

Rare Diseases of the Middle Ear and Lateral Skull Base



Author

Nora M. Weiss

Affiliations

Dept. of Oto-Rhino-Laryngology, Head and Neck Surgery,
University Hospital of Rostock, Germany

Key words

Differential diagnosis, otorrhea, otalgia, rare entity,
manifestation, otitis media

Bibliography

Laryngo-Rhino-Otol 2021; 100: S1–S30

DOI 10.1055/a-1347-4171

ISSN 0935-8943

© 2021. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Dr. med. Nora M. Weiss

Dept. of Oto-Rhino-Laryngology, Head and Neck Surgery,
University Hospital of Rostock

Doberaner Straße 137–139

D-18057 Rostock

Germany

nora-magdalena.weiss@med.uni-rostock.de

ABSTRACT

Otalgia, otorrhea and hearing loss are the most common ear-related symptoms that lead to the consultation of an otolaryngologist. Furthermore, balance disorders and affections of the cranial nerve function may play a role in the consultation. In large academic centres, but also in primary care, the identification of rare diseases of the middle ear and the lateral skull base is essential, as these diseases often require interdisciplinary approaches to establish the correct diagnosis and to initiate safe and adequate treatments. This review provides an overview of rare bone, neoplastic, haematological, autoimmune and infectious disorders as well as malformations that may manifest in the middle ear and the lateral skull base. Knowledge of rare disorders is an essential factor ensuring the quality of patient care, in particular surgical procedures. Notably, in untypical, complicated, and prolonged disease courses, rare differential diagnoses need to be considered.

Contents

1	Introduction	S2	3.5.2	Hand-Schüller-Christian syndrome	S10
2	Malformations	S2	3.5.3	Letterer-Siwe syndrome	S10
2.1	Minor and major ear malformations	S2	3.6	Proteus syndrome	S10
2.2	Vascular anomalies of the temporal bone	S4	4	Autoimmune Diseases	S10
3	Diseases of the Bone	S5	4.1	Granulomatosis with polyangiitis	S10
3.1	Paget's disease (osteodystrophia deformans, osteitis deformans, Paget's syndrome)	S5	4.2	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	S11
3.2	Osteogenesis imperfecta	S6	4.3	Recurrent polychondritis (relapsing polychondritis)	S11
3.3	Fibrous dysplasia	S7	4.4	Rheumatoid arthritis	S11
3.4	Osteopetrosis ("Albers-Schönberg syndrome", "marble bone disease")	S8	5	Neoplasms	S11
3.5	Langerhans cell histiocytosis	S9	5.1	Neoplasms of the haematopoietic system	S11
3.5.1	Unifocal eosinophilic granuloma	S10	5.1.1	Leukaemia of the temporal bone	S12
			5.1.2	Myeloma of the temporal bone	S12

5.2	Malignant epithelial neoplasms
5.3	Glandular neoplasms
5.3.1	Adenoma
5.3.2	Pleomorphic adenoma
5.3.3	Adenoid cystic carcinoma
5.3.4	Adenocarcinomas
5.3.5	Carcinoid of the middle ear
5.4	Sarcomas
5.4.1	Osteogenic sarcoma
5.4.2	Rhabdomyosarcoma
5.4.3	Chondrosarcoma
5.5	Paragangliomas of the temporal bone (tympano-jugular paragangliomas)
5.6	Metastases
5.7	Benign blood and lymphatic neoplasms
5.8	Teratoma
5.9	Tumours of the internal auditory canal, the inner ear, the cerebellopontine angle and the pyramidal tip
5.9.1	Vestibular schwannoma
5.9.2	Meningioma
5.9.3	Epidermoid cyst
6	Infectious Diseases
6.1	Tuberculosis
6.2	Otosyphilis
6.3	Necrotizing (malignant) external otitis
6.4	Cholera
7	Varia
7.1	Pneumatocele of the temporal bone
7.2	Otogenic primary mucocoele of the mastoid
7.3	Otogenic pneumocephalus
7.4	Spontaneous (meningo)encephalocele
7.5	Ectopic brain tissue
7.6	Idiopathic or spontaneous hematotympanum
7.7	Gorham-Stout syndrome
7.8	Cholesterol granuloma
7.9	Giant cell granuloma
	Conclusion
	Acknowledgements
	Conflict of interest
	Literature

1 Introduction

Otalgia, otorrhoea and hearing loss are among the most common ear-related symptoms leading to the consultation of an otorhinolaryngologist. Balance disorders and cranial nerve disorders may also play a role in the consultation. In addition to the most common diseases associated to these symptoms, such as acute otitis media, these symptoms can also point to systemic diseases that may initially present with an otological manifestation, but require

further treatment by other medical specialties, e. g. internal medicine. Furthermore, hearing and balance disorders, tinnitus and disorders of the lower cranial nerves can indicate neurological diseases or be the first manifestation of tumours and lesions of the temporal bone. In addition to common diseases in which the ear, nose and throat (ENT) physician has clinical routine and safe treatment options are available, the differentiation of rare diseases of the middle ear and lateral skull base play a central role in both large academic centres and in primary care. Rare diseases of the middle ear and lateral skull base usually require an interdisciplinary approach in order to establish the correct diagnosis and initiate adequate treatment. A well-known symptomatology may conceal a rare entity, which, however, requires a different and more complex examination or further treatment compared to the more common diseases. As a consequence, a focus of this review is on rare osteological, neoplastic, haematological, autoimmune and infectious diseases as well as on malformations that manifest in the middle ear and lateral skull base. An interdisciplinary cooperation is essential when the initial symptoms of a disease lead to the consultation of an ENT physician, but the diagnosis of a rare disease necessitates further treatment by other medical specialties. The middle ear and lateral skull base may be affected by all systemic diseases affecting bone and mucosa. ► **Table 1** shows an overview of the typical symptoms of diseases that may manifest in the middle ear and lateral skull base.

2 Malformations

2.1 Minor and major ear malformations

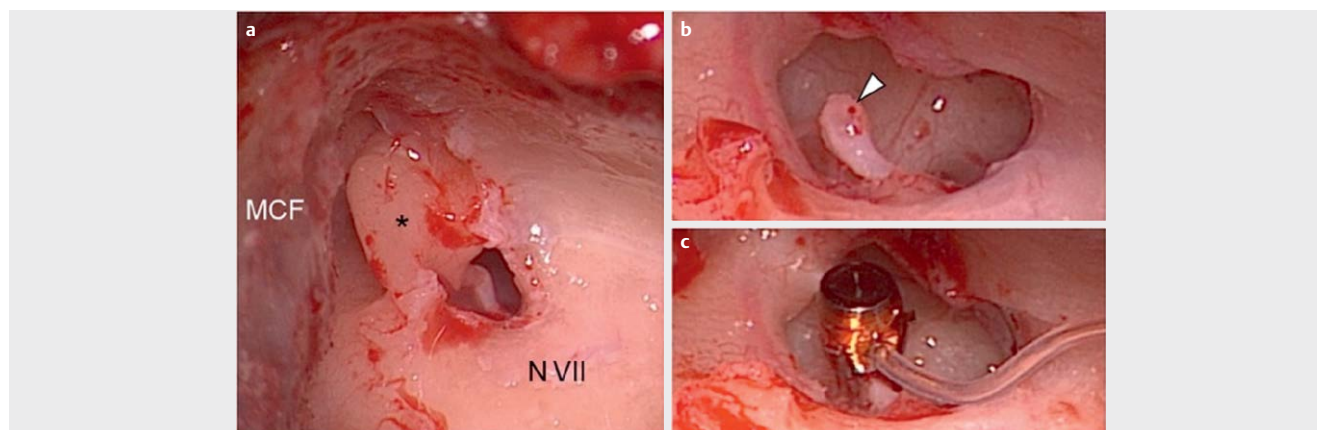
Malformations of the middle ear are often associated with malformations of the external ear (in particular the auricle) or may occur as part of syndromes. According to Jahrsdoerfer, they are subdivided into different degrees of severity depending on the extent and the structures involved [1–3]. The development of the middle ear and external ear occurs at different gestation times and can be disturbed by genetics or by drugs and medications. The combination with inner ear malformations is rare, but must be considered for later treatment [2, 4]. In the so-called “minor malformation”, there are normally wide middle ear spaces and external auditory canal. The ossicles, primarily the stapes are usually affected [5]. Other possible changes also affect other ossicles and can lead to fixation or interruption of the ossicular chain due to bony bridges, adhesions (► **Fig. 1**) or aplasia [6].

