glucocorticoids (leading to tumor reduction and spontaneous remission)
- local excision in cases of well-delimited unifocal lesions as therapy of choice
- in cases of incomplete excision, adjuvant radiotherapy for local control [186, 187, 194]

### 5.2.7 Histiocytic diseases

Orbital xanthogranulomatous diseases are characterized by proliferation of histiocytes and summarized within the term ‘non-Langerhans cell histiocytosis’. In contrast, Langerhans cell histiocytosis has its origin in dendritic cells, associated with the Rosai-Dorfman syndrome and monocytes/macrophages. These diseases are described below.

#### 5.2.7.1 Non-Langerhans cell histiocytoses

##### 5.2.7.1 Juvenile xanthogranuloma

- Definition
  - benign proliferative cutaneous disease, mainly affecting the eyes and skin
  - primary effects on the orbit with proptosis quite rare
- Numerous differential diagnoses in childhood
- Diagnostics: biopsy confirmation of diagnosis required
- Therapy and prognosis
  - mostly spontaneous remission
  - in symptomatic patients with non-resectable lesions, corticosteroids and chemotherapeutics are applied

### 5.2.7.1.2 Adult-onset xanthogranuloma (AOX) and adult-onset asthma with periocular xanthogranuloma (AAPOX)

- Etiology and pathogenesis
  - unknown, probably autoimmune genesis with deposits of immune complexes and subsequent foreign body reactions in the tissue
  - unknown cause of the affinity for orbital adnexa structures [188]
- Clinical
  - yellowish infiltrates in the area of the conjunctiva and eyelids (xanthelasmas)
  - bilateral occurrence possible
- Diagnostics
  - confirmation of the diagnosis by biopsy: histologically lipid-charged macrophages (xanthoma cells) in the dermis and deeper tissue layers, along with foreign body giant cells and Touton giant cells
  - association with hematological diseases (lymphoproliferative lesions, hepatosplenomegaly) possible, requiring thorough physical evaluation
  - determination of the orbital extension by CT to assess infiltration of the orbital fat, EOM, and lacrimal gland
  - in cases of association with asthma, the term ‘adult-onset asthma with periocular xanthogranuloma (AAPOX)’ is used [189]
- Therapy
  - surgical debulking and plastic reconstruction
  - irradiation
  - systemic corticosteroids and other immunosuppressants (► Fig. 14a, b)
  - intralesional triamcinolone highly effective [190]
- Prognosis
  - progressive disease
  - vision-threatening course without therapy

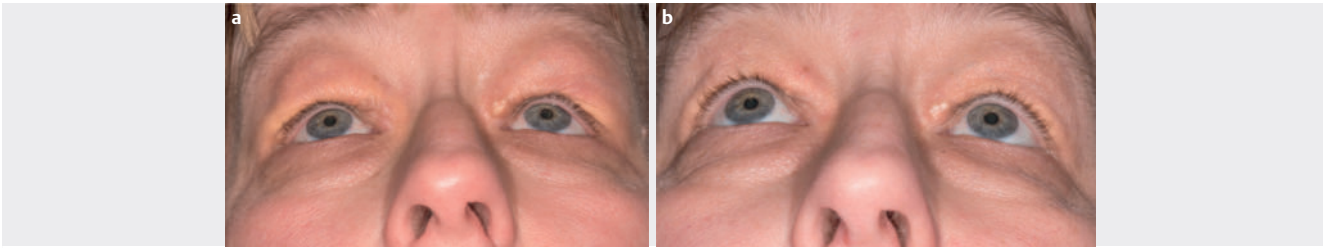
### 5.2.7.1.3 Necrobiotic xanthogranuloma

- Epidemiology
  - rare disease occurring in patients between the 5<sup>th</sup> and 6<sup>th</sup> decades of life
- Pathogenesis
  - foreign body giant cell reactions to deposits of lipid serum immunoglobulin complexes in the skin [188]
  - necrobiosis as histopathological key characteristic: eosinophilic degeneration of collagen in a granulomatous inflammation reaction with foamy histiocytes, foreign body giant cells, Touton giant cells, and lymphocytes
- Location
  - development of infiltrates at the eyelids and ocular adnexa structures as well as the extremities
  - effects on inner organs and hematological neoplasms also possible [61]
- Clinical
  - reddish-yellow lesions or flesh-colored nodules with extension into the anterior orbit with subsequent proptosis, ptosis as well as scar-related lagophthalmos
- Therapy

- many different therapeutic alternatives in use, including surgery, radiation, plasmapheresis, intralesional and systemic steroid application as well as cytostatic agents
- case reports describing successful application of thalidomide in combination with dexamethasone [191]
- overall, pharmacotherapy superior to radiation and surgical debulking
- Prognosis
  - progression after biopsy or debulking possible
  - lifelong follow-up because of increased risk of hematological malignancy

### 5.2.7.1.4 Erdheim-Chester disease

- Definition
  - rare type of non-Langerhans cell histiocytosis with progressive course, characterized by bone pain, retroperitoneal fibrosis, and infiltrations in the face
  - pathological characteristics: wide-spread infiltration of foamy (lipid charged) non-Langerhans cell histiocytes
- Epidemiology
  - first manifestation mostly between the 5<sup>th</sup> and 7<sup>th</sup> decades of life
  - predominantly in males
  - more than 600 cases described since 1930 [192]
- Etiology
  - not completely understood
  - association with different immunological diseases as hint for abnormal interaction between T cells and macrophages (uncontrolled activation of the macrophages by functional disorders of natural killer (NK)-T cells or cytotoxic T cells)
- Clinical
  - characteristic: bone pain, especially in the distal lower extremities because of osteosclerosis of the long bones
  - often bilateral orbit effects: xanthogranulomas with partly deep retrobulbar infiltration, thus ophthalmoplegia and compressive optic neuropathy also possible in addition to exophthalmos
  - general symptoms such as fever and weight loss
  - severe disorders possible, including diabetes insipidus, cerebellar and pyramidal tract signs, cranial nerve paresis, adrenal insufficiency, pulmonary fibrosis, and cardiac decompensation [192–194]
  - variable course that can include fulminant organ failure
- Therapy
  - interdisciplinary treatment essential in cases of orbital involvement
  - systemic therapy with, e. g., interferon, glucocorticoids, cladribine, imatinib, anakinra
  - since 2012, also infliximab and vemurafenib
  - orbital decompression in cases of compressive neuropathy of the optic nerve [192, 194–195]
- Prognosis
  - poorest among all non-Langerhans cell histiocytosis with mortality rates of >60% within 3 years [196]



► **Fig. 14** Adult-onset asthma with periocular xanthogranuloma. A 50-year-old patient with significant thickening of the upper eyelid skin with subcutaneous xanthomatous changes before (a) and after (b) initial prednisolone boost therapy; because of a good response to cortisone, the treatment was shifted to methotrexate as off-label therapy based on positive study results. ► **Figures 14a, b** are from the archive of the Department of Ophthalmology, University Hospital of Halle.

#### 5.2.7.1.5 Disseminated xanthogranuloma

- **Definition**
  - very rare, non-familial, histiocytic, infiltrative disease primarily affecting skin, mucosa, and hypothalamus
- **Epidemiology**
  - about 100 cases reported
  - disease onset mostly in young adults [197]
  - male:female ratio, 2:1
- **Etiology and pathogenesis**
  - causes or risk factors not known
  - characteristic: accumulation of histiocytes at the entire integument and CNS with accumulation of cholesterol and other lipids, leading to a histologically foamy appearance (typical for xanthomatous lesions)
- **Clinical**
  - reddish cutaneous nodes, mainly at the surface of the flexors
  - cornea, conjunctiva, and eyelids affected (20%)
  - dysphagia or dysphonia because of involvement of the upper airways (40%)
  - diabetes insipidus from meningeal involvement (40%)
- **Diagnostics**
  - pathognomonic: triad of typical skin alterations, dysphagia, and diabetes insipidus [198]
  - bone marrow biopsy and serum electrophoresis required to exclude myeloid melanoma (observed in more than 50% of the patients)
  - histologically, not differentiable from Erdheim-Chester disease
- **Therapy**
  - currently, causal therapy not possible
  - therapy attempts with numerous different medications, e. g., corticosteroids, lipid reducers, and several immunosuppressants; cladribine (purine-nucleoside analogue) currently most promising [199]
- **Prognosis**
  - possible local control by surgical excision or CO<sub>2</sub> laser ablation

#### 5.2.7.2 Langerhans cell histiocytosis Definition

- spectrum of diseases characterized by skeletal or soft tissue infiltration with Langerhans cells (synonym: Langerhans cell granulomatosis, histiocytosis X) [200–201]
- **Epidemiology**
  - rare, predominantly occurring in children and adolescents
  - prevalence of 4–5:1,000,000
  - involvement of the orbit in 25% of cases
- **Etiology and pathogenesis**
  - unclear, presumably clonal proliferation of phenotypically abnormal Langerhans cells
  - expression of atypical surface proteins and deposits in the tissue where Langerhans cells otherwise are not present (e. g., bones)
- **Types**
  - unifocal manifestation: eosinophilic granuloma (most frequent type)
  - multifocal manifestation: Hand-Schüller-Christian disease with the triad of exophthalmos, diabetes insipidus, and osteolysis, very rarely Letterer-Siwe syndrome with progressive involvement of bone marrow and other organs [202]
- **Clinical**
  - typical orbital findings: proptosis, ptosis, and papillary edema, bone destruction or the temporal orbital part
  - additional inflammatory reaction
- **Diagnostics**
  - CT scan for detection of bone lesions
  - MRI to assess the cranial extension [203]
  - diagnosis based on typical clinical lesion, immunohistochemical identification of the surface markers of CD1a and CD207 as well as electron microscopic evidence of typical Birbeck granulae
- **Differential diagnoses in pediatric patients**
  - acute infections (eyelid edema), inflammatory pseudotumor, dermoid cyst, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, or neuroblastoma, Erdheim-Chester disease
- **Prognosis**
  - better with increasing age at first diagnosis
  - rather poor in cases of multifocal involvement

- 5-year survival rate maximum of 50% in cases of Letterer-Siwe syndrome despite modern chemotherapeutics
- Therapy
  - local excision as therapy of choice in cases of isolated orbital involvement
  - intralesional injection of corticosteroids (prompt resolution described)
  - low-dose radiation in cases of lesions that cannot be approached surgically
  - systemic therapy for incomplete resection or with recurrence
    - prednisone for disseminated disease
    - chemotherapeutics in cases of poor response
  - hormone substitution in cases of hypopituitarism [61]

### 5.2.7.3 Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorman syndrome)

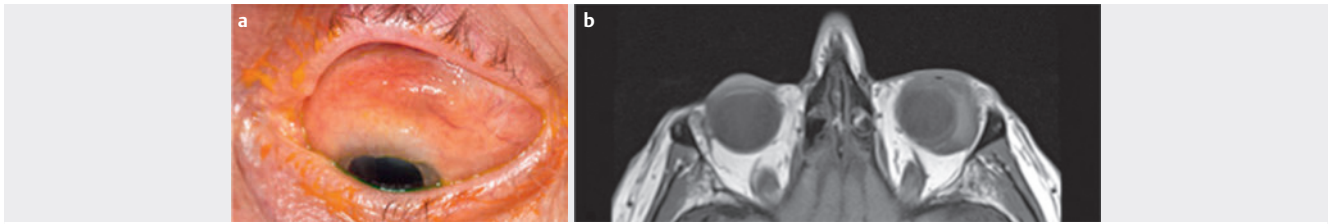
- Definition
  - rare disease with massive infiltration of S-100 positive histiocytes in the tissue and cervical lymph nodes [204]
- Etiology and pathogenesis
  - possibly viral genesis and genetic component
  - histopathologically characteristic: emperipolesis with phagocytosis of lymphocytes, erythrocytes, and neutrophilic granulocytes by large S-100 positive histiocytes
- Epidemiology
  - age peak in adolescents between 15 and 20 years
  - increased occurrence in people with darker skin [204–206]
- Clinical
  - first manifestation mostly as indolent cervical lymph node swelling with accompanying fever, weight loss, and night sweats
  - extranodal manifestations in >40% of patients: eye, salivary glands, nose, bones, skin, or CNS [204, 207], necessitating systemic examination
  - in cases of massive lymph node swelling, possible life-threatening compression of the upper airways [208]
  - orbital manifestation: proptosis, swelling of eyelids or lacrimal glands
  - intra- or extranodal involvement: possible compressive neuropathy of the optic nerve and uveitis [208]
- Therapy
  - generally self-limiting, indication for treatment mainly in cases of airway obstruction resulting from sudden size progression of massive cervical lymph node swellings
  - first-line pharmacotherapy: systemic high-dose therapy with corticosteroids
  - surgical intervention (excision or debulking) according to the severity of the orbital manifestation, further functional and esthetic corrections possible
  - in cases of idiopathic eyelid edemas, systemic corticosteroids or other immunosuppressants
  - in cases of life-threatening obstruction of the airways: surgical therapy or emergency radiation inevitable
  - chemotherapy if needed in cases of severe orbital involvement with optic neuropathy [204, 209]

### 5.2.8 Castleman's disease

- Definition
  - rare lymphoproliferative disease
- Classification in two clinical categories
  - monocentric type
    - benign localized hyperplasia of lymphatic tissue
    - curative treatment by excision of the affected lymph nodes
  - multicentric type
    - systemic disease with potentially life-threatening symptoms
    - classification in HHV-8-associated type and idiopathic multicentric type (pathogenetic cytokine dysregulation) [210–211]
- Classification into three histological categories
  - hyaline vascular type (80–90%)
  - plasma cell type (10–20%)
  - rare mixed type
- Location
  - extranodal involvement of the orbit quite rare, with few cases reported
  - monocentric variant with hyaline vascular type in more than 90% of the orbital cases
- Clinical
  - mostly indolent swelling (proptosis)
  - in some cases, B symptoms
- Diagnostics
  - histological confirmation [211–212]
  - imaging procedures for orbital assessment and for exclusion of a multicentric occurrence recommended
- Therapy
  - primary therapy option: surgical excision [211–212]
  - in cases of multicentric variant, an interdisciplinary treatment approach required
  - monoclonal antibodies, if needed combined with cytostatics [211, 213–214]

### 5.3 Conclusion

The large spectrum of possible diagnoses and the frequently overlapping clinical and radiological presentations of orbital inflammation emphasize the significance of biopsies for identifying the cause. In addition to the many infectious diseases that can entail possibly severe complications, autoimmune diseases often present initially in the orbit and must be assessed accurately with regard to serology and clinical manifestation. Among non-infectious inflammatory lesions, idiopathic orbital inflammation is most frequently observed. IgG4-associated diseases have gained in importance in recent years as a cause of orbital inflammation. Because of their similarity to lymphoproliferative diseases, non-infectious diseases of the orbit require thorough assessment. Histiocytic diseases remain important rare conditions that cause inflammation and fibrosis of the orbit and can lead to severe organ failure.



► **Fig. 15 a** Prominent amyloid masses along the upper circumference. **b** MRI of the orbit. Axial image with “surrounding” of the eyeball by amyloid.

## 6. Degenerative Diseases: Orbital Amyloidosis

### 6.1 Orbital amyloidosis

The term ‘amyloidosis’ describes a heterogenic group of diseases characterized by extracellular accumulation of insoluble proteins in the  $\beta$  leaflet structure. Organ function may be disturbed by compression or direct cytotoxicity. Amyloidosis may present as a primary condition or secondarily as sequela of another disease. A genetic predisposition has been described [215] for this rare systemic or localized disease.

- Location
  - deposits of amyloid possible in all structures of the orbit and the ocular tissue [216–218]
  - cases described with involvement of the lacrimal gland, eyelids, conjunctiva, and eye muscles including the palpebral levator muscle (► **Fig. 15a, b**)
- Clinical
  - ptosis, exophthalmos, motility impairment with diplopia, bulbous deviation, ectropium or entropium, palpable tumor [218]
- Differential diagnoses
  - chronic inflammatory gut diseases, tuberculosis, multiple myeloma
  - examinations required of heart, kidneys, gastrointestinal tract, and CNS [215]
- Diagnostics
  - difficult diagnosis because of a lack of typical symptoms
  - MRI: inhomogeneous and contrast-enhancing deposits
  - CT scan: calcifications
  - histopathology: amyloid-typical apple-green staining as well as polarization with microscopically double-refractive properties
  - in cases of localized involvement, exclusion of a systemic variant required
- Therapy
  - depending on the type, ranging from systemic chemotherapy with cortisone application to transplantation of the affected organs
  - in cases of localized orbital amyloidosis: surgical removal as therapy of choice if needed correcting interventions, e. g., for eyelid malpositions [215, 216, 218–219]
  - radiotherapy as prophylaxis against recurrence recommended by some authors [216, 220]
- Prognosis

- highly variable course in cases of orbital involvement, from complication-free localized findings to severe organ damage with loss of vision [215]

### 6.2 Storage diseases [221–225]

Patients with storage diseases like Pompe’s disease or Gaucher’s disease have a high prevalence of clinically significant ophthalmological symptoms such as ptosis, bulbar motility disorders, strabismus, myopia, and astigmatism, in particular in classic infantile manifestations. These symptoms are mainly the result of the accumulation of glycogen (Pompe’s disease) or glucocerebroside (Gaucher’s disease), especially in the EOM, which may affect other ocular adnexa structures.