In a “major ear malformation”, the external auditory canal is not developed. This causes a backward displacement of the temporomandibular joint, resulting in an anterior displacement of the mastoid. The result is an underdevelopment of the middle ear space. Affected patients may at best have a rudimentary os tympanicum. Underdevelopment of the mastoid and external auditory canal can affect the course of the facial nerve in the Fallopian canal. There is a forward displacement of the nerve in the tympanic and mastoid course, which leads to a localization in the oval window or in the round window niche [7]. The incidence of major ear malformation lies between 1:8 000 and 1:10 000 [2, 8].

Malformations of the middle ear can also occur as part of syndromal diseases. 20–30 % of middle ear malformations occur bilaterally [9] and 7 % are associated with congenital malformations. A combi-

► **Table 1** Summary of selected rare differential diagnoses with manifestation in the middle ear and lateral skull base.

Disease	Symptoms	Specialities	Differential diagnosis	Diagnostics
Malformation				
Minor and Major Malformation	Visible malformation of the outer ear (major ear deformity) Conductive hearing loss (minor and major ear malformation)	Association to other (syndromal) malformations Increased surgical risk situation due to anatomical aberrations	Otosclerosis (minor ear malformation)	CT / MRI: Malformation of anatomical structures (e.g. ossicles, vessels, nerves)
Diseases of the bone				
Morbus Paget	Conductive hearing loss	Conductive hearing loss of the inner ear Surgical therapy not promising	Otosclerosis	Alkaline phosphatase elevated CT: Bone thickening
Osteogenesis imperfecta	Conductive hearing loss		Otosclerosis	Clinical manifestation CT: fractures Bone densitometry Genetic analysis
Fibrous Dysplasia	Mastoid swelling Stenosis of the external auditory canal	Clinical similarity to Hyperparathyroidism	Exostoses of the external auditory canal	Calcium and phosphate normal, alkaline phosphatase elevated CT: Focal sclerotic milky glass-like bone expansion
Osteopetrosis	Tympanic effusions Stenosis of the external auditory canal Conductive hearing loss	Fetal Stapes Bone thickening with narrowing of the neuroforamina	Otitis media Exostoses of the external auditory canal Idiopathic Facial nerve palsy	X-ray/CT: "Sandwich vertebrae", "bone-in-bone" phenomenon
Langerhans cell histiocytosis	Mastoid swelling Otorrhoea Dizziness Hearing loss	Fistulas of the external auditory canal	Otitis media Postoperative granulation tissue	CT: Osteolytic lesions, mastoid swelling. Biopsy: evidence of histiocyte infiltrates
Autoimmune diseases				
Granulomatosis with polyangiitis	Tympanic effusions Otalgia	Possible exacerbation after surgical intervention	Otitis media	Skin biopsy: non-specific leukocytoclastic vasculitis Nasal biopsy (high false negative rate) Granulomatous inflammation c-ANCA
Relapsing polychondritis	Inflammation of the cartilage of the auricle and/or the auditory canal	Involvement of the Eustachian tube	Otitis externa diffusa Perichondritis Erysipelas Otitis media Tympanic effusion	Clinical: Multilocular cartilage inflammation, polyarthritis, ocular involvement, cochleovestibular involvement.
Rheumatoid arthritis	Otorrhoea Facial nerve palsy		Chronic Otitis media	Joint involvement Rheumatoid factors and/or antibodies against cyclic citrullinated peptide, CRP and/or ESR elevated
Neoplasms				
Benign Neoplasms	Painless swelling Hearing loss		Lymph node swelling Mastoiditis Exostoses of the external auditory canal	Biopsy
Malignant Neoplasms	(Bloody) Otorrhoea Hearing loss Otalgia Diplopia Balance disorders, dizziness Visual disturbances Hypaesthesia of the facial skin Facial nerve palsy	Chondrosarcoma: Destructions clivus and mastoid apex, early metastasis Metastases: Occurrence mainly in the petrous apex	Otitis media Mastoiditis	Biopsy
Paraganglioma	Hearing loss Pulsating tinnitus Otalgia Vertigo	Reddish pulsating mass behind the lower tympanic quadrants	Protruding bulb of the jugular vein Abnormal course of the internal carotid artery Schwannoma in the region of the jugular foramen Plasmocytoma Meningioma Neurofibroma	MRI: "salt-and-pepper" pattern Angiography: "Tumour Blush" PET-CT biochemical examination for catecholamine secretion
Neoplasms of the haematopoietic system				
Leukaemia	Otalgia	Leukaemia: Occurrence mainly in the petrous bone apex	Otitis media	CT MRI Bone marrow puncture
Lymphoma	Otorrhoea			
Myeloma	Facial nerve palsy			
Infectious diseases				
Tuberculosis	Otorrhoea	Tuberculosis: Perforations of the tympanic membrane	Otitis media Otitis externa	Tuberculosis, cholera: microbiological pathogen detection by smear or biopsy Necrotizing (malignant) external otitis: CT (bony destruction)
Syphilis	Otalgia			
Necrotizing (malignant) external otitis				
Cholera				



► **Fig. 1** Auditory canal atresia in a case of major ear malformation in an 8-year-old child with conductive hearing loss. **a** Intraoperative view of the fixed malleus-incus complex (asterisk). **MCF**: middle cranial fossa; **NVII**: Facial nerve. **b** View on the stapes head (white arrowhead) after removal of the malleus-incus complex. **c** Coupling of the floating mass transducer of a Vibrant Soundbridge to the stapes head on the mobile stapes using a Clip Coupler.

nation with other malformations of the first two pharyngeal arches, such as mandibular hypoplasia, e. g. in oculo-auriculo-vertebral dysplasia (Goldenhar syndrome) is frequent [10]. Symmetrically occurring dysostosis mandibulofacialis (Treacher-Collins syndrome) shows hypoplasia of the mandible and zygomatic bone, a laterally sloping eyelid axis and eyelid anomaly [11, 12]. Dysostosis acrofacialis (synonymous with dysostosis otomandibularis, rodent syndrome), which has no ocular symptoms, must also be distinguished. In addition, middle ear malformations can also occur in craniofacial dysostoses such as dysostosis craniofacialis (Crouzon syndrome) or acrocephalosyndactyly (Apert syndrome), as well as in malformation syndromes with spinal malformations such as Klippel-Feil syndrome or Wildervanck syndrome. In addition, cases of malformations of the middle ear and external ear have been described as an adverse event when taking certain medications during pregnancy, e. g. in the context of thalidomide (Contergan®) embryopathy [13].

Apart from aesthetic aspects, the treatment of deformities consists of functional rehabilitation of the hearing. This can be achieved by hearing aids, by surgical means or in combination. The decision on therapeutic options depends on the age of the patient and the severity of the malformation. The age of the patient has an influence on the maturity of the auditory system and thus the ability to benefit from (bilateral) stimulation. The severity of the malformation limits the type of auditory rehabilitation [14]. Intraoperatively, a slit-like anatomy of the middle ear with little pneumatization and only rudimentary ossicles may be found (hammer-anvil conglomerate) [15]. Reconstructive surgery is usually limited to patients with favourable anatomical conditions or mild cases where otoplasty can be performed in combination with ossiculoplasty [14]. Active middle ear implants offer a suitable alternative [16]. In severe malformations of the temporal bone, the risk of implantation of an active middle ear implant may be particularly high, for example due to a forward displacement of the facial nerve in the tympanomastoid course or accompanying vascular anomalies (see subsequent section), so that bone conduction hearing systems are preferred [14, 15].

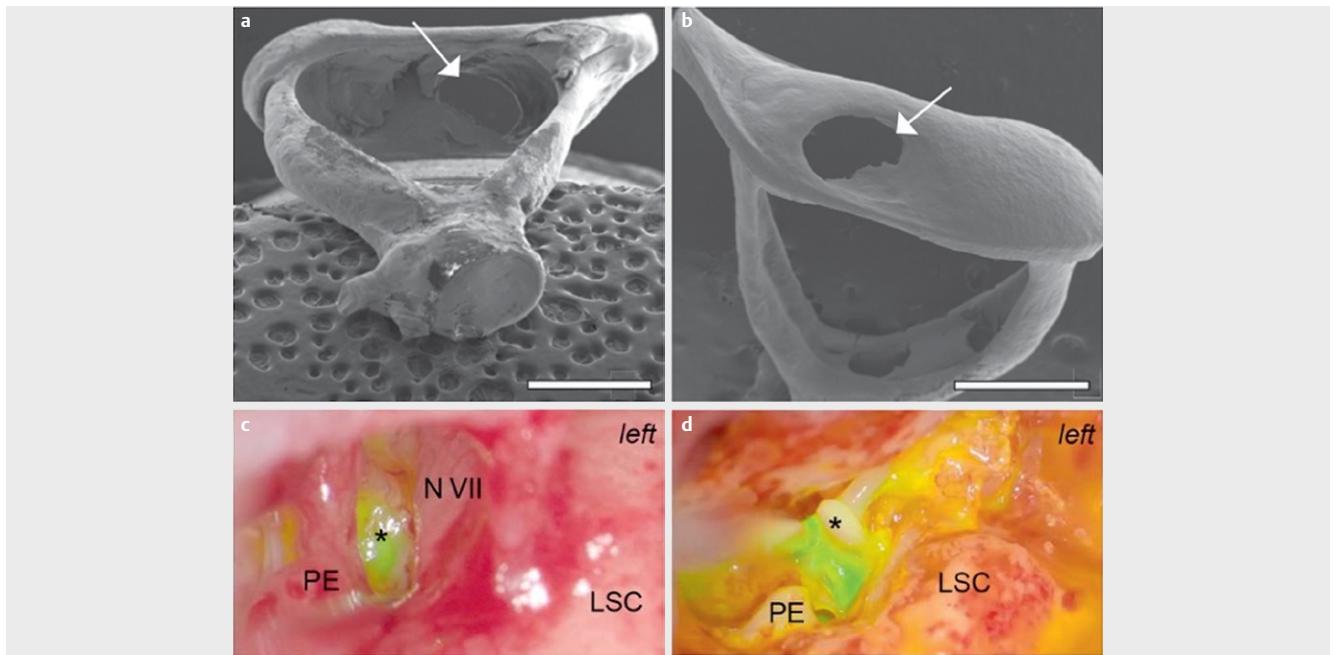
Clinical example: congenital stapes footplate defect

From a developmental point of view, the malleus and incus arise from the cartilage of the first pharyngeal arch, while the stapes superstructure arises from cartilage of the second pharyngeal arch. Like the annular ligament, the stapes footplate arises from the otic capsule. Here, the central footplate as well as the stapes superstructure arise from the neural crest during embryogenesis [17], while the outer part of the stapes footplate and the annular ligament are of mesodermal origin. Dysplasia of the inner ear is often associated with a malformed otic capsule, which may lead to congenital weakness or fistula formation in the stapes footplate or annular ligament. In addition, pressure fluctuations in the cerebrospinal fluid (CSF) can lead to thinning of the stapes footplate or tears in the annular ligament. As a result, patients with inner ear dysplasia are more prone to oto- or rhinoliquorrhoea following trauma or barotrauma, with an associated risk of vertigo, deafness and recurrent otogenic meningitis ► **Fig. 2** [18–20].

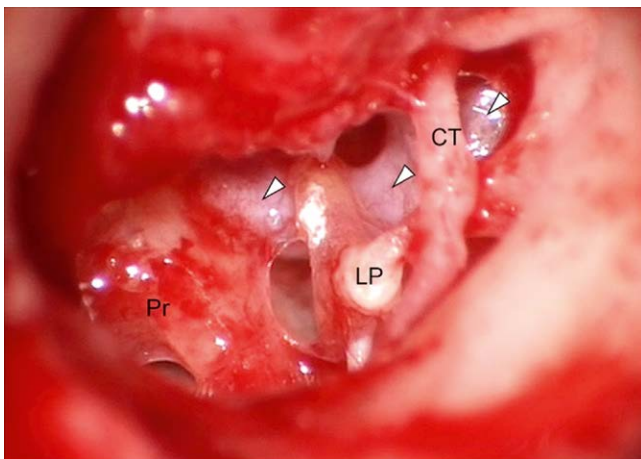
2.2 Vascular anomalies of the temporal bone

Advancement of the sigmoid sinus, protrusion of the bulbus venae jugularis or the internal carotid artery can lead to problems in the surgical management of minor and major ear malformations. This plays a role in the creation of a new auditory canal, in ossiculoplasty or in implantable hearing aid surgery [1, 7, 15, 21]. Furthermore, an stapedia artery that has not regressed ► **Fig. 3** can lead to complications during surgery. In cases of malformation, the stapedia artery is present in up to 1:5,000 to 1:10,000 cases [22]. Ligation can lead to central reduced perfusion and injury to life-threatening bleeding [23].

Furthermore, vascular anomalies must be considered in the differential diagnosis of a pulse-synchronous tinnitus. Anomalies of the jugular bulb, the sigmoid sinus, the internal carotid artery as well as arteriovenous fistulas and malformations are possible [24]. In most malformations, tinnitus can also be audible to the examiner [25]. In the case of a venous malformation, tinnitus is more often perceived on the right side, as the size of the right jugular vein



► **Fig. 2** Congenital stapes footplate defect of the left ear in a 20-month-old boy with bilateral temporal bone malformation (cochlear aplasia on the right, incomplete partition type I on the left). Due to minor trauma, the stapes foot plate malformation on the left side led to oto-rhino-liquorrhea and finally to the diagnosis. **a–b** Electron microscope image of the congenital stapes foot plate defect (arrow). Scale bar: 1 mm. **c–d** Intraoperative visualisation of the perforation in the stapes footplate (asterisk) with intrathecal fluorescein application. **c** View of the stapes in situ shows fluorescein-labelled CSF leakage through the stapes footplate. **d** When the stapes is removed, CSF leakage occurs from the oval window. **LSC**: lateral semi-circular canal; **NVII**: facial nerve; **PE**: pyramidal eminence. Fig modified after [20].



► **Fig. 3** Intraoperative tympanoscopic view of a persistent stapedia artery in a 20-year-old patient with conductive hearing loss of the left ear. The persistent stapedia artery passes under the anterior limb of the stapes (white arrowheads). **LP**: lenticular process, **Pr**: promontory, **CT**: chorda tympani, white arrowheads: Stapedial artery.

usually dominates over the left [26]. A high-riding jugular bulb may cause conductive hearing loss in addition to vertigo and tinnitus [27–29]. These symptoms arise either from direct contact with the ossicles or from invasion of the bony labyrinth, causing a third window lesion (with conductive hearing loss of the inner ear) [29, 30]. An aberrant internal carotid artery is caused by maldevelopment during embryogenesis. Otoscopy reveals a reddish pulsating mass

behind the tympanic membrane resembling a paraganglioma of the glomus tympanicum. The diagnosis of the respective anomalies is made by a combination of CT/MR angiography and diagnostic digital subtraction angiography [25], which is commonly indicated in every case of pulsatile tinnitus. CT can also provide information on the bony coverage of the vascular structures [31–33]. Treatment depends on the severity and subjective impairment. Arterio-venous fistulas are associated with a substantial risk for apoplexy, epilepsy or cerebral haemorrhage [34]. Treatment options include interventional radiological embolization, neurosurgical resection or radiotherapy, symptomatic drug therapy and clinical radiological follow-up [35, 36]. In the case of venous malformations, ligation can be performed [25].