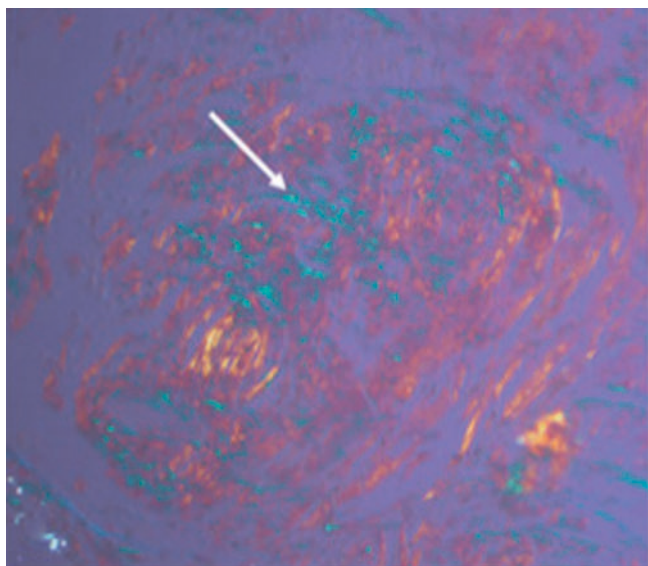
### 6.3 Mitochondrial diseases

#### 6.3.1 Chronic progressive external ophthalmoplegia (CPEO)

- Definition
  - very rare systemic muscle disease with slowly progressive paresis of all external eye muscles
- Epidemiology
  - in addition to Leber’s hereditary optic neuropathy, the most frequently observed mitochondrial disease of adults with eye involvement
  - prevalence: about 12:100 000 [226]
  - onset mostly between the 20<sup>th</sup> and 50<sup>th</sup> years of life
- Clinical
  - ptosis often the first symptom [227]
- Differential diagnoses
  - other mitochondrial diseases, e. g., Kearns-Sayre syndrome (also ptosis and external ophthalmoplegia, onset mostly before the age of 20 years, additionally cardiac conduction disorders, cerebellar ataxia, and/or increased liquor albumin)
  - MELAS syndrome, (ocular) myasthenia gravis, oculopharyngeal muscle dystrophy
- Diagnoses
  - MRI: atrophy of the extraocular muscles [228]
  - skeletal muscle biopsy: evidence of numerous “ragged red fibers” and COX-negative fibers

#### 6.3.2 Leigh syndrome

- Definition
  - neurodegenerative disease (mitochondriopathy) in children
- Epidemiology



► **Fig. 15 c** Amyloid deposits on polarization microscopy showing the typical green staining. Courtesy of Georg-Thieme-Verlag (taken from Kesper C, Viestenz A et al., *Orbital Amyloidosis: Comparison of Two Different Clinical Courses*. *Klin Monatsbl Augenh* 2020, 237: 35–40).

- most frequent pediatric presentation of mitochondriopathy
- onset mainly in the 2<sup>nd</sup> year of life
- prevalence: about 1:40 000 [229]
- in rare cases, occurrence in adults also possible [230]
- Etiology
  - genetically very heterogenic, up to now identification of mutations in 75 genes [231]
- Clinical
  - highly variable symptoms
  - in the context of infection, development of neurological symptoms such as ataxia and dystonia and also ophthalmological symptoms, mainly strabismus, melanotic retinopathy, optic nerve atrophy, ptosis, and nystagmus [232]
  - later symptoms in other organs such as heart, liver, kidneys, or gastrointestinal tract
- Prognosis
  - progress in phases, mostly with death in the 3<sup>rd</sup> year of life

## 7. Tumors of the Orbit [2, 201, 233]

### 7.1 General remarks

With an incidence of 6–10 per 1 million people, orbital neoplasms are rare, but they encompass a multitude of different entities that can lead to difficulties in the context of diagnostics. About 60% in adults are benign and 40% are malignant. “True” orbital neoplasms have to be differentiated from inflammatory orbital lesions without identifiable origin (idiopathic orbital inflammation, formerly called pseudotumors). They represent about 5–7% of all orbital masses and respond well to steroids and immunosuppressants. In the con-

text of history-taking and diagnostics, the exact location, invasiveness, and status should be clarified. Diagnostics and therapy are often performed in an interdisciplinary context.

#### 7.1.1 Symptoms

Neoplasm of the orbit may be classified as described below.

Because of the anatomical circumstances, typically the following symptoms are observed (with decreasing incidence) [201]:

- Exophthalmos/bulbus protrusion (key symptom)
- Bulbus dislocation
- Motility disorders, diplopia
- Pain
- Loss of vision
- Impaired visual field

Intraconal lesions tend to lead to axial exophthalmos, whereas extraconal masses tend to lead to bulbus dislocation to the contralateral side of the tumor (e. g., a tumor of the lacrimal gland leads to dislocation into the inferior nasal direction).

#### 7.1.2 Classification and overview [2, 201]

Neoplasms of the orbit may be classified as follows:

- Neoplasms of **epithelial** origin
- Neoplasms of **non-epithelial** origin
- Neoplasms of **lymphatic** tissue

In each category, **benign** and **malignant** entities are found. The only epithelial structure in the orbit is the **lacrimal gland**, and **primary epithelial neoplasms** thus occur there. **Vascular lesions** are sometimes not considered to be neoplasms but instead are viewed as malformations and have a special status. However, they may behave clinically like “true” neoplasms.

#### 7.1.3 General therapeutic principles of benign neoplasms of the orbit [2, 201]

In general, the following therapy options are possible:

- “Watch-and-wait” in cases of asymptomatic benign neoplasms without diagnostic uncertainty (e. g., incidentally discovered hemangioma)
- Surgical resection as most frequently performed therapy in cases of symptomatic benign lesion
- Other treatment strategies such as radiotherapy or chemotherapy in the context of specific entities

In the context of symptomatic benign processes, a thorough weighing of the expected therapeutic benefit against the risk of functional damage is necessary. Resection of an optic sheath meningioma, for example, is associated with a high risk of optic nerve atrophy.

## 7.2 Particularities

### 7.2.1 Neoplasms of the lacrimal gland

- Epidemiology [233–236]
  - incidence: 0.6–1:1 000 000 people per year; about 80 newly diagnosed diseases per year in Germany

- tumors of the lacrimal gland encompass about 25 % of orbital neoplasms
- the distribution of tumors of different tissue types in the lacrimal gland is as follows [237]:
  - epithelial origin: > 50–65 %
  - lymphatic origin (special type of mesenchymal neoplasm): about 30–35 %
  - mesenchymal origin or metastases: 10–15 %
- ratio of benign to malignant epithelial neoplasms is almost 1:1
- Differential diagnoses [233]
  - inflammatory diseases
    - acute dacryocystitis
    - chronic dacryocystitis
    - idiopathic orbital inflammation (formerly called pseudotumor orbitae, dacryoadenitic type, representing about 20–40 % of all cases)
  - structural changes (e. g., lacrimal gland cyst)
  - secondary tumors (not originating from glandular tissue, e. g., metastases, schwannomas)
- General therapeutic strategies [235–236]
  - for suspected epithelial tumor of the lacrimal gland, incision biopsy is contraindicated because of association with significantly worse prognosis of benign as well as malignant tumors
    - e. g., pleomorphic adenoma: 5-year recurrence rate of 32 % after biopsy vs. 3 % without biopsy prior to tumor resection
    - in addition, possible malignant degeneration of locally recurrent pleomorphic adenomas
    - lacrimal gland malignancy: 5-year survival rate of 29 % after biopsy vs. 70 % in cases of initially complete resection
  - precise preoperative diagnostic assessment desirable, based in part on symptom duration, pain, and radiological characteristics
  - the most effective and safe therapy in cases of epithelial tumors: complete resection during the first surgical intervention
  - complete resection indicated for encapsulated and well-circumscribed processes, without prior incision biopsy

- surgical access via lateral orbitotomy and rarely in combination with coronal incision

### 7.2.1.1 Benign neoplasms of the lacrimal gland

► **Table 3** summarizes the most important benign neoplasms of the lacrimal gland. Because of their specific characteristics, lymphoid neoplasms are also dealt with in the section on malignant diseases even if they are, strictly speaking, neoplasms of mesenchymal origin.

#### 7.2.1.1.1 Benign epithelial neoplasms of the lacrimal gland

##### 7.2.1.1.1.1 Pleomorphic adenoma

[233, 234, 236, 238–244]

- Epidemiology
  - most frequent epithelial tumor of the lacrimal gland (< 50 %)
  - about 20 % of all lacrimal gland tumors [237]
  - manifestation in the 4<sup>th</sup> to 5<sup>th</sup> decades of life
  - male : female ratio, 1:1
- Typical clinical findings
  - very slow growth
  - bulbus dislocation in inferior nasal direction (95 %), impaired motility, sometimes with diplopia (40 %), epiphora
- Diagnostics
  - CT scan as diagnostic measure of choice
  - MRI provides only minor additional information (hyperintense signal in T2 weighting)
  - extraconal round-oval, sharply delimited lesion in the lateral superior quadrant of the orbit, inhomogeneous structure, displacing growth, dilation of the bony lacrimal gland fossa (81 % in CT scan), calcifications as possible hint of malignant transformation
  - ultrasound: well-delimited, hypoechoic mass with dorsal sound amplification, low internal echo; on color duplex sonography, vascularization and perfusion identified only in the area of the capsule
- Other diagnostic criterion
  - **score** for differentiation between pleomorphic adenoma and carcinoma of the lacrimal gland **according to Rose and Wright** [242] (► **Table 4**)
- Biopsy
  - risk of incision biopsy doubted by some authors; however, most authors confirm this risk
  - benefit and risk of fine needle aspiration cytology are controversially discussed
- Therapy
  - complete tumor extirpation without opening the tumor capsule with a margin of glandular tissue (access: lateral orbitotomy, palpebral glandular parts should be preserved)

► **Table 3** Benign neoplasms of the lacrimal gland.

Tissue type	Neoplasm
Epithelial	Pleomorphic adenoma Warthin's tumor Oncocytoma Myoepithelioma Cystadenoma Sclerotic polycystic adenosis
Mesenchymal	Solitary fibrous tumor Myxoma Fibrous histiocytoma
Lymphoid	Reactive lymphoid hyperplasia

► **Table 4** Score according to Rose and Wright [242].

Characteristic	Score -1	Score +1
Duration of symptoms	< 10 months	> 10 months
Persistent pain	+	-
Sensitivity disorder	+	-
Well-delimited, round-oval (CT scan)	-	+
Growth along orbital structures (CT scan)	+	-
Calcifications (CT scan)	+	-
Bone destructions (CT scan)	+	-
Relation of symptom duration and tumor size	Large tumor with short duration of the symptoms	Small tumor with long duration of the symptoms

Score of -8 to +2: rather suspicious for carcinoma -> incision biopsy. Score of +3 to +8: suspicious for pleomorphic adenoma -> tumor resection in toto (incision biopsy is contraindicated).

- after previous biopsy: enbloc resection of the scar with the biopsy pathway as well as the lacrimal gland
- Prognosis
  - in cases of incomplete resection and incision biopsies or untreated status, risk of recurrence (32% within 5 years after incision biopsy vs. 3% after complete capsule-preserving resection) or malignant transformation (20% within 30 years)

#### 7.2.1.1.1.2 Warthin's tumor (cystadenolymphoma) [245–246]

- One of the monomorphic adenomas
  - synonyms: adenolymphoma, cystadenolymphoma, papillary cystadenoma lymphatosum (however, to avoid confusion with malignant lymphomas or lymphadenomas, the term 'Warthin's tumor' should be used)
- Epidemiology
  - second most frequent benign tumor of the parotid gland, sometimes also found in periparotid lymph nodes
  - rarely in other salivary glands
  - extremely rare in the lacrimal gland (until now, fewer than 10 cases described worldwide)
- Therapy
  - complete surgical resection via lateral orbitotomy

#### 7.2.1.1.1.3 Oncocytoma [247–254]

- Synonyms
  - oxyphilic adenoma, oncocytic adenoma, Hürthle cell adenoma
- Epidemiology
  - extremely rare in the lacrimal gland (MEDLINE analysis of the literature between 1959 and 2004 provided only 5 well-documented cases [248])
  - more frequently in salivary glands, kidney, adenohipophysis, (para)thyroid gland, caruncle, and conjunctiva of the eye
  - affects older women especially
- Etiology

- development probably from a mutation in the mitochondrial DNA
- Histology
  - benign, slowly growing tumor originating from the epithelia of the excretory glandular ducts; malignant transformation extremely rare
  - granulated, large, eosinophilic, mitochondria-rich tumor cells, so-called oncocytes ("Hürthle cells")
- Therapy of choice
  - complete surgical resection

#### 7.2.1.1.1.4 Myoepithelioma [241, 255–259]

- One of the monomorphic adenomas
- Epidemiology
  - extremely rare in the area of the lacrimal glands: 2 of 272 (<0.01%) histologically examined lacrimal gland tumors [241]; elsewhere, up to 2005, only 7 case reports [255])
  - other occurrences in the head and neck: salivary glands (<1% of parotid tumors), palate
- Imaging
  - on CT, well-delimited encapsulated mass
  - in other locations, difficult to differentiate from other soft tissue tumors or sarcomas by clinical radiology
- Therapy
  - complete and intact resection via orbitotomy, if needed, combined with coronal incision [255]
- Follow-up
  - radiological follow-up recommended
- Prognosis
  - local recurrence rate of 20%

#### 7.2.1.1.1.5 Cystadenoma [260–263]

- Epidemiology
  - rare in the lacrimal gland
  - mainly found in the bile duct, pancreas, ovaries, epididymides, and kidneys
  - rare in the salivary glands (<1% of the salivary gland tumors)



- Pathology
  - papillary and mucinous subtypes (the latter may degenerate)
  - first report in 2002 describing a bilateral cystadenoma of the lacrimal glands [260]
- Differential diagnosis
  - papillary cystadenoma histologically similar to the papillary cystadenoma lymphomatosum (i. e., Warthin’s tumor)

#### 7.2.1.1.1.6 Sclerotic polycystic adenosis (SPA) [264–265]

- Definition
  - new entity in the current WHO classification of epithelial salivary gland tumors
  - formerly considered as inflammatory/reactive change, current term ‘neoplasm’ controversially discussed but favored by most authors
- Synonym
  - sclerotic polycystic adenoma
- Epidemiology
  - first case report of SPA of the lacrimal gland in 2013 [264]
  - 60 cases described to date (involvement mostly of the parotid gland, sometimes of the minor salivary glands)
- Differential diagnoses
  - pleomorphic adenoma, adenoidcystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma (often histopathological misinterpretation and confusion)
- Prognosis
  - recurrence in 30% of cases
  - no metastatic spread or disease-related increased mortality because of SPA

#### 7.2.1.1.2 Benign non-epithelial neoplasms of the lacrimal duct

##### 7.2.1.1.2.1 Mesenchymal tumors

##### Solitary fibrous tumor [266–271]

- Epidemiology
  - quite rare overall, regardless of location
  - 2.8 cases per 100,000 patients in a Mayo Clinic population [268]
  - about 10 case reports of lacrimal gland involvement
  - typical locations: most frequently the pleura, more rarely abdomen, pelvis
- Pathology
  - in the area of the lacrimal glands, possibly originating from periductal connective tissue
  - mostly benign, but malignant appearance (10–37%) as well as recurrences and metastases observed
  - slow, displacing growth
- Differential diagnosis
  - in the area of the lacrimal gland, similar clinical and radiological appearance to pleomorphic adenoma
- Therapy
  - complete resection via lateral orbitotomy
  - no clear evidence for benefit of radiotherapy or chemotherapy in cases of residual tumor
- Prognosis

- correlation between confirmed microscopically non-tumor-free surgical margins and increased development of local recurrences and distant metastases
- local recurrences and distant metastases described mainly for tumors > 10 cm, largely in the thorax or abdomen
- extra-thoracic location linked to increased risk for local recurrences but not to the development of distant metastases

##### 7.2.1.1.2.1.1 Myxoma [272–276]

- Definition
  - neoplasm of mesenchymal/connective tissue origin
- Epidemiology
  - 1 case report involving the lacrimal gland
  - other locations at the eye: conjunctiva, cornea, orbit
  - other locations: predominantly heart, and also bones, skin, skeletal muscles, urogenital tract
- Pathology
  - histologically few cells and vessels with abundant myxoid (mucus-like) matrix rich in hyaluronic acid
- Diagnostics
  - well-circumscribed oval isodense mass on CT
- Therapy
  - complete surgical resection (with excellent prognosis)
  - radiotherapy without relevant effect

##### 7.2.1.1.2.1.2 Fibrous histiocytoma [261, 277]

- Epidemiology
  - report on fibrous histiocytoma of the lacrimal gland in an 11-year-old girl, no other published case reports [277]
  - more frequent in the orbit of adults
- Pathology
  - classification of benign, locally aggressive, and malignant types

##### 7.2.1.1.2.2 Benign lymphoid tumors – reactive lymphoid hyperplasia [278]

- Definition
  - benign lymphoproliferative disease
  - not a “true” neoplasm, being neither monoclonal nor autonomous
  - polyclonal lymphocytic proliferation
  - formerly called pseudolymphoma
  - **atypical lymphoid hyperplasia** as special type (borderline lesion between reactive lymphoid hyperplasia and lymphoma; today mostly classified as low-grade B cell lymphoma)
- Epidemiology
  - about 6% of all lesions of the lacrimal gland [279]
  - similar incidence in conjunctiva, lacrimal glands, and other locations of the orbit (mostly extraconal), rarely in the eyelid
  - rarely bilateral or additionally outside the eye region (e. g., parotid, lung)
- Clinical
  - slowly growing mass with minor functional impairment, only rarely reddening or pain
  - in the lacrimal gland, sometimes palpable as a rather solid, elastic mass with smooth or nodulous surface

- Therapy [237]
  - high-dose glucocorticoids and/or radiotherapy (about 25 Gy)
  - rituximab for therapy-resistant cases
- Prognosis
  - malignant transformation possible

### 7.2.1.2 Malignant neoplasms of the lacrimal gland

► **Table 5** summarizes the malignant neoplasms of the lacrimal gland.