3 Diseases of the Bone

3.1 Paget's disease (osteodystrophia deformans, osteitis deformans, Paget's syndrome)

The disease was first described by Czerny in 1873 and was called "osteitis deformans". The disease received its name from Sir James Paget [37, 38]. The aetiology is unknown and there is still no reliable evidence that the cause of the disease is of inflammatory origin. Infectious causes such as syphilis infection and paramyxoviruses [39], endocrine dysfunction, autoimmune causes, vascular lesions, inflammatory causes and hereditary factors are discussed [40]. Several gene loci have been associated with Paget's disease. Among others, a mutation has been described in the *SQSTM1* gene, which encodes the sequestome-1 protein [41]. This is an autophagosome-cargo protein that binds other proteins for selective auto-

phagocytosis. The disease affects men and women equally, with an incidence of up to 3 % at the age of 40 years and increases in prevalence with increasing age (up to 10 % in 90-year-olds) [42, 43]. Apart from osteoporosis, Paget's disease, which is diagnosed in only about 30 % of cases during life, is the second most common disease of the bone. Involvement of the middle ear in Paget's disease is rare with an estimated prevalence of temporal bone involvement of up to 1 % in Caucasian adults [44]. Paget's disease does not always cause deformities of the limb bones, as the term "osteitis deformans" may suggest. About one third of patients are symptom-free. Possible symptoms are bone pain, bending or shortening of the legs ("saber tibia") or an increase in the circumference of the head.

Typically, there is a phasic course, which in the first stage is associated with an increased vascularization and fibrous re-modelling of the bone due to a stimulation of bone resorption (osteolytic phase). In the second stage (mixed phase), there is excessive bone accretion. The third, osteoblastic phase is characterized by increasing de-vascularization. This results in a distended, less stable bone with an increased tendency to fractures. In the middle ear, microfractures may affect the stapes footplate (► Fig. 4 a-c) [45]. In the fourth stage, there is a slow re-modelling process into an almost normal-looking lamellar bone. This last stage is predominantly found in subclinical cases with cranial involvement and therefore exclusively histologically. The disease most commonly affects the pelvis, femur and tibia. Rarely, there is involvement of the ossicles [46], for example manifesting with stapes fixation [47]. The clinical symptoms of middle ear involvement are characterized by unremarkable ear microscopic findings, conductive or mixed hearing loss and absent stapedius reflexes [44]. However, conductive hearing loss is not associated with ossicular re-modelling [48]. Besides an involvement of the ossicles and bone in the epitympanic or oval window, possible explanations for the conductive component include ear canal narrowing, fibrosis of the tympanic membrane, calcifications in the annulus fibrosus of the tympanic membrane, atrophy of the tympanic membrane, narrowing of the Eustachian tube or tympanofibrosis [46]. However, such changes are not reliably detectable histologically [49]. It is also discussed that the hearing loss can be explained by changes in bone density, mass and shape, which lead to an attenuation of the fine mechanics in signal transmission [49]. Monsell et al. described a correlation between the bone density of the cochlear capsule and the air conduction threshold as well as the sound conduction component [50, 51]. Merchant and Rosowski examined eight temporal bones of patients with Paget's disease using laser Doppler vibrometry. In three cases, they found a relative hypermobility of the umbo that has also been demonstrated in cases of dehiscence of the superior semicircular canal [27]. Furthermore, multiple microfractures of the otic capsule were observed in all 8 cases. Consequently, it is assumed that the acoustic energy is diverted away from the cochlea by the fractures that constitute a third window lesion and thus lead to a conductive hearing loss of the inner ear [27, 52]. Due the presence of conductive hearing loss, there is a risk of misdiagnosing Paget's disease as otosclerosis with the risk of unsuccessful surgical treatment [47].

The diagnosis of Paget's disease includes pure tone audiometry and stapedius reflexes in the case of middle ear involvement, as

well as laboratory diagnostics, which show an elevated alkaline phosphatase. Conventional x-rays show osteolysis in early manifestations. Computed tomography (CT) may show bone thickening in the temporal bone, displacement of the internal carotid artery, widening of the mastoid with reduction of pneumatization, narrowing of the internal auditory canal and, very rarely, nerve compression [53]. More frequently, a widening of the internal auditory canal is described due to the growth of the mastoid [45, 48]. Scintigraphy shows an increased technetium-99m uptake in the affected bone and may be a useful addition to the radiological examinations. A biopsy of the affected bone can contribute to a histological confirmation of the disease.

The treatment of Paget's disease consists of inhibiting osteoclast activity with bisphosphonates, which can prevent the deformity. Analgesics are also used. Further treatment is symptomatic by treating the fractures (► Fig. 5), by the supplementation of calcium and vitamin D, and by physiotherapy.

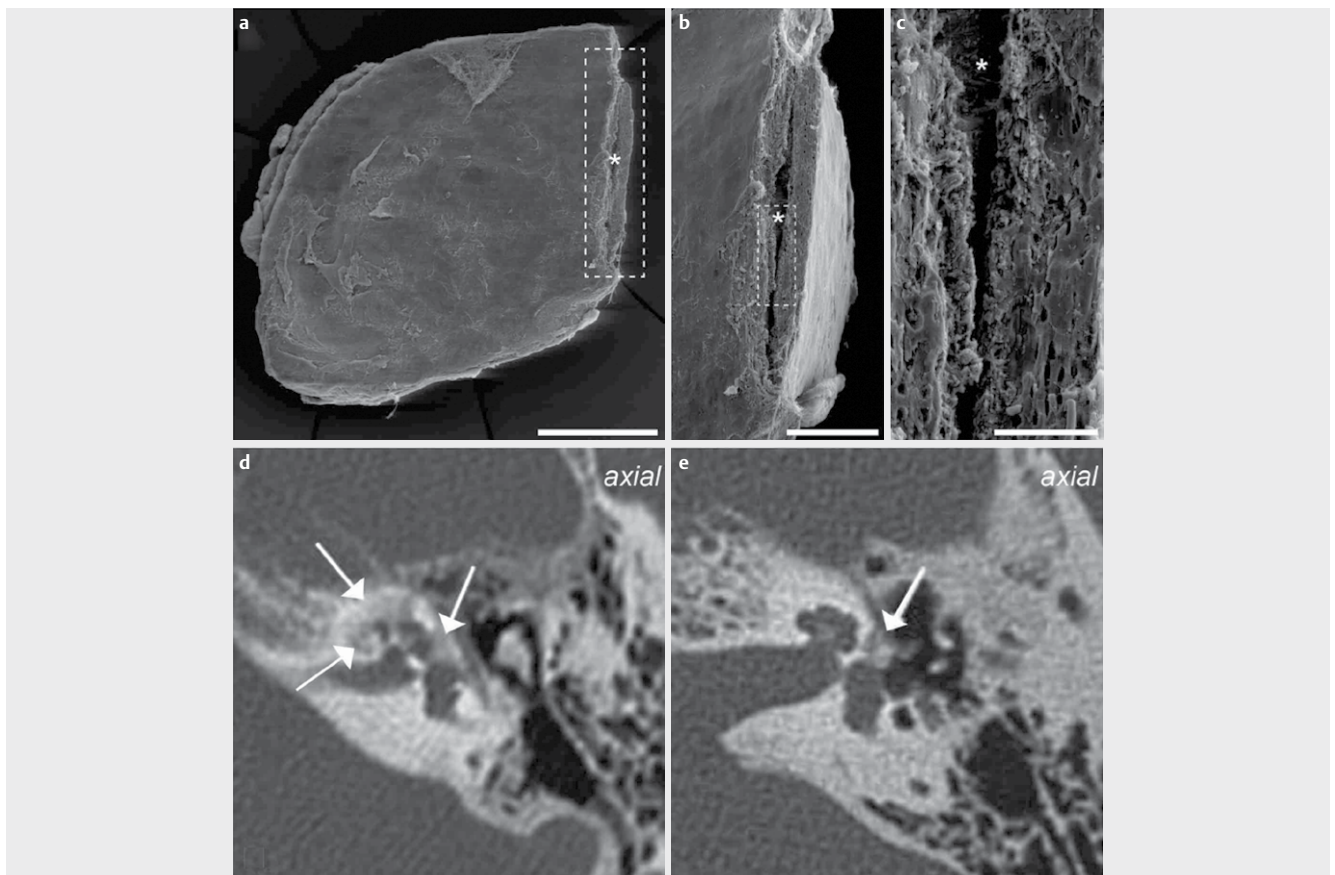
Paget's disease can manifest in the middle ear and mastoid, leading to conductive hearing loss (most likely localized in the inner ear). However, treatment is systemic. In patients with conductive hearing loss and other clinical indications of Paget's disease, imaging (► Fig. 4 d-e) may be helpful to differentiate the disease from otosclerosis and to avoid surgical treatment by ossiculoplasty, which is not considered to be a successful treatment option in Paget's disease [47, 54].