#### 7.2.1.2.1. Malignant epithelial neoplasms of the lacrimal gland

Comparing all types of carcinomas of the lacrimal and the major salivary glands, tumors with similar histology seem to have a less favorable prognosis when they appear in the lacrimal glands. For carcinomas of the lacrimal gland, a classification exists in the current TNM classification of malignant tumors of the UICC. According to this classification, preauricular, submandibular, and cervical lymph nodes are considered as regional lymph nodes. Assignment to the T categories T1–3 is based on tumor size; depending on the involvement of the periosteum and/or bone, the subcategories a–c are differentiated. An involvement of neighboring structures, e. g., paranasal sinuses, cavernous sinus, or brain, leads to categorization as T4 [280].

A singular **histopathological classification** for lacrimal gland tumors does not exist. Instead, many authors consider the lacrimal gland as a minor salivary gland and classify tumors based on the system for salivary glands.

► **Table 5** Overview of the malignant neoplasms of the lacrimal gland described in the text

Tissue type	Neoplasm
Epithelial	Adenoidcystic carcinoma Carcinoma in pleomorphic adenoma Adenocarcinoma (NOS) Mucoepidermoid carcinoma Ductal carcinoma Acinar cell carcinoma Sebaceous gland carcinoma Myoepithelial carcinoma Squamous cell carcinoma Oncocytic carcinoma Polymorphic adenocarcinoma Secretory adenocarcinoma
Non-epithelial	Synovial sarcoma Granulocytic sarcoma Malignant peripheral nerve sheath tumor Malignant rhabdoid tumor
Lymphoid	Extranodal marginal zone B cell lymphoma Follicular lymphoma Diffuse large cell B cell lymphoma Mantle cell lymphoma

► **Table 6** shows a proposal for a **classification of malignant epithelial lacrimal gland tumors**, modified according to Weis et al., in analogy to the WHO classification of salivary gland tumors and with updates of the current version [237, 261, 285, 286]. It is worth mentioning that still some years ago primary adenocarcinomas of the lacrimal as well as salivary glands were not further subclassified. Meanwhile, it is known that they form a group of tumors with different morphologies and biological behaviors, and hence with different prognoses.

#### 7.2.1.2.1.1 Adenoid cystic carcinoma (ACC) [279, 287–295]

- Epidemiology
  - second most frequent epithelial lacrimal gland tumor [296]
  - most frequent malignant tumor of the lacrimal gland (20–30%) [237]
  - mean age at disease onset: about 40 years
  - male:female ratio, 1:1
- Pathology
  - perineural invasion of the tumor as a typical sign
  - frequently hematogenous metastatic spread (more typical than regional lymph node metastasis), even after several years (mainly in the lung, besides bones, liver, and brain)

► **Table 6** Classification of malignant epithelial tumors of the lacrimal gland.

Classification	Neoplasm
Low-grade	Carcinoma in pleomorphic adenoma (minimally invasive carcinoma [ $\leq 1.5$ mm]) Polymorphic adenocarcinoma Mucoepidermoid carcinoma grade ½ Epithelial–myoepithelial carcinoma Acinar cell carcinoma Basal cell (adeno) carcinoma Mucinous adenocarcinoma Clear cell carcinoma Cystadenocarcinoma [281] Secretory carcinoma
High-grade	Carcinoma (adenocarcinoma or adenoidcystic carcinoma) in pleomorphic adenoma (minimally invasive carcinoma [ $> 1.5$ mm]), “malignant mixed tumor” Adenoidcystic carcinoma (NOS) Adenocarcinoma (NOS) Mucoepidermoid carcinoma grade 3 Ductal adenocarcinoma Squamous cell carcinoma Sebaceous gland carcinoma Myoepithelial carcinoma Oncocytic carcinoma Lymphoepithelial carcinoma Carcinosarcoma (in pleomorphic adenoma, “true malignant mixed tumor”) [282]) Neuroendocrine carcinoma [283] Merkel cell carcinoma [284] Other rare and non-classified carcinomas Dedifferentiation of one of the above

- Clinical
    - bulbus dislocation, proptosis, S-shaped ptosis, diplopia, epiphora
    - pain (in 38–79% of cases) and hypesthesia in the fronto-temporal area (indicating the presence of an aggressive tumor)
    - symptom duration at first presentation typically <6 months
  - Diagnostics
    - high-resolution CT scan: bone erosion, irregular margins of the mass, possibly focal calcifications within the tumor
    - MRI: best option to identify involvement of the cavernous sinus, brain, and bone marrow
  - Therapy
    - still no clarity and no consensus regarding optimal therapy; mostly resection with safety margins and adjuvant radiotherapy
    - surgical options
      - according to extension, local resection, exenteration, or radical exenteration (with resection of the orbital roof, lateral orbital wall, and parts of the temporal muscle)
      - radical surgery without clear advantage for local tumor control up to T2, exenteration in cases of tumors at T3 or greater appears beneficial [297]
      - (elective) neck dissection: the rate of regional lymph node metastases (including the intraparotid lymph nodes) appears low in ACC (especially of the lacrimal gland) [297, 298]; elective neck dissection appears unjustified in most cases (but should be discussed in advanced stages, solid histological subtypes, or high-grade malignant degeneration) [298]; higher lymphogenic metastasis rate with ACC of the salivary glands, with elective neck dissection thus leading to longer survival in advanced stages [299].
    - radiotherapy
      - in some trials, no significant survival benefit with additional radiation [288]; improved local control after adjuvant radiotherapy in larger tumors, per other studies [297]
      - particle therapy: satisfactory outcomes in ACC of the lacrimal gland with proton and heavy ion radiation [300–303]
      - brachytherapy may be part of the therapeutic concept, e. g., for treatment of patients after R1 resection [304–305]
    - chemotherapy: hints at improved prognosis with intraarterial cytoreductive chemotherapy (IACC) before (and after) therapy by means of surgery and radiation [289, 290]; furthermore, confirmed higher rate of eye-preserving surgeries after neoadjuvant IACC [306]
  - Prognosis
    - high rate of local recurrence
    - poor long-term prognosis: median survival of 5 years, 10-year survival rate of 20%
    - ACC of the lacrimal gland mainly involves high-grade phenotypes with aggressive behavior and shorter median survival (2.5 years) [297]
  - often death because of intracranial tumor growth or pulmonary metastases
- ### 7.2.1.2.1.2 Carcinoma in pleomorphic adenoma [252, 261]
- Definition
    - according to the WHO classification of salivary gland tumors of 2017, the term ‘carcinoma in pleomorphic adenoma’ is only used together with the histological subtype [265]
  - Synonyms
    - pleomorphic (adeno-)carcinoma, malignant mixed tumor (misleading because only the epithelial (carcinoma) and not the mesenchymal part degenerates; different situation for carcinosarcoma (“true” malignant mixed tumor), also described in the lacrimal gland [282]
  - Epidemiology
    - second most frequent malignant epithelial tumor of the lacrimal gland (4–18%) [279, 291, 307–309]
    - appears typically in the 6<sup>th</sup>/7<sup>th</sup> decades of life (about 10 years later than pleomorphic adenoma)
    - adenocarcinomas more frequently observed in males, adenoid-cystic carcinomas more frequent in females [287]
  - Classification
    - non-invasive (intracapsular relation to pleomorphic adenoma)
    - minimally invasive (<4–6 mm above the capsula)
    - invasive (>4–6 mm above the capsula) [265]
  - Histology
    - mostly poorly differentiated adenocarcinoma or undifferentiated carcinoma, more rarely adenoidcystic carcinoma
    - also possible: differentiated squamous cell carcinoma and spindle cell sarcomas [235, 261, 308, 310]
  - Clinical
    - sudden development of tumor recurrence after incomplete removal of a pleomorphic adenoma or significant sudden progress (possibly with accompanying pain) of a tumor that has been symptom-free for several years
  - Therapy
    - tumor resection (possibly radical orbitectomy including bone areas, depending on extent) with removal of regional (parotid) and cervical lymph nodes (adenocarcinomas may metastasize early lymphatically)
    - adjuvant radiotherapy afterwards as a useful completion of treatment [296, 311]
  - Prognosis
    - mostly considered unfavorable but depends on several factors such as histological subtype and invasiveness
    - non-invasive and minimally invasive types: very good prognosis after complete surgical resection (without adjuvant therapy)
    - invasive type: very aggressive tumors with poor prognosis but favorable prognostic effect of adjuvant therapy [312–313]
    - causes of death: intracranial spread, distant metastases (lung, thoracic wall, bones)

### 7.2.1.2.1.3 Adenocarcinoma (not otherwise specified, NOS) [233]

Annotation: In the current WHO classification of salivary gland tumors, the number of entities was reduced from 39 to 33 to reduce complexity and make the classification clearer. Among others, this change led to the inclusion of several, sometimes extremely rare entities under the term “adenocarcinoma NOS” [285].

- Epidemiology
  - third most frequent malignant epithelial tumor of the lacrimal gland (5–10%) [237, 279]
- Etiology
  - de novo or within pleomorphic adenoma
- Pathology
  - highly malignant
  - earlier metastasis comparison to adenoidcystic carcinomas
  - early lymphatic and hematogenous metastasis, mainly in the lung, brain, and mediastinum [314]
- Therapy
  - frequently in an advanced stage at first presentation so that adequate surgical resection is difficult or even impossible
  - surgical therapy, if needed with orbital exenteration or craniofacial orbitectomy and regional lymph node dissection [291, 315]
  - adjuvant radiotherapy [306, 315–316]
  - with observed Her-2 overexpression in some adenocarcinomas of the lacrimal gland, pharmaceuticals such as lapatinib are possible therapeutic options [317]
- Prognosis
  - shorter survival rates in comparison to adenoidcystic carcinoma

### 7.2.1.2.1.4 Mucoepidermoid carcinoma

- Epidemiology
  - fourth most frequent malignant epithelial tumor of the lacrimal gland (2–3%) [237, 279]
  - until 2000, fewer than 30 case reports published [318]
  - mean age at disease onset: 49 years
  - males a little more frequently affected [291, 319–320]
- Clinical
  - typically indolent, slowly growing mass
- Differential diagnosis
  - often confused with pleomorphic adenoma [296, 319–320]
- Therapy
  - high-grade tumors: exenteration (with resection of affected bones)/orbitectomy, and adjuvant radiation
  - low-grade tumors: tumor extirpation (with or without radiation) [296, 319]
  - regional lymph node dissection (parotidectomy and neck dissection), mainly in higher grading and/or tumor size
- Prognosis [314]
  - tumor-free survival and overall prognosis mainly grading dependent (classification into grades I–III based on histopathological characteristics)
  - Thorvaldsson et al. (1970): mean follow-up of 12 years in cases of mucoepidermoid carcinomas of the major salivary

glands; survival rates of 100% or 97% in patients with grade I or grade II tumors, but only 43% in grade III tumors (high-grade) [314, 321]

### 7.2.1.2.1.5 Ductal adenocarcinoma

- Epidemiology
  - first described by Katz et al. in 1996 [322]
  - very rare, 2% of all epithelial lacrimal gland tumors [286]
  - Yang et al. (2018): review of 24 cases in the literature and two of their cases [323]
  - male:female ratio, 3–4:1 [237, 323]
- Etiology
  - possible development as carcinoma in pleomorphic adenoma [324]
- Pathology
  - equivalent of ductal adenocarcinoma of the salivary gland, histopathological similarities with ductal breast cancer
  - metastases most frequently observed in cervical lymph nodes, brain, bones, lung, and liver
  - androgen receptor positive in 46–83% of cases; Her-2 positive in 35–67% [237, 323, 325]
- Therapy [317, 323, 326]
  - therapy recommendations along the same lines as for ductal salivary gland carcinoma
  - surgical resection, if needed with adjuvant radio(chemo)therapy
  - orbital exenteration in > 50% of the patients undergoing surgery
  - primary radiochemotherapy in non-resectable tumors
  - chemotherapy in palliative settings with response rates of 15–20%
  - if needed, pharmaceutical androgen deprivation therapy in the recurrent or metastatic setting, e. g., bicalutamide for androgen receptor–positive tumors or trastuzumab or lapatinib with Her-2/neu expression
- Prognosis
  - aggressive tumor, with more than one third of patients dying even after aggressive therapy [237, 323]
  - high recurrence rate, with more than half of patients developing metastases (58%), sometimes very early [323, 327]

### 7.2.1.2.1.6 Acinar cell carcinoma [328–331]

- Epidemiology
  - very rare in the area of the salivary glands (2–4% of parotid tumors)
  - even more rare in the area of the lacrimal gland, with only single case reports in the literature
  - females appear more frequently affected
  - age of manifestation: 6<sup>th</sup> decade of life
- Diagnostics/differential diagnosis
  - uncharacteristic in CT/MR imaging, resulting in a high risk of confusion with pleomorphic adenoma
- Therapy
  - surgical resection, eye preservation depending on the extent of the lesion, if needed, exenteration or advanced exenteration (in cases of bone infiltration)

#### 7.2.1.2.1.7 Primary sebaceous carcinoma [332–335]

- Epidemiology
  - extremely rare, only single case reports
- Hypotheses of pathogenesis
  - originating from heterotopic tissue
  - malignant transformation and sebaceous-like differentiation of other epithelial tumors of the lacrimal gland
  - originating from degenerated pluripotent cells
- Pathology
  - highly malignant tumor often identified very late (high-grade)
- Differential diagnoses
  - must be differentiated from secondary invasion (e. g., originating from upper eyelid carcinoma) and metastasis
  - histologically sometimes difficult to delimit from other entities such as squamous cell carcinoma or basal cell carcinoma (40–75% of sebaceous carcinomas of the lacrimal gland confused initially with squamous cell carcinoma; special staining for fat can avoid this confusion)
- Therapy
  - surgical therapy, if needed, orbital exenteration or advanced exenteration
  - parotidectomy/neck dissection depending on the extension (infiltration of surrounding structures, e. g., the upper eyelid)
  - adjuvant radiotherapy (local recurrence rate after resection: 9–36%)
  - radiotherapy alone in cases of non-resectable tumors
  - particle therapy (e. g., heavy ions, C<sup>12</sup>) [336]

#### 7.2.1.2.1.8 Myoepithelial carcinoma [337–341]

- Epidemiology
  - very rare in the head and neck region, mostly affecting the parotid gland
  - extremely rare in the lacrimal gland; in larger case series, < 1% of all lacrimal gland tumors [286]
  - Mahdi et al. (2018): at the time of their writing, only 9 published case reports [324]
- Pathology
  - difficult histopathological diagnostics, misinterpretation occurs because of the rarity of the disease and histological polymorphism [286, 342]
- Therapy
  - overall, so rare that no therapy concept established
  - surgical therapy
    - wide surgical excision, if needed, orbital exenteration
    - cervical lymph node metastases are rather rare so that elective neck dissection is not routinely recommended [341, 343]
  - radiotherapy
    - applied in myoepithelial tumors of the lacrimal gland at least in the palliative setting [344]; if the parotid gland or other locations of the head and neck involved, adjuvant therapy after surgical resection in half of cases [341]
    - primary radiotherapy if surgical resection not possible
    - significance of adjuvant radiation unknown; several authors report no effect on local recurrence rate [345]

- chemotherapeutics partly described as effective, but systematic data are lacking
- Prognosis
  - high-grade malignancy with poor prognosis and high recurrence rate [286, 341]
  - myoepithelial carcinoma of the head and neck: 5-year survival rate of 32% [341]
  - distant metastasis rate of 35% (mainly pulmonary metastases) [341]
  - distant metastases with primary tumor in the lacrimal gland rarely described (**caution**: low number of cases) [342]

#### 7.2.1.2.1.9 Squamous cell carcinoma

- Epidemiology
  - according to a review by Weis et al. (2009), only 8 case reports published at the time of their writing [286]
- Etiology/pathogenesis
  - development of a few cases on the floor of a lacrimal gland cyst lined with epithelium (dacryops) [346–347]
- Therapy
  - surgical resection (if needed, orbital exenteration) and adjuvant radio(chemo)therapy [346–348]

#### 7.2.1.2.1.10 Oncocytic carcinoma [349–350]

- Epidemiology
  - according to Kalantzis et al. (2013), at the time of their writing, four published cases with involvement of the lacrimal gland [350]
- Pathology
  - high-grade tumor with infiltrative growth pattern, tendency to local recurrences and distant metastases
- Therapy
  - radical resection (if needed, orbital exenteration) followed by adjuvant radio(chemo)therapy

#### 7.2.1.2.1.11 Polymorphic adenocarcinoma [265, 351]

- Formerly used term (until 2017)
  - polymorphic low-grade adenocarcinoma
- Epidemiology
  - according to Selva et al. (2004), at the time of their writing, four published cases with involvement of the lacrimal gland [351]
  - appears almost exclusively in the minor salivary glands, mainly at the palate (female:male ratio, 2:1)
- Differential diagnosis
  - often confused with adenoidcystic carcinoma
- Pathology
  - infiltrative growth and perineural invasion
  - metastases in regional lymph nodes relatively rare (6.5–10%), distant metastases extremely rare
- Therapy
  - surgical resection (if needed, orbital exenteration); because of the relatively favorable prognosis according to Selva et al. [351], eye-preserving procedures to be considered
  - necessity of adjuvant radiation questionable [351]
- Prognosis

- clearly better compared to other adenocarcinomas of the salivary gland (overall survival of  $\geq 95\%$ )
- if salivary glands involved, local recurrence in 5–33 % of cases (generally well controllable with re-resection)

#### 7.2.1.2.1.12 Secretory carcinoma [265, 352–353]

- Definition
  - new entity, first described in 2010 in the head and neck as mammary analogue secretory carcinoma, designated as “secretory carcinoma” by the WHO
  - previously assigned to other entities despite not always typical histopathological characteristics (e. g., granule poor acinic cell carcinoma)
  - first described in 2018 in the lacrimal gland [352–353]
- Pathology
  - similar to the secretory carcinoma of the breast, also identification of the specific ETV6-NTRAK3 fusion gene
  - occurring in the head and neck mainly in the parotid gland (70 %), and also in the buccal, lip, and palatal mucosa, rarely in the submandibular or sublingual glands
  - regional lymph node metastases in up to 25 % of cases
- Therapy
  - surgical resection
  - tropomyosin receptor kinase (TRK) inhibitors (larotrectinib, entrectinib) as future therapy options for tumors with NTRK fusion
- Prognosis
  - overall, not very aggressive tumor with relatively favorable prognosis (survival exceeding 95 %)

#### 7.2.1.2.2 Malignant non-epithelial tumors of the lacrimal gland

Malignant non-epithelial tumors of the lacrimal gland are summarized in ► **Table 7**. Lymphomas of the lacrimal gland are discussed specifically in section 7.2.1.2.3.