3.2 Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a genetic disease of connective tissue that is characterized by fragile, fracture-prone bone. A gene mutation of one of the two type I collagen genes (*COL1A1* or *COL1A2*) is described in 80 % to 90 % of the patients.

OI is classified into 4 types according to clinical manifestation, radiological criteria and pattern of inheritance [55, 56]: OI type I is inherited in an autosomal dominant pattern. It is the mildest form. Clinically, it is characterized by blue sclerae, non-deforming fractures and a normal body size. Hearing loss may occur in 50 % of the cases. OI type II is the most severe form, associated with multiple fractures in utero and is often resulting in stillbirth. OI type II is either transmitted in an autosomal dominant fashion or results from a sporadic new mutation. OI type III manifests with frequent fractures and progressive bone deformity from childhood on. Initially there are bluish sclerae, later they are white. Hearing loss is present in 50 % of cases. In addition, kyphoscoliosis, weak joints, funnel chest, dental changes and small accessory bones within the cranial sutures may occur. Inheritance is autosomal dominant or recessive. The pattern of inheritance of OI type IV is autosomal dominant. Clinically, it resembles OI type I, but is associated with white sclerae. Hearing loss is present in only 10–30 % of cases.

Otological symptoms are most commonly observed in OI type I, with hearing loss being most relevant. It may occur as conductive hearing loss or a combined hearing loss, which is mostly due to bone re-modelling processes at the stapes that may resemble otosclerosis. Intraoperatively, soft, calcareous thickening of the stapes footplate, vascularized bone in the oval niche covered by vascularized periosteum, fibrous degeneration of the stapes suprastructure and osteoporotic fixation of the footplate similar to otosclerosis are described [57–60]. Surgical hearing rehabilitation by



► **Fig. 4** **a-c** Electron microscope image of a stapes footplate fracture. Figure modified from [323]. **a** One part of the footplate is turned downwards, showing a fracture gap (asterisk). Scale bar: 500 μ m. Dotted region shown in **b**. **b** View of the fracture gap (asterisk). Scale bar: 200 μ m. Dotted region shown in **c**. **c** Magnified view of the fracture gap. Scale bar: 50 μ m. **d-e** CT morphological distinction between Paget's disease and otosclerosis. **d** Paget's disease shows remodelling processes within the cochlea (arrows). **e** Fenestral otosclerosis shows plaques in the fissula ante fenestram with a mixed otospongiotic-otosclerotic phase (arrow). Figure **d-e** modified after [54] (Courtesy of S. Kösling, Institute of Radiology, University Hospital Halle (Saale)).

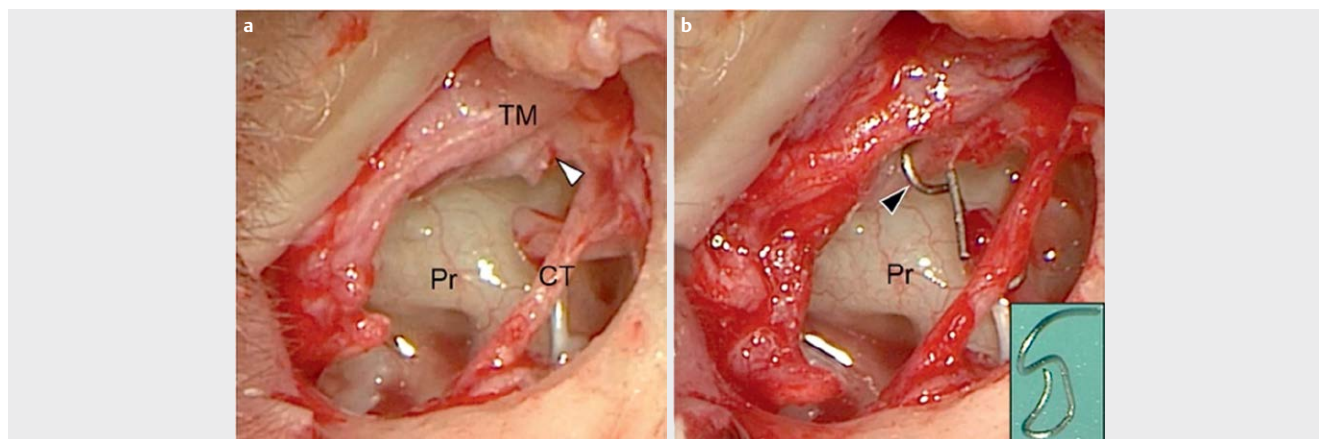
stapedotomy is possible, but is considered to be surgically challenging due to soft porous bone and the risk of a floating footplate [57–59]. Other general treatment approaches include the treatment of fractures, orthoses, physiotherapy and bisphosphonates as an inhibitor of bone resorption. New approaches include bone marrow transplantation [61, 62], intrauterine stem cell implantation [63], growth factors [64] and antibody therapy [65, 66].

3.3 Fibrous dysplasia

Fibrous dysplasia was first described by Weil [67]. It is a chronic, slowly progressive disease that may also occur in the context of Albright syndrome with bony lesions, abnormal pigmentation ("café-au-lait spots"), endocrine dysfunction and pubertas praecox [68]. Histologically, the disease is characterized by resorption of bone and fibrous re-modelling into stroma, as well as bony lesions from immature mesenchymal osteoblastic progenitor cells. These are caused by a non-heritable activating mutation in the α -subunit gene of the stimulatory G-protein coding gene. Consequently, there is an increase in cyclic adenosine monophosphate, which leads, among other effects, to the pathological bone lesions by activation of numerous protein kinases [69, 70].

The disease becomes symptomatic during childhood. A distinction is made between the monoostotic and the polyostotic type. The polyostotic type is progressive throughout lifetime and usually involves the long bones. The skull bone is affected in over 50 % of cases. The monoostotic type is the more common variant and often disappears at puberty. It involves the long bones, facial bones and membranous bones. Sarcomatous degeneration of the bone lesions is possible [71–73]. The prevalence is about 2.5 % [74]. Due to frequent bone pain and a laboratory elevation of alkaline phosphatase, the clinical appearance of fibrous dysplasia may resemble hyperparathyroidism. For this reason, patients with fibrous dysplasia are frequently reported to have undergone frustrated surgical procedures under the suspicion of a parathyroid tumour [75]. Isolated fibrous dysplasia is distinguished from hyperparathyroidism by laboratory diagnostics (calcium, phosphate, alkaline phosphatase). Laboratory diagnostics show an elevated alkaline phosphatase, which occurs in 30 % in the polyostotic type. Calcium and phosphate, on the other hand, are usually normal in fibrous dysplasia.

There are more than 100 reported cases of fibrous dysplasia with temporal bone involvement in the literature. In 70 % of cases, the monoostotic type, in 23 % of cases the polyostotic form is descri-



► **Fig. 5** **a** Intraoperative view into the tympanic cavity in a 30-year-old female patient with conductive hearing loss after malleus handle fracture (white arrowhead). **TM**: tympanic membrane, **Pr**: promontory, **CT**: chorda tympani. **b** View after reconstruction of the ossicular chain by a malleostapedioplasty (black arrowhead). Insertion bottom right: Malleostapedioplasty prosthesis made of titanium wire.

bed and 7% occurred in the context of McCune-Albright syndrome [48]. Clinically, temporal bone involvement may result in painless swelling of the mastoid, further bony deformities, pathological fractures and cranial nerve palsies. Progressive narrowing of the external auditory canal can lead to conductive hearing loss. It is the most common symptom of temporal bone fibrous dysplasia and is reported in 80% of cases with temporal bone involvement. Misinterpretation as auditory canal exostoses is common. Intraoperatively, however, unlike exostoses, vascularized bone with a cancellous, coarse-grained consistency is seen. Involvement of the middle ear or Eustachian tube obstruction may also be an explanation of conductive hearing loss. Radiologically, there are radiolucent areas with soft roundish borders and sometimes radiopaque areas (► **Fig. 6**).

The general treatment of fibrous dysplasia consists of physiotherapy and treatment of the fractures. Surgical therapy only comes to use symptomatically or in terms of biopsy to confirm the diagnosis. Canaloplasty may be useful for the symptomatic treatment of conductive hearing loss or of recurrent otitis externa. Prior to surgical ablation of exostoses, CT may reveal evidence of fibrous dysplasia with areas that are partly radiolucent and partly radiopaque. Regular follow-up is necessary because of the risk of progressive narrowing of the facial canal and progressive hearing loss.

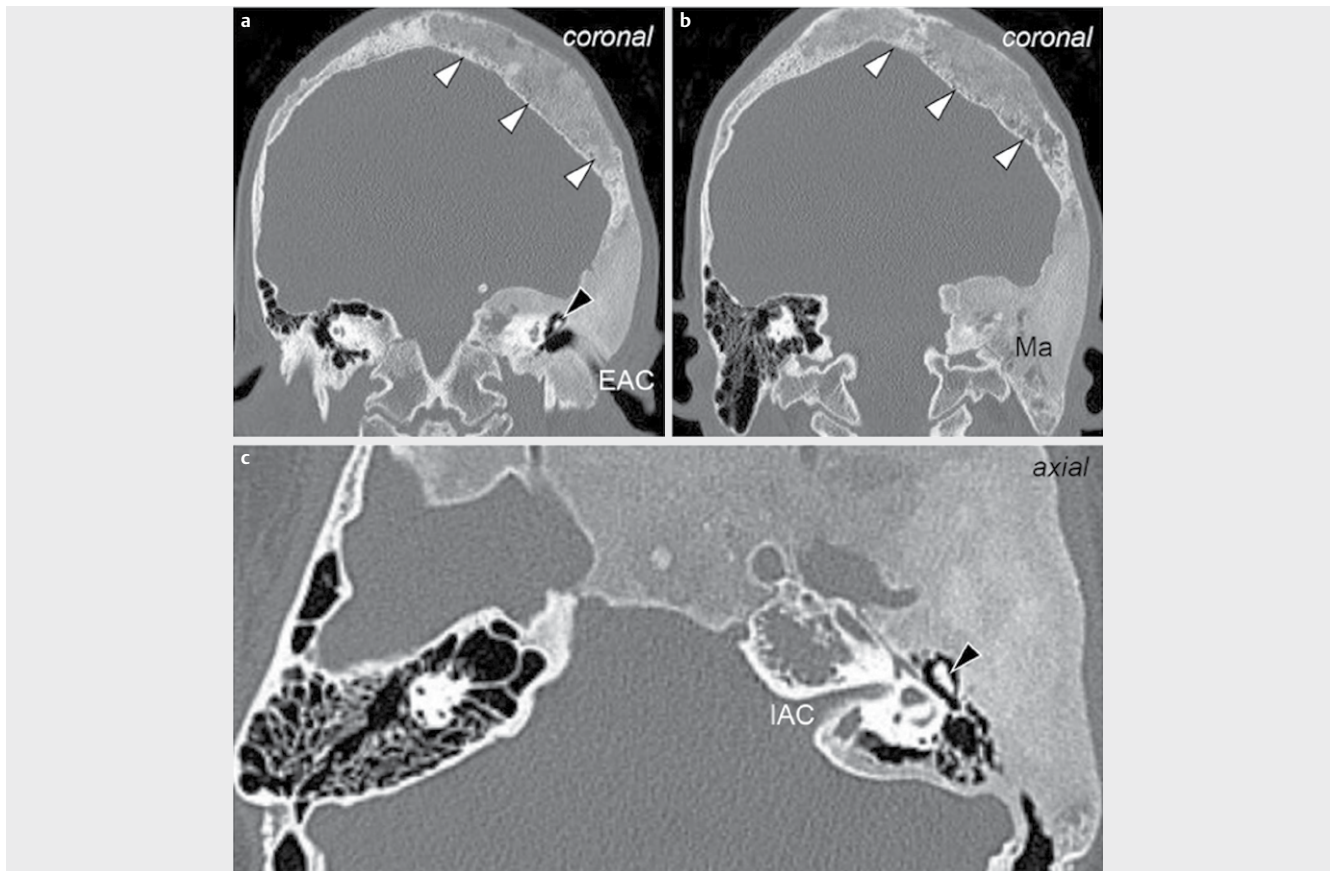
3.4 Osteopetrosis (“Albers-Schönberg syndrome”, “marble bone disease”)

Osteopetrosis manifests with a marked increase of bone density [76, 77], that is caused by defective osteoclasts and a resulting abnormal bone resorption. At the same time, there is an undisturbed osteoblast activity with increased formation of mineralized bone and cartilage. The prevalence is estimated at 1:20 000 [78]. There is defective resorption of calcified cartilage and primitive bone, resulting in the persistence of mineralized cartilage and primitive bone matrix, which prevents the maturation of bone. The disease exists as a dominantly inherited benign and recessively inherited malignant variant.

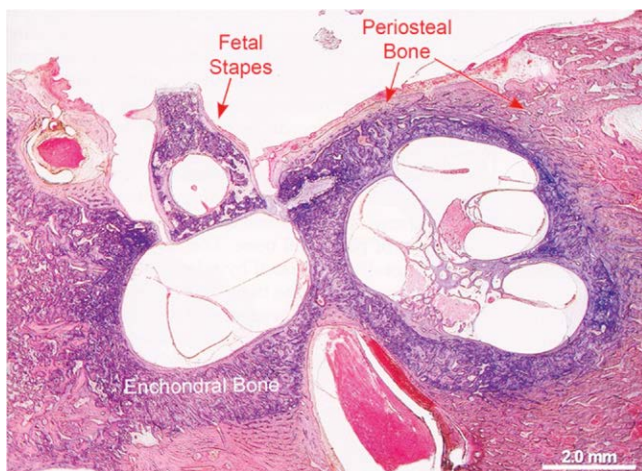
In the malignant type, osteopetrosis usually appears in childhood, is rapidly progressive and has a high mortality rate. In the majority of cases, malignant osteopetrosis is caused by a gene mutation in the *TCIRG1* gene [78], which encodes a subunit of the vacuolar proton pump. As a result of osteopetrosis, the bone marrow is repressed, leading to anaemia and thrombocytopenia. In addition, hepatosplenomegaly, an infectious tendency, narrowing of the neuroforamina with neurodegeneration, frontal protrusion, growth retardation, facial paresis, hearing and vision loss, fractures as well as mental retardation may occur. There is a significantly limited life expectancy (first to second decade of life). Histologically, the temporal bone shows dense, calcified bone of the labyrinth and ossicles [79], a non-pneumatized mastoid and a fetal stapes (► **Fig. 7**). Ear-specific symptoms may include recurrent otitis media, tympanic effusions, ear canal stenosis and conductive hearing loss [80, 81]. Bone marrow transplantation is used as therapy for the malignant type [82].