#### 7.2.1.2.3 Malignant lymphoproliferative diseases – lymphomas of the lacrimal gland [233, 237, 365–366]

- Definition
  - belongs to ocular adnexa lymphomas
- Epidemiology
  - lymphomas are the most frequent orbital malignancies [365]
  - 37 % of all malignant tumors of the lacrimal gland are lymphomas [366]
  - predominantly older people affected; mean age of 60 (+) years
  - female:male ratio, 2.4:1
- Classification: by decreasing incidence, the following entities are found in the lacrimal gland
  - extranodal marginal zone lymphoma
  - follicular lymphoma
  - diffuse large cell B cell lymphoma (DLBCL)
- Etiology/pathogenesis
  - in rare cases, development on the floor with chronic inflammatory diseases (Sjögren’s syndrome, IgG4-associated diseases, reactive lymphatic hyperplasia)

- Clinical
  - main symptoms: mass, bulbus dislocation, diplopia
  - pain rarely reported (in the context of bone infiltration in cases of highly malignant types)
  - salmon-colored tumor in the area of the neighboring conjunctiva [233]
  - in 20–25 % of cases, bilateral involvement [365, 367–368]
  - typically, involvement of the orbital and palpebral part of the gland [233]
- Diagnostics
  - imaging procedures
    - CT scan or MRI: smooth and homogeneous mass, mostly without infiltration of the surrounding tissue (but possible bone erosion in highly aggressive types [365])
    - clear morphological differentiation among reactive lymphatic hyperplasia, lymphoma, and non-specific inflammation of the lacrimal gland not possible with clinical assessment or imaging, so biopsy required (incision biopsy preferable to fine needle aspiration cytology) [233]
  - further diagnostics (for assessment of systemic involvement)
    - bone marrow biopsy, whole body CT scan/MRI or PET
    - Ann Arbor classification and TNM staging apply
- Therapy
  - radiotherapy, especially in localized types (Ann Arbor stage IE)
  - polychemotherapy, especially in cases of systemic spread (stages IIE-IVE), in cases of DLBCL also in an early stage [369]
  - antibody therapy, e. g., anti-CD-20 rituximab
  - stem cell transplantation, if needed
  - surgical therapy: surgical therapy alone generally not justified [233]
- Prognosis
  - at the time of first diagnosis, about 80 % at a localized stage (IE), and 20 % showing systemic involvement in the context of staging (stage IIE-IVE) [233]
  - for patients with stage IE at first diagnosis, secondary generalization in the further course in 22–42 % of cases [233]
  - Rasmussen et al. (2011): 5-year survival rate of 70 % in 27 patients with lymphoma of the lacrimal gland [366]

#### 7.2.1.2.3.1 Extranodal marginal zone B-cell lymphoma

- Epidemiology
  - most frequent subtype in the lacrimal gland, with 40 % of all lymphomas [366]
- Therapy
  - early stage (stage IE/IIE, no systemic involvement): radiotherapy (about 30–40 Gy) [370]
  - in cases of systemic involvement or high tumor charge: pharmaceutical combination therapy, e. g., rituximab + cyclophosphamide + hydroxydaunorubicin + vincristine + prednisone (R-CHOP) -> 3-year progression-free survival in 70–80 %
  - rituximab applied for a further 2 years as maintenance dose
- Prognosis

► **Table 7** Malignant tumors of the lacrimal gland of non-epithelial origin (without lymphomas).

Neoplasm	Characteristics
Synovial sarcoma [354]	<ul style="list-style-type: none"> <li>▪ Epidemiology                             <ul style="list-style-type: none"> <li>– One of the more frequent types of sarcoma in adolescents and young adults</li> <li>– In 1–10% of cases, the head and neck area is affected, extremely rare in the orbit</li> <li>– Until 2015: four case reports with involvement of the lacrimal gland</li> </ul> </li> <li>▪ Pathology                             <ul style="list-style-type: none"> <li>– Originating from primitive mesenchymal cells of the connective tissue, not from the synovial membrane (the term only comes from the microscopic similarity)</li> <li>– Mainly the lower extremities are affected (about 75%)</li> </ul> </li> </ul>
Granulocytic sarcoma (myeloid sarcoma) [355–356]	<ul style="list-style-type: none"> <li>▪ Etiology                             <ul style="list-style-type: none"> <li>– Preceding acute myeloid leukemia or simultaneously occurring with it or other myeloproliferative diseases</li> </ul> </li> <li>▪ Therapy                             <ul style="list-style-type: none"> <li>– Systemic therapy required</li> </ul> </li> </ul>
Malignant peripheral nerve sheath tumor [357, 358] (terms that are synonymously used such as neurogenic sarcoma, neurofibrosarcoma, and malignant schwannoma should be avoided)	<ul style="list-style-type: none"> <li>▪ Epidemiology                             <ul style="list-style-type: none"> <li>– Only single case reports with involvement of the lacrimal gland</li> </ul> </li> <li>▪ Risk factors                             <ul style="list-style-type: none"> <li>– Neurofibromatosis</li> <li>– Previous radiotherapy</li> </ul> </li> <li>▪ Pathogenesis                             <ul style="list-style-type: none"> <li>– Frequent lymph node involvement and distant metastases (40–80%)</li> </ul> </li> <li>▪ Diagnostics                             <ul style="list-style-type: none"> <li>– Clinical differentiation of benign tumors is partly impossible because of non-specific initial symptoms</li> <li>– Differentiation is not always possible even with imaging procedures</li> </ul> </li> <li>▪ Therapy                             <ul style="list-style-type: none"> <li>– Radical excision and adjuvant radiotherapy</li> <li>– Little knowledge about chemotherapy</li> </ul> </li> <li>▪ Prognosis                             <ul style="list-style-type: none"> <li>– Poor 5-year survival rate: 50%</li> <li>– Recurrences regularly observed (50%)</li> </ul> </li> </ul>
Malignant rhabdoid tumor [359–363]	<ul style="list-style-type: none"> <li>▪ Definition                             <ul style="list-style-type: none"> <li>– Aggressive soft tissue sarcoma in childhood</li> <li>– Develops mainly in the kidney, liver, peripheral nerves</li> </ul> </li> <li>▪ Epidemiology                             <ul style="list-style-type: none"> <li>– Extremely rare in the orbit (5 case reports until 1998) [393]</li> <li>– Location in the lacrimal gland only in one of these cases (50-year-old male patient)</li> <li>– Age of manifestation generally prior to birth, in newborns, in toddlers and children, rarely later</li> </ul> </li> <li>▪ Etiology/pathogenesis                             <ul style="list-style-type: none"> <li>– In 90% of cases, mutation of the SMARCB1 gene (tumor suppressor gene)</li> <li>– Rarely mutation of the SMARCA4 gene</li> </ul> </li> <li>▪ Therapy                             <ul style="list-style-type: none"> <li>– No standard therapy recommendation available</li> <li>– Resection, chemotherapy, and radiotherapy have been applied [394]</li> </ul> </li> </ul>

- low-grade lymphoma: 5-year survival rate of 75% [366], more favorable in salivary glands (95–100%)

#### 7.2.1.2.3.2 Follicular lymphoma

- Epidemiology
  - with about 28% of all lymphomas, second most frequent subtype in the lacrimal gland [365–366]
- Therapy
  - early stage (stage IE/IIe): radiotherapy -> 5-year survival rate of about 100% [366]
  - in cases of systemic involvement or high tumor charge: pharmaceutical combination therapy, e. g., R-CHOP -> 3-year progression-free survival in 70–80%

- rituximab applied for a further 2 years as maintenance dose

- Prognosis
  - low-grade lymphoma with favorable prognosis (5-year survival of about 80–90%)

#### 7.2.1.2.3.3 Diffuse large-cell B cell lymphoma (DLBCL)

- Epidemiology
  - with 15% of all lymphomas, third most frequent subtype in the lacrimal gland [365–366]
- Pathology

- destructive growth in neighboring structures (e. g., ethmoid, intracranial) observed in 6 of 27 patients [365]
- Therapy
  - already in stage I (only involvement of the lacrimal gland): R-CHOP
  - in patients younger than 60 years with high risk profile (IPI score  $\geq 2$  or increased LDH), etoposide added to R-CHOP (R-CHOEP)
  - in stage IE and absence of B symptoms, additional radiotherapy
- Prognosis
  - high-grade lymphoma; 5-year survival rate: 55–73 %

#### 7.2.1.2.3.4 Mantle cell lymphoma

- Therapy
  - primary therapy: R-CHOP
  - in patients younger than 65 years, additional cytarabine and stem cell transplantation
- Unfavorable prognosis

Annotation: The WHO classification of lymphoid neoplasms encompasses more than 80 lymphoma categories. They are subdivided into three groups: B cell neoplasms, T and NK cell neoplasms, and Hodgkin lymphomas. Lymphomas as well as lymphoid leukemia are included. At this point, only the most important entities are mentioned [371]. The incidence distribution of the subtypes in the lacrimal gland corresponds to that for the salivary glands [366].

#### 7.2.1.3 Metastases in the lacrimal gland

- Epidemiology
  - a malignant disease already known in 80% of cases at the time of first diagnosis of an orbital mass [233]
  - presence of orbital metastases (mostly unilateral) in an estimated 2–3% of all patients with malignancies [233]
  - location in the lacrimal gland quite rare [233, 372]

### 7.2.2 Neoplasms of the orbit (without lacrimal gland neoplasms)

#### 7.2.2.1 Benign neoplasms

##### 7.2.2.1.1 Benign epithelial neoplasms

See Section 6.2.1.1.1, “Benign epithelial neoplasms of the lacrimal gland.”

##### 7.2.2.1.2 Benign non-epithelial neoplasms

Tumors of non-epithelial origin are even more numerous in type than epithelial tumors of the orbit.

##### 7.2.2.1.2.1 Fibro-osseous processes of the orbit

There are several fibro-osseous lesions that can appear in the periorbital region and may lead secondarily to involvement of the orbital soft tissue, including an aneurysmal bone cyst, giant cell granuloma, and cholesterol granuloma. However, in the literature, these lesions are often called ‘reactive bone lesions’ and included in the list of bone tumors of the orbit.

##### 7.2.2.1.2.1.1 Fibroma, ossified fibroma, fibromatosis [201, 373]

###### Fibroma

- Epidemiology
  - quite rare in the orbit
  - 7 fibromas in 2210 orbital tumors in four case series [373–375]
  - occurrence mostly in adolescence and early adulthood
- Pathology
  - mostly originating from the cranial periorbita or muscle conus

###### Ossified fibroma

- Epidemiology
  - occurring mainly in younger patients
- Pathology
  - slowly growing benign tumors, but destructive growth and recurrence possible after incomplete resection
  - location also in the paranasal sinuses of maxillary bones
- Diagnostics
  - radiological differentiation from fibrous dysplasia necessary

###### Fibromatosis

- May have an intermediate character
- Therapy
  - generally surgical resection

##### 7.2.2.1.2.1.2 Aneurysmal bone cyst

- Definition
  - locally expansive osteolytic lesion consisting of blood-filled cavities with surrounding reactive fibro-osseous tissue
- Location
  - predilection site: metaphysis of the long bones and spine
  - rare in the skull [377]
  - orbital occurrence in less than 1% of cases [378, 379], then mostly orbital roof [380]
- Epidemiology
  - preferred occurrence in childhood and adolescence up to the 20th year of life
- Etiology and pathogenesis
  - association with other bone lesions (fibrous dysplasia, chondroblastoma, osteoblastoma, giant cell tumors) that precede development of aneurysmal bone cyst and may be predisposing for the development as a reactive phenomenon [382–383]
  - focal hemodynamic changes with secondary venous hypertension or preexisting trauma discussed as causes [381]
  - current oncogenetic study results: clonal neoplastic lesion with specific genetic rearrangement (USP6 gene upregulation in spindle cells) [384], leading to possible differentiation of similar lesions without USP rearrangement (e. g., osteosarcoma, chondroblastoma, giant cell tumors)
- Clinical
  - initially indolent swelling or bulbar protrusion

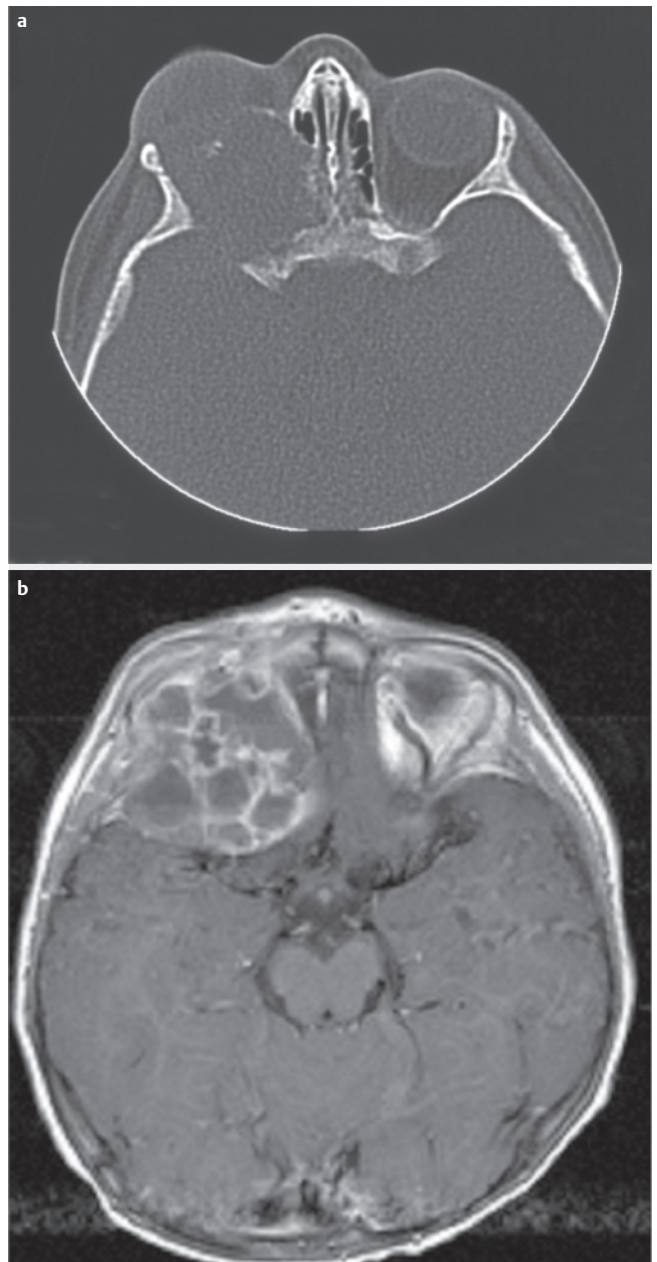


- often slow growth over weeks and months, then episodes of rapid growth and painful exophthalmos, ptosis, diplopia, and further ophthalmological symptoms [378]
- Diagnostics
  - CT scan and MRI (characteristic changes, see ► **Fig. 16a, b**): polylobulated mass with multiple cystic areas, separated by connective tissue septa; furthermore, solid areas, thinning of the surrounding cortex, liquid level in the cystic areas because of non-coagulated blood; clear contrast enhancement, the dura respected in cases of intracranial extension [378, 385]
  - histology: cystic cavities lined with endothelial-like cells; solid parts consisting of spindle-shaped fibroblasts with singular multinucleated giant cells, hemosiderin-charged macrophages, granulation tissue, and extravasated erythrocytes; septa frequently with newly developed bone; no atypical mitoses or other histological malignancy criteria
- Differential diagnoses
  - other bone tumors (e. g., osteblastomas, osteoclastomas, brown tumors)
  - reparative giant cell granuloma and giant cell tumors
  - examination by pathology reference centers required [378]
- Therapy
  - first choice: surgical excision and (depending on the extension and local destruction) reconstruction of the bone defect
  - in extended cases: intralesional curettage and partial removal with adjuvant radiotherapy
  - in cases of high intraoperative risk of bleeding: preoperative embolization or stereotactic radiosurgery
- Prognosis
  - recurrence rate of 10–30%
  - malignant transformation possible but extremely rare [384]
  - follow-up recommended [379, 380, 386]

#### 7.2.2.1.2.1.3 Giant cell granuloma [387–391]

- Definition
  - rare, reactive benign mass with locally aggressive growth
- Epidemiology
  - mostly in females in the 1st to 3rd decades [392]
- Location
  - epiphyses in the long bones (>90% of cases)
  - skull (about 2% of cases): mostly mandible and maxilla, more rarely sphenoid and petrous bone, ethmoid, or orbit [387, 391]
- Pathogenesis
  - still unknown
  - inflammation, trauma, and intraosseous hemorrhages are possible causes
  - because of the association with other symptoms such as Noonan syndrome, neurofibromatosis type I, and cherubism, a still unidentified chromosomal anomaly appears possible [393]
- Clinical
  - symptoms mostly the result of processes involving masses: swelling, deformity, sometimes pain

- exophthalmos, visual impairment, diplopia as first clinical symptoms
- Diagnostics
  - CT scan: mostly sharply delimited osteolytic process with expansive character, but highly variable and non-specific
  - histopathology: characteristic accumulation of multinucleated large osteoclast-like giant cells with a tendency to cluster around hemorrhagic foci
- Differential diagnoses



► **Fig. 16 a, b** CT and MRI of an aneurysmal bone cyst in a 2-year-old child. Cystic tumor measuring 4 cm in diameter with bleeding and inhomogeneous contrast enhancement. Ethmoid and orbital roof are eroded and distended, with significant expansion in an intracranial direction respecting the dura (courtesy of Prof. Dr. Dr. W. Wohlgemuth, Professor and Chair of the Department of Diagnostic Radiology, University Hospital of Halle).

- osteoclastoma, osteosarcoma, eosinophilic granuloma, aneurysmal bone cyst, “brown tumors” in cases of hyperparathyroidism, non-ossified fibroma, Langerhans cell histiocytosis (radiological differentiation sometimes difficult)
- differentiation of giant cell tumors is controversially discussed in the literature [394]: in the described cases, definite diagnosis of orbital giant cell granuloma was only possible by biopsy or surgical excision
- Therapy
  - first choice: complete resection
  - not always possible as radical intervention in the area of the skull
  - radiation: controversially discussed in cases of resistance to radiation and possible malignant cell degeneration; however, recommended by some authors after partial resection
  - medication for adjuvant therapy: corticosteroids, calcitonin, bisphosphonates, imatinib, and interferon- $\alpha$  [393, 395]
  - denosumab (monoclonal antibody): neutralization by binding to the RANK ligands produced by the tumor cells in cases of unresectable or locally advanced findings [391]
- Prognosis
  - recurrence in 10–50% of cases

#### 7.2.2.1.2.1.4 Cholesterol granuloma

- Definition
  - rare benign lesion developing because of foreign body reaction to cholesterol crystals
- Epidemiology
  - occurring typically in middle-aged males [396]
- Etiology and pathogenesis
  - presumed development from traumatic genesis or intrinsic anomaly of diplopia
  - inflammatory reaction against degradation products of blood components or in cases of hypoxic tissue destruction
  - granulomatous inflammatory reaction on cholesterol with subsequent erosion of the surrounding bone [397–398]
- Location
  - mostly in the temporal bone
  - possible also in the area of the facial skull
  - rarely orbital, but if so, typically in the area of the frontal bone above the lacrimal fossa (superotemporal or superior) because the weakest connection of the periorbita to the bone is found with frequent occurrence of trauma [399–401]; in cases of unclear lesions of the orbit from imaging, location, and often positive trauma history, cholesterol granuloma to be considered [401]
- Clinical
  - exophthalmos, diplopia, visual impairment
  - more rarely periorbital pain or ptosis
- Diagnostics
  - CT scan: osteolytic lesions of the frontal diploe with erosion of the adjacent cortex and sometimes expansion into the extradural space

- MRI: differentiation of other soft tissue tumors is possible; typically high signal intensities in the T1- and T2-weighted sequences because of liquid content [402]
- histology: cholesterol crystals surrounded by multinucleated giant cells; differentiation of epidermoids and dermoid cysts because of absence of epithelial elements; differentiation of aneurysmal bone cyst or giant cell tumors by the prominent xanthomatous component
- Differential diagnoses
  - difficult clinical and CT morphological differentiation of dermoid or epidermoid cyst
  - others: neoplasms of the lacrimal gland, metastases, aneurysmal bone cyst, or chondroma [61]
- Therapy
  - first choice: drainage of the lesion contents and meticulous removal of the cyst wall as well as surrounding bone -> minimization of recurrence risk
  - different techniques, depending on the size and location of the lesion [400, 401, 403]

#### 7.2.2.1.2.1.5 Osteoma [201]

- Epidemiology
  - most frequently a tumor originating from the orbital bone (often also from the paranasal sinuses)
- Diagnostics
  - CT scan: bone-dense, well-delimited mass (often incidental finding)
- Therapy
  - surgical resection, only in symptomatic/progressive cases

#### 7.2.2.1.2.1.6 Chondroma [201, 404]

Annotation: The trochlea is the only cartilaginous structure of the orbit, and the sphenoid has cartilaginous precursor structures.

- Epidemiology
  - Garrity and Henderson (2007) [405] and Shields et al. (2004) [279]: only one case each out of 1373 and 627, respectively, of mesenchymal orbital tumors
  - Rootman et al. (2004): one case out of 62 primary tumors of the orbital bone in a period of 24 years [405–407]
  - in the area of the facial skull, mainly occurring in adolescents and young adults
- Clinical
  - often asymptomatic
  - in cases of progression, ptosis/proptosis
- Location
  - superior nasal quadrant
- Pathology
  - histopathological differentiation of low-grade chondrosarcomas is difficult
  - partly aggressive behavior of chondrogenic tumors of the facial skeleton (discrepancy between histological appearance and biological behavior)
- Therapy
  - resection, with a safety margin if possible
  - long-term follow-up recommended [404]

#### 7.2.2.1.2.2 Neuroma [201, 408]

- Synonyms
  - schwannoma, Schwann cell tumor
- Epidemiology
  - 0.7–2.3 % of orbital tumors
  - usually singular occurrence
  - in up to 18 % of cases, association with neurofibromatosis
- Pathology
  - benign tumor of the peripheral nerves
- Therapy
  - surgical resection, especially in symptomatic processes

#### 7.2.2.1.2.3 Neurofibroma [201, 409]

##### Plexiform neurofibroma

- Epidemiology
  - most frequent subtype in the orbit
  - often congenital or in early childhood
  - neurofibromatosis type I is often the primary disease
- Pathology
  - multinodular mass with infiltrative behavior (eyelid, skull base, periorbita) and relatively strong vascularization
  - degeneration rate (transformation into malignant peripheral nerve sheath tumor): 2–4 %
- Clinical
  - severe visual impairment is typical
- Therapy
  - surgical resection
  - difficult because of irregular borders, often multiple intervention until exenteration

##### Localized neurofibroma[[409],[410]]

- Epidemiology
  - rarely associated with neurofibromatosis
  - manifestation peak: 3rd-5th decades of life
- Location and pathology
  - typically cranial location in the orbit (frontal nerve), less vascularized, better encapsulated
- Therapy
  - surgical resection
- Pathology
  - in contrast to schwannomas, additionally fibroblasts and perineural cells are found, higher contents of connective tissue substance, not (well-)encapsulated, cannot be separated surgically from the nerve, requiring sacrifice of the nerve

#### 7.2.2.1.2.4 Meningioma [201, 411]

- Epidemiology
  - according to estimations, about 4–8 % of all orbital neoplasms
  - age of manifestation: typically around the 45th year of life, optic nerve sheath meningioma in younger patients
  - women significantly more frequently affected than men
- Risk factors
  - previous radiotherapy of the head region
  - neurofibromatosis type 2

- Typical locations
  - lateral orbital wall, orbital roof (“primary ectopic meningiomas,” only single cases)
  - optic nerve sheath meningioma (most frequent optic nerve sheath tumor), in 90 % of cases, already growth through the optic nerve canal in direction of the chiasma at diagnosis [412]
  - ingrowth of meningiomas of the cavernous sinus or the medial sphenoid wing (optic nerve compression)
- Pathology
  - orbital meningiomas usually grade 1 meningiomas according to the WHO grading for meningiomas (grade 1: benign; grade 2: anaplastic; grade 3: malignant) [413]
- Clinical
  - leading symptoms
    - slowly progressive, painless loss of vision (key symptom)
    - visual field defects
    - transient obscurations
    - protrusion or motility disorders (with diplopia) often in advanced stage
- Therapy [411, 412, 414–415]
  - with small and/or less impairing findings: “watch-and-wait” and initially half-yearly MRI controls
  - therapy indication [412]: progressive visual impairment, visual decline to 0.4; increasing visual field disorders, endangered chiasma
  - optic nerve sheath meningioma
    - therapy of first choice: fractionated radiotherapy (50–55 Gy) with probably best functional outcome (vision)
    - surgical therapy, especially in cases of extension in intracranial direction or blindness and disfiguring protrusion
    - in cases of growth into the optic canal, optic nerve decompression, if needed
    - surgical resection (if necessary, embolization prior to surgery), possibly with adjuvant radiotherapy

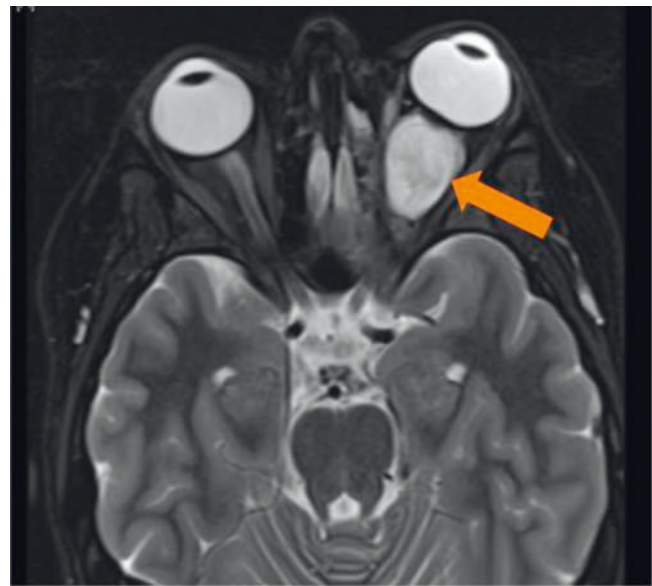
#### 7.2.2.1.2.5 Opticus glioma [201, 412]

- Definition
  - special type of pilocystic astrocytoma (juvenile pilocystic astrocytoma, WHO grade I) [412]
- Epidemiology
  - manifestation in 90 % of cases before the 20th year of life, in 50 % of cases before the age of 5 [412]
  - underlying neurofibromatosis type I possible and should be excluded
- Differential diagnosis
  - optic nerve schwannoma [416] (observed, even though extremely rare [fewer than 10 cases have been described], even if the myelin sheath of the optic nerve does not contain Schwann cells; most probably originating from small sympathetic nerve fibers)
- Clinical
  - bilateral location possible (especially in neurofibromatosis)
  - slow growth
  - exophthalmos
  - squint position of the affected eye

- visual and visual field impairment
- phase-wise increase of the complaints in cases of bleeding
- nystagmus
- endocrinological accompanying symptoms possible (e. g., diabetes insipidus, obesity, precocious puberty)
- Therapy [417–419]
  - controversial because a spontaneous course is not predictable, spontaneous remission is possible, and all procedures have some significant side effects
  - proximity to the optic canal is crucial for the course
  - follow-up by means of MRI and visual/visual field examinations (more decisive for the therapy indication than radiologically found increase) in cases of newly diagnosed gliomas
  - (partial) resection, especially in cases of large, progressive intraorbital gliomas with blindness, growth in direction of the chiasma, or disfiguring exophthalmos
  - probably transection of the optic nerve in front of the chiasma to avoid extension to the contralateral side
  - fractionated radiotherapy was former therapy of choice, but in children, especially age < 7 years, associated with the risk of neurological-cognitive deficits and later secondary tumors (in particular with neurofibromatosis), so currently indicated mainly in progressing chiasma-near tumors in older children or adults
  - chemotherapy to reduce tumor size and growth and to delay other therapies
  - first-line therapy in cases of loss of vision/tumors requiring action especially in small children: pharmaceuticals such as carboplatin combined with vincristine

### Case report 3

- History
  - 18-year-old female patient
  - increasing exophthalmos for about 4 months and visual impairment for 5 days, left side
- Diagnostics
  - ophthalmological examination
    - vision: right side 1.25, left side 0.6
    - Hertel exophthalmometry: right side 20, left side 24 mm
    - congestive papilla, left side
  - MRI (► Fig. 17)
    - suspected optic nerve glioma measuring 28 × 17 mm
    - no intracerebral growth
- Procedure
  - transnasal endoscopic medial orbital decompression with biopsy
  - histopathology: optic nerve glioma
  - definitive fractionated stereotactic radiotherapy (50.4 Gy)
- Course
  - initially fluctuating but good vision (around 0.8–0.9)
  - about 6 months after radiation: ophthalmological optic nerve atrophy, clearly deteriorated vision of the left eye (0.25), increasing edema of the papilla, secondary strabismus divergens, cosmetically disturbing progressive exophthalmos (► Fig. 18), and insufficient eyelid closure



► Fig. 17 MRI (T2, axial) with intraconal, retrobulbar tumor measuring 28 × 17 mm (arrow) (courtesy of Prof. Dr. Dr. W. Wohlgemuth, Professor and Chair of the Department of Diagnostic Radiology, University Hospital of Halle).

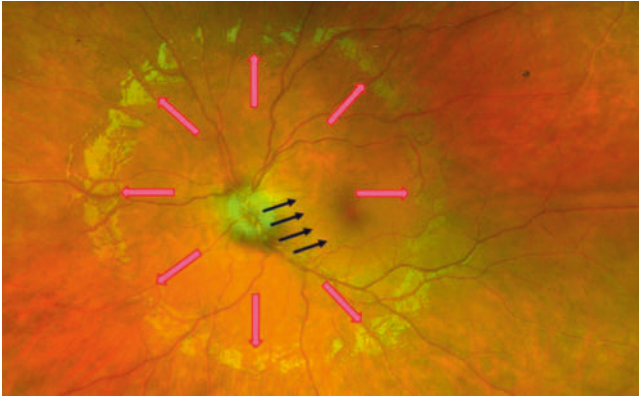


► Fig. 18 Progressive exophthalmos and strabismus divergens to the left after radiotherapy. The figure is from the archive of the Department of Ophthalmology, University Hospital of Halle.

- further deterioration during the following 3 months (vision 0.1, Hertel exophthalmometry on the left side 27 mm, increasing suffering, funduscopy findings (► Fig. 19)
- bulbus enucleation and tumor resection, implantation of Guthoff implant, later prosthesis
- genetic assessment to exclude neurofibromatosis

#### 7.2.2.1.2.6 Myxoma [272–276]

- Definition
  - neoplasm of mesenchymal/connective tissue origin
- Epidemiology
  - few case reports published about the orbital area
  - men and women equally affected
- Pathology
  - histologically containing few cells and vessels with abundant myxoid (mucus-like) hyaluronic acid-rich matrix
  - other locations: predominantly heart, along with bones, skin, skeletal muscles, urogenital tract
- Diagnostics



► **Fig. 19** Funduscopy of the left eye with impression-related fundus reflex (red arrows). Black arrows: choroid folds. The figure is from the archive of the Department of Ophthalmology, University Hospital of Halle.

- association of orbital myxomas with Carney syndrome (familial myxoma syndrome), Mazabraud syndrome, McCune-Albright syndrome
- should be considered in patients with increased numbers of chloasma, cardiac history, and orbital mass
- a well-circumscribed, oval, isodense mass seen on CT
- radiotherapy without relevant effect

Further examples of benign non-epithelial orbital neoplasms are listed in ► **Table 8**.

## 7.2.2.2 Malignant neoplasms

### 7.2.2.2.1 Malignant epithelial neoplasms

See Section 7.2.2.2.3, “Malignant epithelial tumors of the lacrimal gland.”

### 7.2.2.2.2 Malignant non-epithelial neoplasms

Annotation: Lymphomas of the orbit are described in Section 6.2.2.2.3.

#### 7.2.2.2.2.1 Rhabdomyosarcoma [434]

- Epidemiology
  - most frequent orbital malignancy in children
  - embryonic subtype: most frequent, about 60–70% of all pediatric rhabdomyosarcomas
  - alveolar subtype: 30% of all pediatric rhabdomyosarcomas, in 80% associated with specific gene translocation/-fusion (PAX3 on chromosome 2 or PAX7 on chromosome 1 with FOXO1 on chromosome 13)
- Clinical
  - rapidly progressing exophthalmos
  - eyelid swelling/reddening
  - ptosis, possibly palpable tumor
- Diagnostics
  - biopsy
- Therapy
  - standard: chemotherapy + radiotherapy

- exenteration not to be performed primarily, only with confirmation of residual tumor/recurrence in the biopsy after chemotherapy + radiotherapy
- Prognosis
  - key problem of local recurrence
  - unfavorable prognosis in cases of confirmed gene translocation/fusion

#### 7.2.2.2.2.2 Fibrosarcoma [435–437]

- Epidemiology
  - mean age at manifestation: 50 years
  - men preferentially affected (independent of location)
  - several case reports of orbital involvement in children
- Etiology and pathogenesis
  - occurrence as post-radiogenic secondary tumor in the orbit (e. g., after radiotherapy of retinoblastoma)
  - increased risk after implantation of foreign material
- Pathology
  - aggressive tumor (in more than 80% grade 2/3 according to FNCLCC)
  - metastases mainly in the lung, bones, and regional lymph nodes
  - only single case reports of orbital fibrosarcomas after application of modern diagnostic procedures
  - in recent years, improved histopathological diagnostic procedures and classification systems for sarcomas have led to a rare diagnosis of exclusion (< 1% of all adult soft tissue sarcomas)
- Therapy
  - resection with wide safety margins up to exenteration
  - exenteration especially in cases of local recurrences
  - significance of postoperative radio- or chemotherapy unknown, in particular in cases of rare locations in the orbit
- Prognosis
  - 5-year survival rate of about 55%

#### 7.2.2.2.2.3 Retinoblastoma [438–440]

- Definition
  - malignant tumor in the retina; precondition for its development are mutations in both alleles of the retinoblastoma gene (located on chromosome 13, band q14)
- Epidemiology
  - incidence of about 1:20 000 live births
  - most frequent intraocular malignancy in children
  - male:female ratio, 1:1
  - usually occurring before the age of 5 years
- Types
  - 45% inherited
    - heterozygous for mutations in the retinoblastoma gene, with an additional mutation arising in the second allele
    - both eyes usually affected
  - mean age at the time of diagnosis: 12 months
  - 55% non-inherited
    - both mutations occurring in the same cell
    - mainly unilateral
    - mean age at the time of diagnosis: 23 months
  - 75% unilateral, 25% bilateral

► **Table 8** Benign neoplasms of the orbit of non-epithelial origin.