The benign type of osteopetrosis is usually asymptomatic. Affected patients have a normal life expectancy. It is caused by a gene mutation in the *CLCN7* gene, which encodes the α -subunit of the chloride transporter *ClC-7* [76]. Osteopetrosis can lead to constriction of the cranial nerves due to cranial thickening (optic nerve, trigeminal nerve, vestibulocochlear nerve and facial nerve). Spontaneous facial nerve paresis with spontaneous recovery occurs as a frequent initial symptom. Consequently, in cases of defective recurrent facial pareses in young adulthood or childhood radiological imaging needs to be considered. In addition, attention should be paid to dental infections due to osteomyelitis, jaw thickening, intracranial venous congestion due to cranial thickening and a resulting increase in intracranial pressure, as well as cutaneous syndactyly, which often leads to the initial diagnosis.

Hearing loss can be caused by a narrowing of the middle ear space, by bony deposits in the oval niche and a resulting fixation of the auditory ossicles [83, 84]. Furthermore, constriction of the annulus fibrosus may lead to a loss of tension of the tympanic membrane and narrowing of the Eustachian tube may lead to tympanic effusion that may further cause conductive hearing loss [85]. With regard to facial paresis occurring in the context of osteopetrosis, therapeutic success has



► **Fig. 6** CT of the skull in a 23-year-old female patient with fibrous dysplasia. **a, b** The pathognomonic focal sclerotic ground-glass bone expansion with involvement of the cranial bone (white arrowheads), os zygomaticum, os sphenoidale and temporal bone on the left is shown. The external auditory canal (**EAC**) is narrowed. The malleus is properly configured (black arrowhead). The left mastoid (**Ma**) shows almost complete loss of pneumatization. **c** The internal auditory canal (**IAC**) is normally wide. There is a properly configured malleus and incus (black arrowhead) in a ventilated middle ear.



► **Fig. 7** Osteopetrosis of the temporal bone in an axial histopathological temporal bone section of a 15-month-old boy. The patient suffered from mental retardation and congenital bilateral deafness. The stapes shows a fetal shape, characterised by a thickening of the stapes legs and foot plate. The immature bone consists of a combination of calcified cartilage and thin trabeculae of lamellar bone. The immature bone is thickened and shows increased density. Figure and legend modified after [48].

been reported with complete intratemporal facial decompression [83, 86, 87]. In cases of increased intracranial pressure, decompressive craniotomy can lead to a reduction in intracranial pressure. Tympanoplasty may contribute to hearing improvement.

3.5 Langerhans cell histiocytosis

Langerhans cell histiocytosis is a neoplasia-like disease that leads to acute disseminated infiltrations of various organ systems and has a high mortality if left untreated. Langerhans cell histiocytosis is characterised by a proliferation of benign histiocytes and the accumulation of pathologically altered Langerhans cells occurs. Langerhans cells are inactive dendritic cells in the stratum spinosum of the epidermis that express CD1a, S100 protein and langerin [88, 89] and serve the antigen presentation. Langerhans cells belong to the mononuclear phagocytic system. The cause of Langerhans cell histiocytosis is most likely a proliferation of Langerhans cells due to immunological dysfunction. The incidence is between 1:200 000 and 1:2 000 000. Three subtypes of Langerhans cell histiocytosis are distinguished, that will be discussed below.

3.5.1 Unifocal eosinophilic granuloma

Eosinophilic granuloma usually occurs in young adults and children. It is the mildest form of the disease and results in solitary osteolytic lesions. Usually there is only skeletal involvement of the long tubular bones, ribs, vertebrae, skull, and also the mastoid. There may be small temporal bone lesions with possible auditory canal fistulae, otalgia, mastoid swelling, cranial nerve palsies due to bony lesions at the jugular foramen and otorrhoea. Treatment consists of local curettage and where appropriate of radiation [90,91].

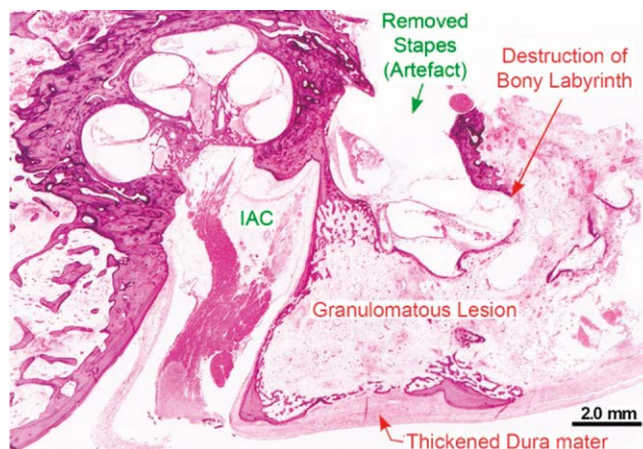
3.5.2 Hand-Schüller-Christian syndrome

Hand-Schüller-Christian syndrome occurs in children under the age of 5 years, rarely also in the second or third decade of life. In 15–30%, the outcome is fatal. In contrast to eosinophilic granuloma, multifocal lesions in bones and organs (e. g. in the liver or spleen) with embedded histiocytes, cholesterol deposits and multinuclear cells are common. Extraskelatal manifestations of the skin, lymph nodes and organs are rare. Systemic symptoms include fever, recurrent upper respiratory tract infections, loss of appetite and lymph node swelling. Clinical symptoms in the ear may mimic acute or chronic otitis media. The diagnosis is made by biopsy and the detection of histiocytes. Occasionally, spontaneous regression occurs. Treatment consists of low-dose chemotherapy under the aim of systemic symptom control.

3.5.3 Letterer-Siwe syndrome

Letterer-Siwe syndrome is a disseminated, rapidly progressing type of the disease, usually occurring in children under the age of three years. It leads to a diffuse organ involvement. Hepatosplenomegaly, lymph node swelling, anaemia, skin rash and skeletal lesions (especially of the skull) may occur. The course of the disease is acutely febrile and is associated with a poor prognosis and a high mortality rate [92]. Treatment consists of corticosteroids, cytotoxic substances such as methotrexate, vincristine and cyclophosphamide. Radiation, bone marrow transplantation or stem cell transplantation [93] are also available. In case of survival, there are permanent stigmata such as short stature, diabetes insipidus, exophthalmos, pulmonary fibrosis and vertebral body compression. In up to 25% of cases, there are destructive bone lesions with calvarial defects. These may involve the temporal bone and lead to otological symptoms. Initially, the disease often manifests in the external, middle and/or inner ear with the appearance of granulation tissue, polyps, otorrhoea, retroauricular swelling, vertigo, hearing loss and occasionally a positive fistula sign [94–101]. Because of its similarity to chronic otitis media, frequent mastoid surgery prior to correct diagnosis has been reported in the literature [95,96,102,103]. Bone destructions are found on temporal bone CT [95,96,104]. The diagnosis is confirmed by deep biopsy from the lesion (► Fig. 8) [105].

In summary, all forms of Langerhans cell histiocytosis can lead to an inflammatory disease pattern. Consequently, in case of CT-morphologically bilateral destructive ear disease associated with increased erythrocyte sedimentation rate and without other evidence of infection, or in cases of long-term granulation tissue after ear surgery with persistent otorrhoea and skin lesions or auditory



► **Fig. 8** Langerhans cell histiocytosis (Letterer-Siwe disease) in an axial histopathological section of the temporal bone of a 23-month-old child with bilateral otorrhoea. The diagnosis of Langerhans cell histiocytosis was made by biopsy of the auditory canal. Histology showed destructive granulomatous lesions in the mastoid and bony labyrinth and a thickened dura mater. The missing stapes is considered to be an artefact. IAC: internal auditory canal. Figure and legend modified after [48].

canal fistulas, Langerhans cell histiocytosis needs to be considered as a differential diagnosis and a biopsy has to be performed.