Neoplasm	Characteristics
Granular cell tumors [420] (Abrikossoff tumor)	<ul style="list-style-type: none"> <li>▪ Definition               <ul style="list-style-type: none"> <li>– Mostly benign tumor of neurogenic origin</li> <li>– Preferred occurrence in the upper aerodigestive tract</li> </ul> </li> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– Rarity in the orbit</li> </ul> </li> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– Infiltrative growth possible (morphological imaging)</li> </ul> </li> <li>▪ Therapy of choice               <ul style="list-style-type: none"> <li>– Complete surgical excision</li> <li>– Postoperatively regular clinical and morphological imaging controls are necessary (risk of recurrence)</li> </ul> </li> </ul>
Paraganglioma [421–422]	<ul style="list-style-type: none"> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– Originating from ciliary ganglion</li> <li>– 93% located intraconally, almost half in contact with the optic nerve</li> <li>– About 50% are locally invasive (mainly external eye muscles)</li> <li>– Metastasis possible</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Resection (if needed, previous embolization)</li> <li>– Exenteration in very large and rapidly growing tumors, advanced loss of vision, invasive growth with cranial nerve failures, local recurrences</li> <li>– If necessary, adjuvant radiation; primary radiation not first choice</li> </ul> </li> <li>▪ Prognosis               <ul style="list-style-type: none"> <li>– Frequent functional loss of the eye because of disease or therapy (about 40%)</li> <li>– Local recurrence in half of cases</li> <li>– Disease-related death reported</li> </ul> </li> </ul>
Ganglioneuroma [423, 424] (benign type of neuroblastic tumors)	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– In the head and neck, mainly in the area of the sympathetic trunk</li> <li>– In the orbit, only single case reports</li> </ul> </li> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– Benign tumor of neuroblastic origin, originating from sympathetic nerves</li> <li>– Endocrine activity (catecholamines, vanillinmandelic acid) in about 40%</li> </ul> </li> <li>▪ Pathogenesis               <ul style="list-style-type: none"> <li>– Association with metastatic neuroblastoma, neurofibromatosis type 1, or multiple endocrine neoplasm (i.e., MEN)</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Resection</li> </ul> </li> </ul>
Ganglioneuroblastoma [423] (intermediary type of neuroblastic tumors)	<ul style="list-style-type: none"> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– Intermediary status (between ganglioneuroma and neuroblastoma)</li> </ul> </li> </ul>
Rhabdomyoma [425–427]	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– Only single case reports published</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Resection</li> </ul> </li> <li>▪ Prognosis               <ul style="list-style-type: none"> <li>– Recurrence reported</li> </ul> </li> </ul>
Leiomyoma [428–429]	<ul style="list-style-type: none"> <li>▪ Location               <ul style="list-style-type: none"> <li>– Mainly anterior orbit</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Complete resection</li> </ul> </li> </ul>
Lipoma [279, 430]	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– &lt;1% of all orbital tumors</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Resection</li> </ul> </li> </ul>
Melanotic neuroectodermal tumor of infancy (i.e., MNTI) [431–433]; former synonyms: melanotic ameloblastoma, retinal predisposed tumor, melanotic progonoma, melanotic adamantinoma	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– Location mostly in the maxilla, only single cases in the orbit</li> <li>– Since the first description in 1918, about 500 cases reported</li> <li>– Almost all patients younger than 1 year, and most younger than 6 months</li> </ul> </li> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– Rapidly growing mass</li> <li>– Macroscopically often bluish-black because of pigments (melanin)</li> <li>– In general, benign lesion, but locally aggressive, with degeneration in about 3% of cases</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Complete resection possible with safety margins (risk of local recurrences)</li> <li>– (Neo)adjuvant chemotherapy if complete resection not possible</li> </ul> </li> <li>▪ Prognosis               <ul style="list-style-type: none"> <li>– Local recurrence in 15–20% of cases</li> </ul> </li> </ul>

- Clinical
  - leukocoria, strabismus, more rarely: painful reddening of the eye, glaucoma, visual impairment
- Diagnostics
  - ophthalmological examination: unifocal or multifocal whitish, vascularized retinal mass, sometimes with tumor dissemination
  - ultrasound
  - MRI (for evaluation of optic nerve involvement and possible extraocular extension)
  - gene diagnostics (differentiation between hereditary and non-hereditary type)
  - generally no biopsy
  - lumbar puncture in cases of extension in direction of the CNS
  - possibly bone scintigraphy/bone marrow puncture if bone metastasis is suspected
- Therapy
  - objective: preservation of life (primary objective), preservation of function (secondary objective)
  - laser/cryocoagulation, transpupillary thermotherapy (especially in small tumors)
  - chemotherapy as one of the most important options: allows avoiding radiotherapy or enucleation in a significant number of cases
  - enucleation including resection of the optic nerve (especially in advanced unilateral tumors)
  - radiotherapy (former standard therapy with high radiation sensitivity, but significant risk for post-radiogenic secondary tumors – about 36% within 50 years in the hereditary type – so reserved for specific indications such as metastatic spread or response failure on chemotherapy)
  - brachytherapy: primary therapy option in cases of solitary tumors ventral to the equator (in 2/3 of cases with good visual function) or after failure of other therapeutic strategies, adjuvant therapy option
  - adjuvant chemotherapy, especially after enucleation if certain risk factors are present (e. g., choroid invasion, optic nerve invasion, extension into the orbit, dissemination into the anterior chamber)
- Prognosis
  - 5-year survival rate: about 96% in developed countries
  - in the hereditary type: increased risk for secondary (extraorbital) tumors

#### 7.2.2.2.4 Malignant glioma of the optic nerve [412, 441–442]

- Definition
  - corresponds to anaplastic astrocytoma, WHO grade III, or glioblastoma, WHO grade IV; no association with neurofibromatosis
- Epidemiology
  - extremely rare
  - manifestation peak: middle-aged adults
- Symptoms
  - initially similar to acute neuritis of the optic nerve
  - retroorbital pain

- at time of diagnosis, chiasma involvement already present in 75%, early CNS infiltration
- rapidly progressive loss of vision up to blindness
- possibly other neurological symptoms such as seizures
- Therapy [442–443]
  - no effective therapy
  - combined radiochemotherapy with temozolomide
  - surgical resection only in single cases, e. g., strictly unilateral involvement without chiasma involvement
- Prognosis
  - death usually within one year

Further examples for non-epithelial malignant neoplasms of the orbit are listed in ► **Table 9**.

#### 7.2.2.2.3 Lymphoproliferative diseases of the orbit

##### 7.2.2.2.3.1 Orbital lymphomas [365, 463–465]

Annotation: See Section 7.2.1.2.3, “Lymphomas of the lacrimal gland.”

- Epidemiology of lymphomas
  - the most frequent malignant orbital masses (about 50–55% of all orbital malignancies are non-Hodgkin lymphomas)
  - the most frequent primary orbital tumors in older patients (>60 years)
  - lymphoid tumors encompass about 10–20% of orbital masses
  - ocular adnexae (conjunctiva, eyelids, lacrimal gland, orbital soft tissue) affected in 1–2% of all lymphomas and about 8% of all extranodal lymphomas
  - secondary orbital involvement in an estimated 5% of all patients with non-Hodgkin lymphomas
  - mainly older people affected
- Frequency in lymphoma types
  - B cell lymphomas, 97%
  - (extranodal) marginal zone (B cell) lymphomas, about 50–60%
  - follicular lymphoma, about 9–23%
  - DLBCL, about 8–23%
  - mantle cell lymphoma, about 5%
- Locations
  - orbital soft tissue: 32–60%
  - conjunctiva: 15–42%
  - lacrimal gland: 14–20%
  - external eye muscles: 9%
  - lacrimal sac: 2–11%
  - bilateral occurrence: 11–32%
- Clinical
  - lymphomas of the conjunctiva: typically smooth and salmon-colored
  - morphologically sometimes difficult to differentiate from idiopathic orbital inflammation by imaging (formerly so-called orbital pseudotumor) -> biopsy
  - mostly locally limited ocular adnexa lymphomas at the time of diagnosis (exception: mantle cell lymphomas)
- Therapy
  - in localized manifestation: radiotherapy -> good local control and healing rate

► **Table 9** Further examples of malignant orbital neoplasms of non-epithelial origin.

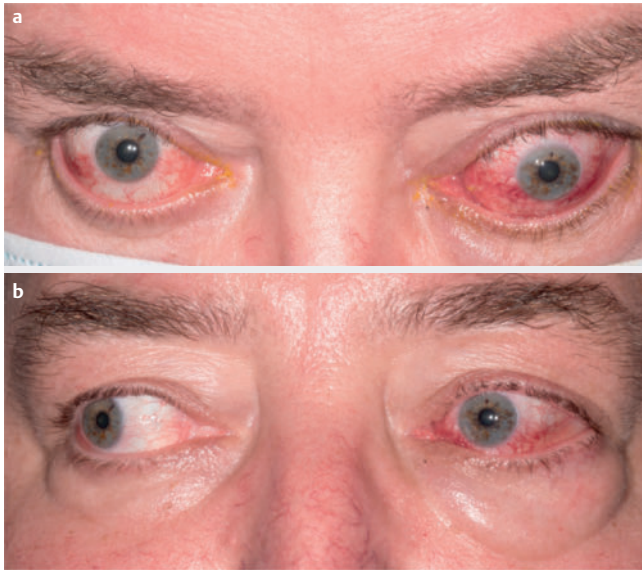
Neoplasm	Characteristics
Medulloepithelioma [444–445]	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– Mostly in children around the age of 5 years but sometimes in adults</li> </ul> </li> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– Ocular type mostly originating from the epithelium of the ciliary body</li> <li>– Intermediary/variable status, transition from benign to malignant types is possible</li> <li>– Metastatic spread rare but has been described</li> </ul> </li> <li>▪ Clinical               <ul style="list-style-type: none"> <li>– Leukocoria possible</li> <li>– Differential diagnosis:                   <ul style="list-style-type: none"> <li>– Rretinoblastoma</li> </ul> </li> </ul> </li> </ul>
Alveolar soft tissue sarcoma [446–448]	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– &lt; 1 % of all sarcomas (that make up only 1 % of adult and 15 % of pediatric malignancies)</li> <li>– In the head and neck, mainly children and adolescents affected</li> </ul> </li> <li>▪ Location               <ul style="list-style-type: none"> <li>– Mainly tongue and orbit in the head and neck area</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Total resection</li> <li>– Then adjuvant radiotherapy</li> </ul> </li> </ul>
Ewing sarcoma [449, 450] (former: tumors of the Ewing sarcoma family [Ewing sarcoma of the bone (ESB), extraosseous Ewing sarcoma (EES), peripheral primitive neuroectodermal tumor (pPNET) of the bone, and Askin's tumor of the chest wall])	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– Mainly in children and young adults</li> </ul> </li> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– At the time of first diagnosis, often already extraorbital extension (mainly intracranial)</li> <li>– Frequently distant metastases at the time of first diagnosis (20–40 %)</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Multimodal therapy (chemotherapy, surgery, radiation)</li> </ul> </li> <li>▪ Prognosis               <ul style="list-style-type: none"> <li>– Highly malignant</li> <li>– Very poor prognosis</li> </ul> </li> </ul>
Leiomyosarcoma [451–453]	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– Single case reports published</li> <li>– Several cases of secondary leiomyosarcoma after malignoma therapy of other entities</li> </ul> </li> </ul>
Liposarcoma [454–455]	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– Rare</li> <li>– Only small case series or single case reports published</li> </ul> </li> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– Often well differentiated</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Resection, if necessary, exenteration</li> <li>– If needed, adjuvant radiotherapy</li> </ul> </li> <li>▪ Prognosis               <ul style="list-style-type: none"> <li>– In cases of good differentiation, relatively favorable prognosis</li> </ul> </li> </ul>
Epitheloid sarcoma [456]	<ul style="list-style-type: none"> <li>▪ Epidemiology               <ul style="list-style-type: none"> <li>– Only single case reports published</li> </ul> </li> <li>▪ Pathology               <ul style="list-style-type: none"> <li>– High metastatic potential</li> </ul> </li> <li>▪ Prognosis               <ul style="list-style-type: none"> <li>– Poor</li> <li>– High rate of local recurrences</li> </ul> </li> </ul>
Neuroblastoma [423, 457–459] (malignant type of neuroblastic tumors)	<ul style="list-style-type: none"> <li>▪ Definition               <ul style="list-style-type: none"> <li>– Undifferentiated malignoma of primitive neuroblasts</li> <li>– Mostly metastases (often bilateral), extremely rare primary orbital neuroblastomas (originating from the ciliary ganglion)</li> </ul> </li> <li>▪ Clinical               <ul style="list-style-type: none"> <li>– Typical sign in children younger than 2 years: racoon eye(s) = hematoma-like bleeding of the upper eyelid and the sclera, mimicking trauma</li> <li>– Endocrine activity (catecholamines, vanillinmandelic acid)</li> </ul> </li> <li>▪ Therapy               <ul style="list-style-type: none"> <li>– Chemotherapy, surgical resection, radiotherapy, myeloablative therapy including stem cell transplantation, immunotherapy</li> </ul> </li> </ul>



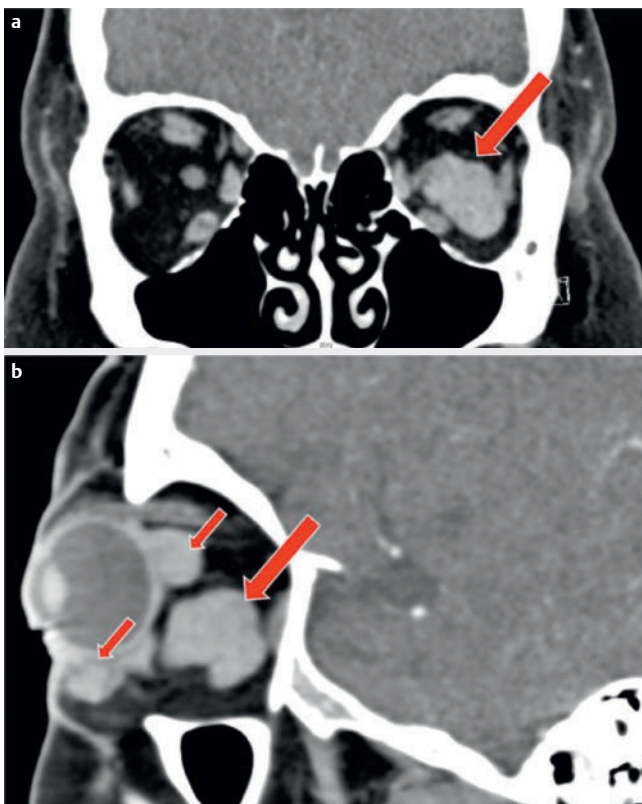
► **Table 9** Continued

Neoplasm	Characteristics
Malignant peripheral nerve sheath tumor [412]	<ul style="list-style-type: none"> <li>▪ See also Section 7.2.1.2.2, “Malignant tumors of the lacrimal gland of non-epithelial origin”</li> <li>▪ Therapy                             <ul style="list-style-type: none"> <li>– Radical surgery, orbital exenteration</li> <li>– If needed, adjuvant radio(chemo)therapy</li> </ul> </li> </ul>
Orbital melanoma [460]	<ul style="list-style-type: none"> <li>▪ Pathology                             <ul style="list-style-type: none"> <li>– Origin in the choroid or conjunctiva, rarely in other parts of the orbit</li> <li>– Primary orbital melanomas extremely rare; orbital melanoma metastases of mucosal melanomas growing from the paranasal sinuses more frequently observed</li> </ul> </li> <li>▪ Clinical                             <ul style="list-style-type: none"> <li>– Typically rapidly progressive ptosis</li> </ul> </li> <li>▪ Diagnostics                             <ul style="list-style-type: none"> <li>– In imaging, often similar to benign tumors</li> </ul> </li> <li>▪ Therapy                             <ul style="list-style-type: none"> <li>– Surgical resection (not necessarily exenteration)</li> <li>– Adjuvant radiotherapy</li> <li>– If needed, antibody therapy</li> </ul> </li> </ul>
Endodermal sinus cell tumor [461–462]	<ul style="list-style-type: none"> <li>▪ Epidemiology                             <ul style="list-style-type: none"> <li>– Most frequent malignant germ cell tumor</li> <li>– Affects young children</li> <li>– Mainly occurring in the pediatric gonads, rarely extragonadal (e. g., mediastinum, liver)</li> <li>– Extremely rare in the orbit (about 20 case reports published)</li> </ul> </li> <li>▪ Pathology                             <ul style="list-style-type: none"> <li>– Schiller-Duval bodies pathognomonic on histology</li> </ul> </li> <li>▪ Clinical                             <ul style="list-style-type: none"> <li>– Extremely rapid growth and acute symptom onset</li> </ul> </li> <li>▪ Diagnostics                             <ul style="list-style-type: none"> <li>– Typical pathological findings</li> <li>– <math>\alpha</math> fetoprotein as tumor marker</li> </ul> </li> <li>▪ Therapy                             <ul style="list-style-type: none"> <li>– Surgical resection (often only debulking possible, if needed, exenteration) and chemotherapy</li> </ul> </li> </ul>

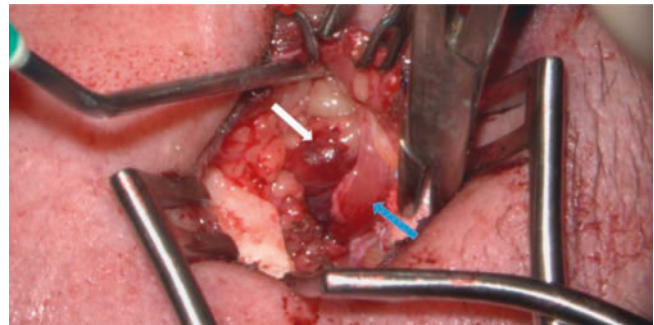
- in cases of bilateral or systemic disease and aggressive subtypes (e. g., DLBCL): chemotherapy
  - immunotherapy with anti-CD-20 antibodies
  - Prognosis
    - low-grade lymphoma (marginal zone lymphoma, follicular lymphoma): good
    - high-grade lymphoma (DLBCL, mantle cell lymphoma): poor
- Case report 4**
- History
    - first presentation of a 58-year-old male patient in the Department of Ophthalmology of the University Hospital of Halle, Germany
    - complaints for 2 years
  - Symptoms
    - left eye protruded and reddened
    - current visual impairment
    - ► **Fig. 20a, b** shows preoperative findings
  - Previous measures and course
    - intensive diagnostics (including MRI examination) and therapy by ophthalmologists in cooperation with a general hospital
  - transconjunctival biopsy of the orbit performed elsewhere: on histopathology, a lymphoplasmacellular infiltrate without a conspicuous IgG4 ratio
    - working diagnosis: idiopathic inflammatory orbitopathy, left more than right
  - therapy-refractory course with high-dose glucocorticoids for about 1.5 years (80 mg prednisolone at the time of first presentation), obvious Cushing symptoms, steroid-induced diabetes mellitus, arterial hypertension, NYHA III heart failure, liver steatosis
  - Diagnostics/clinical findings (relevant aspects)
    - no relative afferent pupillary defect, impaired bulbus motility (especially adduction) on the left, diplopia when looking upwards and to the side
    - anterior segments of the eye
      - congested conjunctival/episcleral vessels
      - lid-parallel conjunctival folds (LIPCOF) + +
    - fundoscopy
      - left papilla temporally faint
      - retina and choroid folds
    - vision
      - right: 1.0
      - left: 0.4
    - Hertel exophthalmometry (mm)



► **Fig. 20 a, b** (preoperative): Mainly exophthalmos, conjunctival injection, axis malalignment (a), an adduction weakness of the left eye (b) are conspicuous. The figures are from the archive of the Department of Ophthalmology, University Hospital of Halle.



► **Fig. 21 a, b** CT of the orbit, coronary (a) and sagittal planes (b). Partly intraconal and partly extraconal mass (red arrows). The biopsy was taken from the dorsal mass (big red arrow) (courtesy of Prof. Dr. Dr. W. Wohlgemuth, Professor and Chair of the Department of Diagnostic Radiology, University Hospital of Halle).



► **Fig. 22** Intraoperative site (lateral orbitotomy): cranial view of the lateral rectus muscle (blue arrow), caudally adjacent is one of the intraorbital neoplasms (white arrow), and in the caudal direction, orbital fatty tissue. Figure is from the archive of the Department of Otolaryngology, University Hospital of Halle.

- 23-123-28
- tension
  - right: 15 mmHg
  - left: 15 mmHg
- CT scan (► **Fig. 21a, b**)
  - on the left, evidence of four polylobulated, homogeneously moderately contrast enhancing, intra- and extraconal lesions, the largest one measuring 18.5 × 26 × 18 mm
  - on the right, significantly smaller intramuscular lesions
- Course
  - first, change in medication to cortisone-saving immunomodulated therapy initially with methotrexate, but because of intolerance shifted to mycophenolate mofetil; additional rheumatological care
  - because of no improvement, ENT-specific consultation and indication of balanced orbital decompression with intraorbital re-biopsy (► **Fig. 22**) for verification of the diagnosis; transfer to the department of otolaryngology
- Therapy
  - balanced medial and lateral orbital decompression on the left and biopsy of a mass (mostly intraconal location protruding in extraconal direction) via lateral orbitotomy
  - stepwise reduction of pharmacotherapy
- Histopathological diagnosis
  - extranodal marginal zone lymphoma
- Further course
  - postoperatively, slight visual improvement (0.5)
  - staging by means of whole-body CT scan and cMRT without hint of further manifestation of the lymphoma
  - case presentation to the tumor board and therapy by the departments of hemato-oncology and radiotherapy
  - local radiotherapy up to 30.6 Gy (ED 1.8 Gy) of the right and left orbits
  - cooperation with the department of hemato-oncology

#### 7.2.2.3.2 Leukemia

- Epidemiology

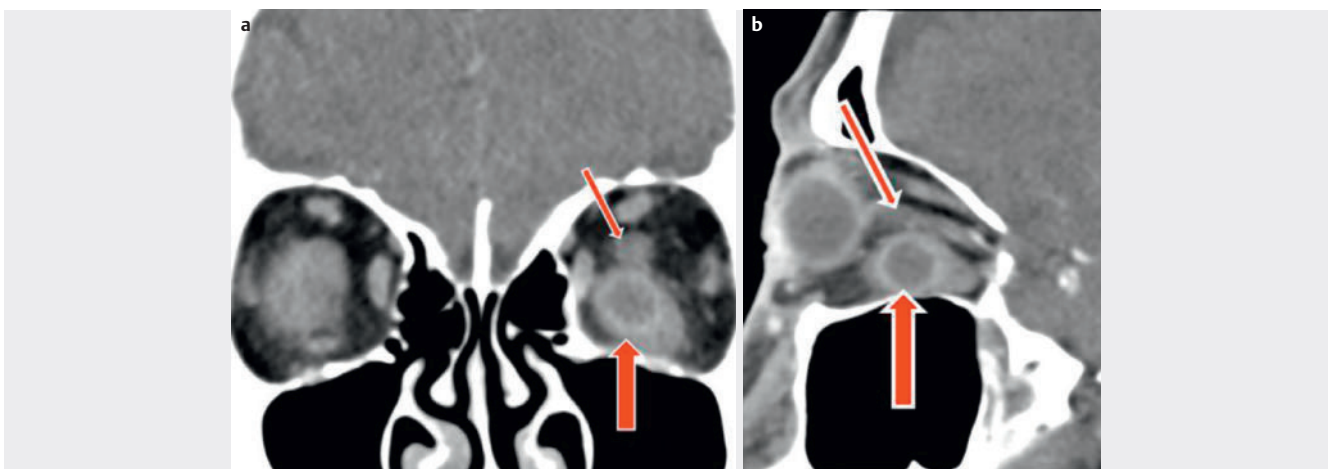
- orbital manifestation in comparison to lymphomas clearly more rare
- percentage of leukemias in malignant lymphoid orbital adnexa diseases: ~4% [365]
- occurrence mostly during the first decade
- Types
  - orbital manifestation possible in acute and chronic leukemias
  - most frequent subtype: acute myeloid leukemia [466–468]
  - mostly secondary orbital involvement (e. g., as recurrence), orbital manifestation also a possible first symptom
  - bilateral occurrence possible
  - orbital involvement mostly a hint of an advanced disease stage
- Therapy
  - chemotherapy and radiotherapy of the affected eye (better outcome compared to chemotherapy alone) [469]

#### 7.2.2.2.4 Metastases [59, 470–471]

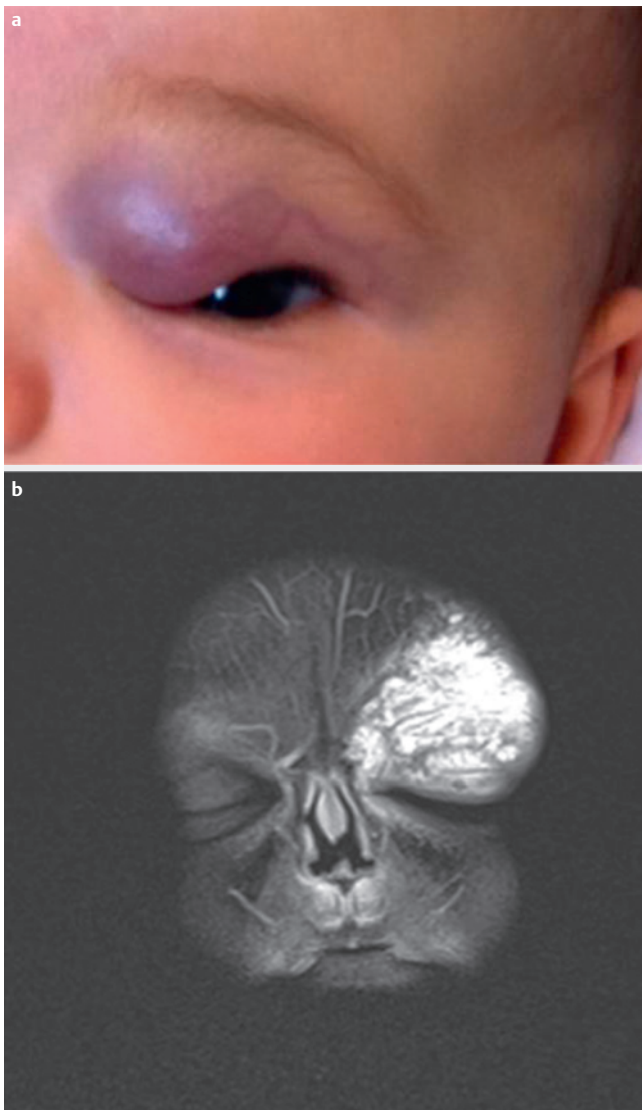
- Epidemiology
  - 7–8% of all orbital neoplasms
  - in up to 25% of cases, evident before identification of the primary tumor
- Differential diagnoses
  - clinically and morphologically, confusion with other diseases possible, for example, abscesses or parasitosis [471]
- Location of the primary tumor
  - in adults mainly in the breast, lung, gastrointestinal tract, prostate, kidney, skin
  - in adults with involvement of the external eye muscles in the breast, skin (melanoma) [471]
  - in children mainly neuroblastoma, Ewing sarcoma
- Therapy and management
  - identification of the primary tumor
  - depending on the tissue type
    - radiotherapy as significant therapeutic pillar (at least for symptom control)

#### Case report 5

- History
  - 62-year-old male patient
  - for 4 days, aqueous rhinorrhea, epiphora, increasing periorbital swelling and reddening, increasing pain in the left eye
  - no infection of the upper airways
- Findings
  - reddening and swelling of the left upper and lower eyelid with extension to the cheek
  - exophthalmos
  - chemosis with conjunctival hyperemia
  - motility impairment of the bulb
  - reduced vision (0.6)
  - intraocular pressure: 14 mmHg on right, 20 mmHg on left
  - leukocytes and CRP slightly increased
  - CT scan (with contrast agent; ▶ Fig. 23a, b)
    - lesion 12 × 11 × 10 mm, strongly contrast enhancing in the area of the inferior rectus muscle, slightly displacing the optic nerve
    - regularly ventilated paranasal sinuses
- Course
  - because of the suspicion of intraorbital abscess, transnasal, transthermoid endoscopic orbitotomy with opening of the lesion releasing only limited turbid secretions; swab and biopsy performed
  - histology: neuroendocrine tumor
  - diagnosis after identification of the primary tumor, and staging (among others DOTA-TOC PET-CT): neuroendocrine tumor (G2) of the ileum with hepatic, orbital, and lymph node metastases



▶ Fig. 23 a, b Contrast-enhancing intraorbital lesion (within the inferior rectus muscle, broad arrow) with contact to the optic nerve (small arrow). a Coronal, b sagittal view. Courtesy of Prof. Dr. Dr. W. Wohlgemuth, Professor and Chair of the Department of Diagnostic Radiology, University Hospital of Halle.



► **Fig. 24 a, b** Infantile hemangioma with orbital involvement. The upper eyelid has a bluish-red mass (a), and MRI shows the extension beyond the visible findings (b). Courtesy of Prof. Dr. Dr. W. Wohlge-muth, Professor and Chair of the Department of Diagnostic Radiology, University Hospital of Halle.

### 7.2.3 Vascular anomalies

Vascular anomalies have a special position and can be classified into **vascular tumors and malformations**.

#### 7.2.3.1 Vascular tumors

Vascular tumors have the following characteristics:

- “True” neoplasms with endothelial proliferation and angiogenesis
- Capacity for regression (at least partly) with increasing age
- Differentiation of benign, locally aggressive (borderline), and malignant subtypes

#### 7.2.2.2.5 Infantile hemangioma [2, 473–475]’

- Synonym: capillary hemangioma (former term)
- Epidemiology
  - most frequent vascular orbital tumor in childhood
  - manifestation typically in the first weeks of life (not at birth) with progression during the first 3–6 months
- spontaneous regression typically from the 6th month to the 9th year of life (75–90% gone by the age of 7 years [476]), rarely only during puberty
  - in general harmless, but in cases of unfavorable location (e. g., orbit, oral cavity), possible functional impairment and permanent deformity (e. g., irreversible amblyopia, astigmatism)
- Location and appearance (► **Fig. 24a, b**)
  - ranging from small and circumscribed to large and multifocal
  - most frequently extraconal, mostly ventral to the bulbus in the area of the eyelids; extraocular muscles and lacrimal gland also possibly affected
  - more rarely, intraconal, e. g., in the area of the orbital fat body [477]
  - in cases of retrobulbar location, risk of compression of the optic nerve (especially with rapid growth)
- Clinical
  - raspberry-like appearance, especially with superficial location
- Differential diagnosis
  - congenital hemangioma
    - much rarer, absolute rarity in the orbit
    - present already at birth and completely developed (no further growth after birth)
- Therapy [478]
  - spontaneous remission in 85–90% of cases
  - treatment only in symptomatic hemangioma cases necessary; in cases of optic nerve compression, therapy urgently needed
  - propranolol 2–3 mg/kg body weight per day applied in 2–4 single doses for 6 months (therapy of first choice in cases of complex infantile hemangiomas; response rate of 98%)
  - meanwhile, systemic steroid application reserved for exceptional cases (e. g., airway obstruction, non-response to other therapeutic procedures)
  - cytostatics (vincristine) and interferon-alpha are obsolete
  - laser/cryotherapy: in small, plain, easily accessible hemangiomas (e. g., eyelid)

#### 7.2.2.2.5 Secondary orbital tumors [59, 472]

##### Origin

- paranasal sinuses
  - classification: grade I (infiltration of the orbital bone), grade II (infiltration of the periorbita), grade III (infiltration of the orbital soft tissue by transgression of the periorbita)
  - therapy: multimodal approach required (among others R0 resection, which is crucial for prognosis)
  - prognosis: with grade III, improved survival by orbital exenteration compared to organ preservation
- intracranial
- eyelid (e. g., basal cell carcinoma)
- conjunctiva (e. g., melanoma)

- surgical resection: indicated rather rarely in the area of the orbit because of the risk of damaging surrounding structures

### 7.2.3.1.2 Hemangiopericytoma [479–480]

- Definition
  - tumor originating from the pericytes of the vascular wall or pluripotent perivascular cells
- Epidemiology
  - only single reports of orbital occurrence [480]
- Diagnostics [480]
  - no pathognomonic clinical or radiological characteristics
  - biopsy required
- Pathology
  - histologically, the whole spectrum of benign to malignant characteristics -> classification into benign, borderline, and malignant
  - behavior rather unpredictable, with even seemingly benign lesions sometimes showing malignant behavior
  - metastasis in about 15 % of cases
  - hemangiopericytoma and solitary fibrous tumors overlapping considerably in histology and immunohistochemistry, and according to some authors, possibly representing an independent entity [479]
- Therapy
  - complete surgical resection
  - if needed, adjuvant radiotherapy
  - if needed, chemotherapy
  - follow-up
- Prognosis
  - local recurrences in about 30 % of cases

► **Table 10** lists examples of other vascular tumors of the orbit. Most are absolute rarities in the orbit, and only single case reports are available [475]. Meanwhile, many authors classify tufted angioma as a borderline tumor and an independent entity together with Kaposi-form hemangioendothelioma – with a histopathological spectrum that has more or less aggressive characteristics, depending on the individual case [494, 495].

### 7.2.3.2 Vascular malformations [2, 473–475, 495]

Vascular malformations have the following characteristics:

- Mesenchymal vasculogenetic developmental disorders with low proliferative activity
- Always present at birth but apparent only later (growth triggered, for example, by hormones or mechanical impact)
- Progressive
- No spontaneous remission

The classification of vascular malformations and therapeutic options is listed in ► **Table 11**. The percentages are general and not specific for the orbit [2, 475] (► **Fig. 25a, b**).

#### 7.2.3.2.1 Venous malformation [201, 412]

- Synonym
  - former ‘cavernous hemangioma’, and according to the current ISSVA classification of vascular anomalies [494], to

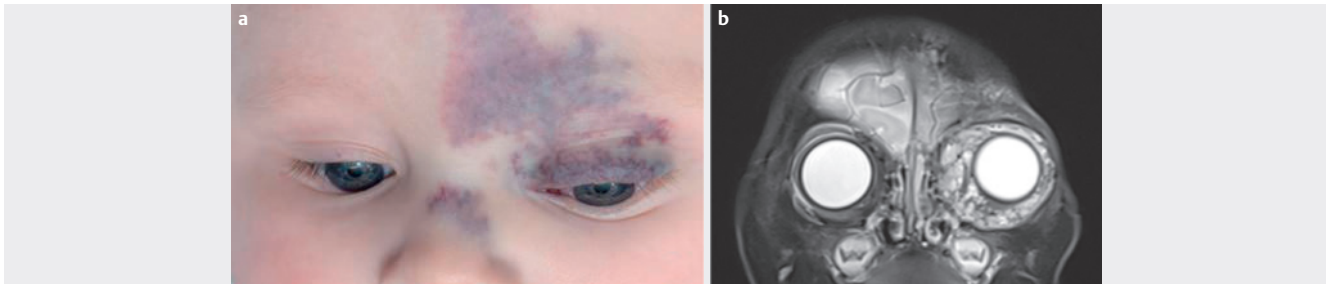
► **Table 10** Vascular tumors of the orbit

Status	Vascular tumors
Benign	<ul style="list-style-type: none"> <li>▪ Infantile hemangioma (90%)</li> <li>▪ Congenital hemangioma (2% of all hemangiomas) [481]</li> <li>▪ Rapidly involuting hemangioma (i. e., RICH), typical: pale halo)</li> <li>▪ Partly involuting hemangioma (i. e., PICH)</li> <li>▪ Non-involuting hemangioma (i. e., NICH)</li> <li>▪ Spindle cell hemangioma [482]</li> <li>▪ Epithelioid cell hemangioma [483 ▪ 485]</li> <li>▪ Lobular capillary hemangioma (former: pyogenic granuloma) [486]</li> <li>▪ Tufted angioma * (former: angioblastoma) [487]</li> </ul>
Locally aggressive/ borderline	<ul style="list-style-type: none"> <li>▪ Kaposi-form hemangioendothelioma * [488–489]</li> <li>▪ Papillary intralymphatic angioendothelioma [490]</li> <li>▪ Kaposi sarcoma [491]</li> </ul>
Malignant	<ul style="list-style-type: none"> <li>▪ Angiosarcoma [492]</li> <li>▪ Epithelioid hemangioendothelioma [493]</li> </ul>

\* In the ISSVA classification, the tufted angioma is listed with the benign tumors; however, it must be considered as a borderline tumor forming an entity together with the Kaposi-form hemangioendothelioma.

► **Table 11** Classification of vascular malformations and therapeutic options

Classification	Therapy [474]
Simple vascular malformations	
<b>Slow-flow</b>	
<ul style="list-style-type: none"> <li>▪ Venous malformation (70%)</li> </ul>	Sclerotherapy, laser therapy, resection
<ul style="list-style-type: none"> <li>▪ Lymphatic malformation (12%)</li> <li>▪ Macrocystic</li> <li>▪ Microcystic</li> <li>▪ Mixed</li> </ul>	Sclerotherapy (macrocystic), laser therapy, resection, mTOR inhibitors (sirolimus) [488]
<ul style="list-style-type: none"> <li>▪ Capillary malformation</li> </ul>	Laser therapy
<b>Fast-flow</b>	
<ul style="list-style-type: none"> <li>▪ Arteriovenous malformation (8%)</li> </ul>	Embolization (transarterial, transvenous, direct), resection of the occluded nidus (= nucleus containing the shunt vessels)
Arteriovenous fistula	Embolization
Combined vascular malformations (6%)	
<ul style="list-style-type: none"> <li>▪ Capillary venous malformation</li> <li>▪ Lymphatic venous malformation</li> <li>▪ Other</li> </ul>	



► **Fig. 25 a, b** Venous malformation in the area of the left orbit with clear blue staining of the skin (a) and extension into the orbit (MRI, b). Courtesy of Prof. Dr. Dr. W. Wohlgemuth, Professor and Chair of the Department of Diagnostic Radiology, University Hospital of Halle.

be called ‘slow-flow venous malformation’ (however, the former term is still widely used)

- Epidemiology
  - one of the most frequent benign masses of the orbit in adults (5–7% of all orbital lesions)
  - typical age of manifestation: 30–50 years
  - women more frequently affected
- Clinical
  - often incidental finding
  - slow growth (exophthalmos developing over years)
  - increased growth during pregnancy
  - typical location: intraconal
- Therapy
  - “watch-and-wait” in smaller/asymptomatic findings
  - sclerotherapy
  - complete surgical resection, e. g., via lateral orbitotomy
- Differential diagnosis
  - ‘orbital varicosities’
    - the term ‘orbital varicosities’ is no longer used, and they are classified as venous malformations
    - pathogenesis: congenital weakness of the venous walls of the valve-less orbital vein -> massive dilation
    - diagnostics: exophthalmos during Valsalva maneuver
    - Clinical: in cases of bleeding, rapid and painful increase in exophthalmos
    - therapy: in general, not required

#### 7.2.3.2.2 Lymphatic malformation [412, 473]

- Synonym (no longer used) lymphangioma
- Epidemiology
  - occurring mainly in childhood and adolescence
- Clinical
  - periorbital swelling
  - slowly progressive, indolent exophthalmos
  - motility disorders
  - bulbus displacement
  - complication: acute exacerbation because of bleeding or infection possible (significant increase within hours or days also possible)
  - no capsula, diffusely infiltrating, compartment borders not respected
  - filled with lymphatic fluid or blood
- Therapy
  - complete extirpation usually not possible



► **Fig. 26** Arteriovenous malformation in the area of the left orbit. Courtesy of Prof. Dr. Dr. W. Wohlgemuth, Professor and Chair of the Department of Diagnostic Radiology, University Hospital of Halle.

- “watch-and-wait”
- in cases of risk of vision loss, volume-reducing measures such as partial resection, injection of sclerotizing substances, mTOR inhibitors

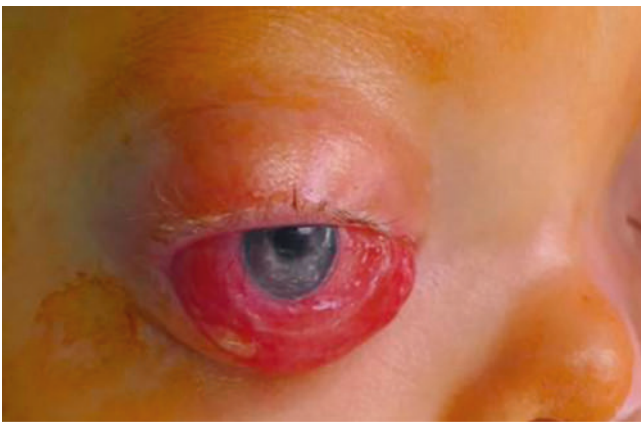
#### 7.2.3.2.3 Arteriovenous malformation (AVM) [473, 475, 495–496]

- Location
  - mainly in the head and neck, including brain (► **Fig. 26**)
  - extremities
  - more rarely, inner organs (e. g., liver, lung)
- Characteristics
  - clinically quite diverse and challenging
  - unexceptionally life-long progressive growth (destructive)
  - reacts to stimuli such as hormonal changes, trauma (e. g., possible increased proliferation after incomplete invasive therapy) [474]
- Clinical classification (Schobinger classification, shortened) [497]
  - stage I: clinically inactive
  - stage II: expansion, pulsation
  - stage III: destructive AVM with ulcerations, necrosis, bleeding, pain, infection
  - stage IV: decompensated AVM with heart failure
- Therapy
  - often quite difficult and risky
  - “watch-and-wait” in cases of asymptomatic AVM

- possibly complete closure by embolization (several sessions) with subsequent resection (if the location allows) to avoid recurrence
- mTOR inhibitors not effective
- Prognosis
  - high tendency to recurrence in cases of incomplete therapy

### Case report 6

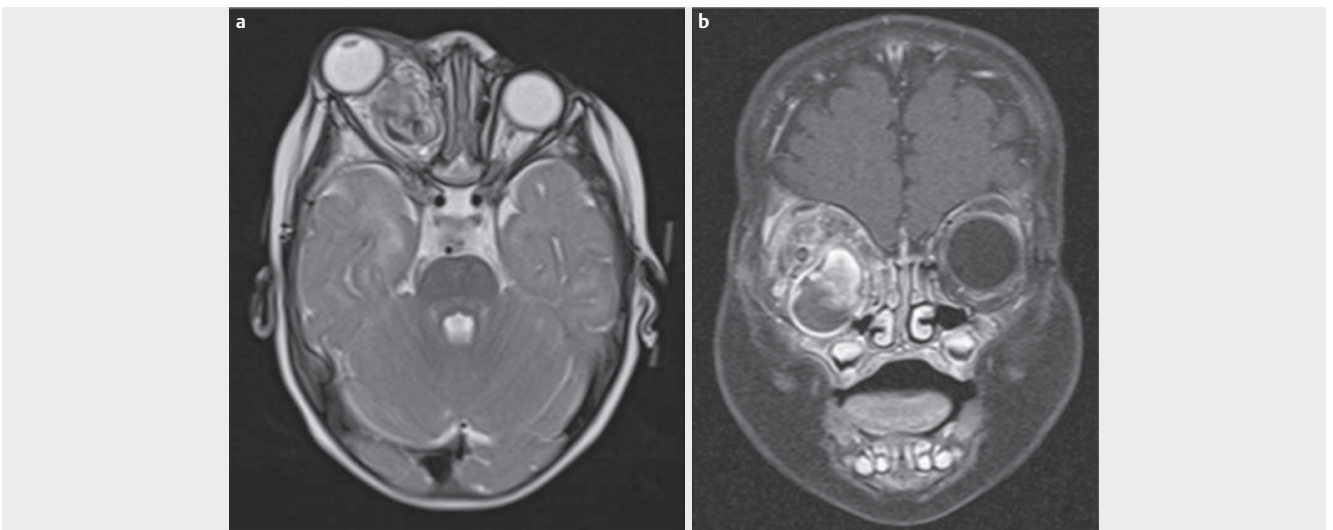
- History
  - emergency presentation of a 9-month-old boy with acute right-sided exophthalmos
  - no relevant previous diseases
- Diagnostics



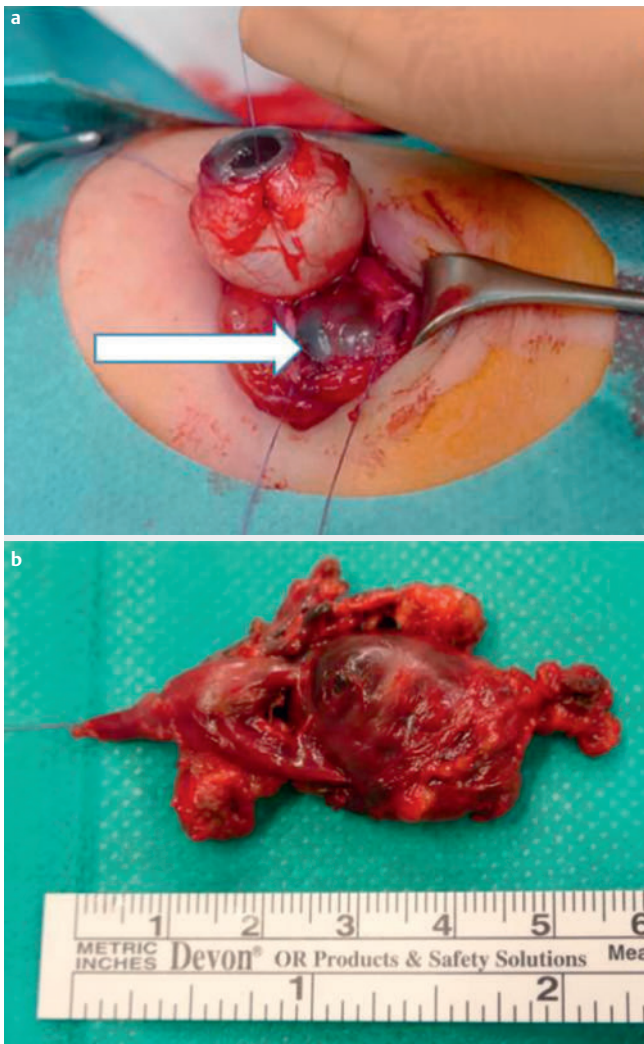
► **Fig. 27** Extended exophthalmos of the right eye with severe conjunctival injection and impossible eyelid closure. The figure is from the archive of the Department of Otolaryngology, University Hospital of Halle.

- inspection: right-sided exophthalmos, increased vascular injection, incomplete eyelid closure (► **Fig. 27**)
- ultrasound at first presentation: suspicion of retrobulbar, acutely bleeding, cavernous venous malformation, MRI for further clarification recommended
- MRI (► **Fig. 28**): retrobulbar bleeding with suspected ruptured, partly thrombosed aneurysma spurium with additional venous malformation portions, DD AVM
- angiography: high-flow AVM in the right-sided orbit, mainly fed from the right ophthalmic artery, dominant venous outflow via dilated venous aneurysms (type II according to the WHO classification), venous drainage via the cavernous sinus

- Course
  - progressive exophthalmos, right-sided
  - increasing defense of the child
  - severe right-sided loss of vision
- Therapy
  - embolization of the AVM with onyx18 (interventional radiology) -> complete closure of the inflow via the ophthalmic artery and another feeder from the maxillary artery -> AVM considered operable
  - because of progressive exophthalmos and onset of corneal ulceration of the right eye, interdisciplinary case discussion and indication for surgery
  - bulbus enucleation, resection of the intraconal AVM after embolization, implantation of a Guthoff implant (16 mm) with tenon and conjunctiva plasty (interdisciplinary by ophthalmologists and otolaryngologists; ► **Fig. 29**)
  - later epithetic treatment
- Histology
  - AVM with condition after embolization
  - no hint of malignancy



► **Fig. 28 a, b** MRI of the head showing an intraconal mass displacing the right bulbus (**a**: axial, T2; **b**: coronary, T1). Courtesy of Prof. Dr. Dr. W. Wohl-gemuth, Professor and Chair of the Department of Diagnostic Radiology, University Hospital of Halle.



► **Fig. 29 a, b** Right-sided enucleation, retrobulbar, mainly intraconal mass (a, white arrow). Resection of an arteriovenous malformation (b). The figures are from the archive of the Department of Otolaryngology, University Hospital of Halle.

### 7.3. Conclusion

Neoplasms of the orbit are rare but diverse. Based on symptoms alone, they cannot be differentiated from structural or inflammatory lesions, and differentiated ophthalmological, radiological, and paraclinical diagnostics are important. In most cases, however, histopathological examination of the excisional biopsy is decisive. Exceptions are tumors of epithelial origin of the lacrimal gland, in which incision biopsies may significantly worsen the overall prognosis. The classification of orbital tumors consists of neoplasms of epithelial and non-epithelial origin as well as neoplasms of the lymphatic tissue, whereas the lacrimal gland is the only organ of the orbit with epithelial structures. Vascular malformations are a special case because they have a highly variable clinical behavior. In addition to watch-and-wait in asymptomatic benign processes, surgical resection of symptomatic benign neoplasms is mainly considered. However, especially in the area of the orbit, the expected benefit must be weighed against the possible functional deficits.

The access pathways mainly depend on the location of the lesions. Radiotherapy as well as systemic therapies with chemotherapeutics and biologicals are important therapeutic pillars and in recent decades have reduced morbidity with orbital tumors. Nonetheless, malignant orbital tumors are mostly associated with a poor prognosis.

Lymphoproliferative lesions of the orbit are indolent so that patients often have a good quality of life after remission. However, mortality rates can be quite high, for example in cases of NK/T cell lymphomas. A better understanding of the molecular genetic correlations will certainly lead to more precise application of targeted therapeutics and thus to a better prognosis with orbital lymphomas. An essential condition, however, is conducting biopsies that are actually representative.

Bone tumors of the orbit encompass highly variable entities, and fibro-osseous lesions have fascinating pathogenetic and pathological properties. Imaging allows differentiation among the possible diagnoses, but biopsy is often necessary for confirmation. These evaluations are reserved mainly for referral centers. Treatment decisions should always be made with consideration of the systemic effects of the disease and new approaches with targeted therapies.

Because of their rarity and diversity, tumors of the lacrimal gland are challenging not only for pathologists but also for clinicians. History and symptom assessment are crucial for the diagnosis but can vary enormously, and even imaging is rarely pathognomonic. Furthermore, controversies exist with regard to the most appropriate therapies, especially in the context of malignant epithelial tumors that generally have a poorer prognosis compared to malignancies of the salivary glands.

Primary and secondary neurogenic tumors are often located in the orbit, presumably because of the high density of nerves in this region. Diagnostics and therapy represent a challenge given that the etiology, pathogenesis, and natural course of the diseases are still not clear.

Tumors of the orbital fatty and connective tissues as well as the striated muscles are mostly heterogeneous neoplasms that are nonetheless similar with regard to clinical symptoms, histogenetics, molecular biology, and prognosis.

Metastases of the orbit are another heterogeneous group of neoplasms with a high variation in presentation, depending on the disease extent and biology of the primary tumor. Most metastases occur in patients with an unknown primary tumor and become apparent because of displaced bulbus, strabismus, and pain. In cases of suspicion, imaging and biopsy are necessary to plan multidisciplinary treatment aimed at preserving vision, reducing pain, and improving quality of life. In some cases, a curative approach is possible.

Vascular anomalies are subdivided into vascular tumors and vascular malformations. Although the former are “true” neoplasms with endothelial proliferation and angiogenesis, malformations are vasculogenetic developmental disorders. They have a low proliferative activity and are already present at birth but become apparent only later and do not show spontaneous remission. The heterogeneous clinical presentation of vascular tumors requires clarification of various differential diagnoses. Therapeutic alternatives span a large spectrum that includes pharmacotherapy, laser, and



classic surgical interventions so that most patients might benefit from one of these options. Dural AV fistulas and carotid cavernous fistulas may have variable orbital manifestations. Despite differences in the lesions, the same examination procedures are applied. Characterization of a lesion and therapy planning require conventional catheter angiography. In benign cases, the therapeutic strategy is conservative, but in rapidly progressing and severe cases, neuroendovascular management is preferred.

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### Conflict of Interest

The authors declare that they have no conflict of interest.

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