3.6 Proteus syndrome

Proteus syndrome causes a growth of skin, bones, muscles, fatty tissue, blood and lymph vessels. The cause of the disease is unknown. Mutations in the *AKT1* and *PTEN* genes or somatic mutations are discussed as possible causes. At birth, affected persons usually have no obvious stigmata. However, patients are at increased risk of developing tumours such as unilateral ovarian cystadenomas, testicular tumours, meningiomas and adenomas of the salivary glands. The disease can lead to bone growths on the mastoid and thus to ear canal obstruction, similar to ear canal exostoses. Surgical widening of the auditory canal may be indicated to improve hearing. Intraoperatively, the exostosis-like bone growths do not appear as compact bone, but as aerated mastoid cells or similar to the consistency of fibrous dysplasia.

4 Autoimmune Diseases

4.1 Granulomatosis with polyangiitis

In granulomatosis with polyangiitis (formerly Wegener's disease/granulomatosis), necrotising granulomas occur in the upper and lower respiratory tract, in the kidney and rarely in other organs. Otolaryngologic manifestations of this systemic vasculitis may occur as recurrent sinusitis, headaches, rhinorrhoea or (bilateral) otitis media. Laboratory findings include normochromic, normocytic anaemia, thrombocytosis, positive rheumatoid factors, hyperglobulinaemia (IgA) and anti-neutrophil cytoplasmic antibodies (c-ANCA). Furthermore, there is an increased erythrocyte sedimentation rate. The cause of the disease is not fully understood, although an immune-mediated disorder is suspected. In this case, tis-

sue destruction occurs as a result of an inflammatory disease pattern with a subsequent immune response including production of c-ANCA, which cause cell damage by an interaction of neutrophils and mucosal tissue [106]. The diagnosis is confirmed by histology with repeated biopsies and the combination of clinical appearance and the detection of c-ANCA in the blood. Cellular necrosis and inflammatory granulomas with multinucleated giant cells, vasculitis and microabscesses may be found [48]. The disease can affect the mastoid, middle ear, tympanic membrane. If the Eustachian tube is affected, the symptoms resemble those of otitis media with effusion. Furthermore, facial paresis [107] or sensorineural hearing loss may occur [108, 109]. Occurrence in the middle ear may be associated with destruction of the round window, the Fallopian canal and the inner ear [110, 111]. Therapy consists of immunosuppressants and steroids, that may lead to a remission of hearing loss [112]. If left untreated, the disease is fatal in 90 % of cases.

Consequently, especially in bilateral, recurrent or protracted otitis media, an autoimmunological disease should be considered and c-ANCA should be sought. Surgical treatment should be carefully indicated in granulomatosis with polyangiitis due to the risk of protracted healing [113].

4.2 Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Eosinophilic granulomatosis with polyangiitis is another type of systemic vasculitis. The leading symptoms include a pulmonary manifestation with severe allergic asthma attacks. A manifestation in the middle ear and mastoid is rare and can lead to the symptoms of acute otitis media, mastoiditis or chronic granulating otitis media [114, 115]. Conventional treatment using antibiotics and myringotomy is often unsuccessful in eosinophilic granulomatosis with polyangiitis. The detection of perinuclear antibodies (p-ANCA) is the guiding factor. Therapy consists of steroids [116].

4.3 Recurrent polychondritis (relapsing polychondritis)

Recurrent polychondritis was first described in 1923 by Jaksch-Wartenhorst [117]. This disease of unknown origin is characterized by recurrent inflammatory reactions of the cartilage. In addition to the auricle and auditory canal, the eye, cardiovascular system, kidney and nervous system can also be affected. There are associations with other autoimmune diseases. It is suspected that the disease is caused by an autoimmune reaction to connective tissue and epitopes that occurs as the result of the failure of regulatory factors [118, 119]. A unilateral or bilateral inflammation of the auricle is typical, but the cartilaginous ear canal can also be affected and thus resemble diffuse acute otitis externa [120]. An occlusion of the Eustachian tube can also lead to acute otitis media with effusion. The diagnosis is made according to clinical criteria and needs be considered in the presence of bilateral infections of the auricle, especially in combination with non-erosive, seronegative polyarthritis, nasal cartilaginous inflammation, ocular inflammation (conjunctivitis, keratitis, scleritis, uveitis), respiratory tract cartilage inflammation (laryngeal or tracheal cartilage) and vestibulocochlear dysfunction [121]. Treatment consists of immunosuppressants and steroids.

4.4 Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disease. Its cause is not yet completely understood. A genetic predisposition is suspected, which leads to an increased immune reaction to an initial infection. In 1989, Hoffman et al. described the case of a 69-year-old female patient with rheumatoid arthritis and involvement of the middle ear and mastoid, who showed the clinical symptoms of chronic otitis media and resulted in facial paresis [122]. Gussen et al. report the case of a 55-year-old female patient with involvement of the malleo-incudial joint [123]. In histopathology, a thickened tympanic membrane and fibrous remodelling of the ossicular chain as well as demineralization of the malleus and incus are described in rare cases [124]. Consequently, the picture of acute otitis media and possibly facial paresis in patients with rheumatoid arthritis may indicate an acute episode of the underlying disease and requires a joint therapy concept together with rheumatology.

5 Neoplasms

Various neoplasms can manifest in the middle ear and lateral skull base. The patient's history (e. g. pulse-synchronous tinnitus of the ear, known neoplastic diseases in the history, drug use, syndromal diseases) may provide initial hints for their origin. Depending on the findings, the diagnosis can be further confirmed by additional diagnostics (e. g. radiological imaging) and by biopsy. Treatment depends on the entity and symptoms and usually consists of either surgical resection, medical therapy, radiotherapy or a combination.

5.1 Neoplasms of the haematopoietic system

Diseases of the blood and haematopoietic system can be grouped into the following four subcategories [125, 126].

1. Myeloid neoplasms, which originate from the progenitor cells in the bone marrow, that usually develops erythrocytes, granulocytes, monocytes and megakaryocytes. These are further subdivided into acute myeloid leukaemia, myeloproliferative neoplasms (chronic myeloid leukaemia, polycythaemia vera, essential thrombocytopenia) and myelodysplastic syndromes.
2. Lymphoid neoplasms arise from the progenitor cells of lymphocytes or mature lymphocytes. Historically, they have been further subdivided into lymphoid neoplasms with bone marrow and blood involvement (leukaemia) and lymphoma masses. However, they are not always distinguished with certainty. A more common classification is B-cell, T-cell or natural killer (NK) cell lymphoma. Hodgkin's lymphoma represents another subcategory and originates from the germ cells of the B cells.
3. Neoplasms with myeloid and lymphoid components, e. g. acute leukaemia.
4. Histiocytic/dendritic neoplasms (e. g. histiocytic sarcoma) originating from the dendritic cells or histiocytes.

Since the majority of the literature describing the occurrence of haematological diseases in the ear was published before the publication of the classification cited above, an older terminology (leukaemia, lymphoma, myeloma) will be used here.

5.1.1 Leukaemia of the temporal bone

Leukaemia of the temporal bone is histologically characterized by diffuse infiltration, haemorrhage and remodelling of the mastoid bone (especially the petrous apex) by leukaemia cells (► **Fig. 9**) [127–130]. The tympanic membrane and mucosa of the middle ear may be thickened by leukaemic infiltrates and exhibit an inflammatory exudate. Secondary infections are common.

A special type is granulocytic sarcoma, which is an extramedullary accumulation of immature cells with myeloid differentiation outside the bone marrow. Symptoms, that are primarily due to growth, include aural fullness, otalgia, otorrhoea and facial paresis. The symptoms resemble those of acute otitis media [131]. Diagnosis includes CT, that may show bony destructions, and magnetic resonance imaging (MRI), that shows a signal enhancement in the corresponding lesions after contrast administration.

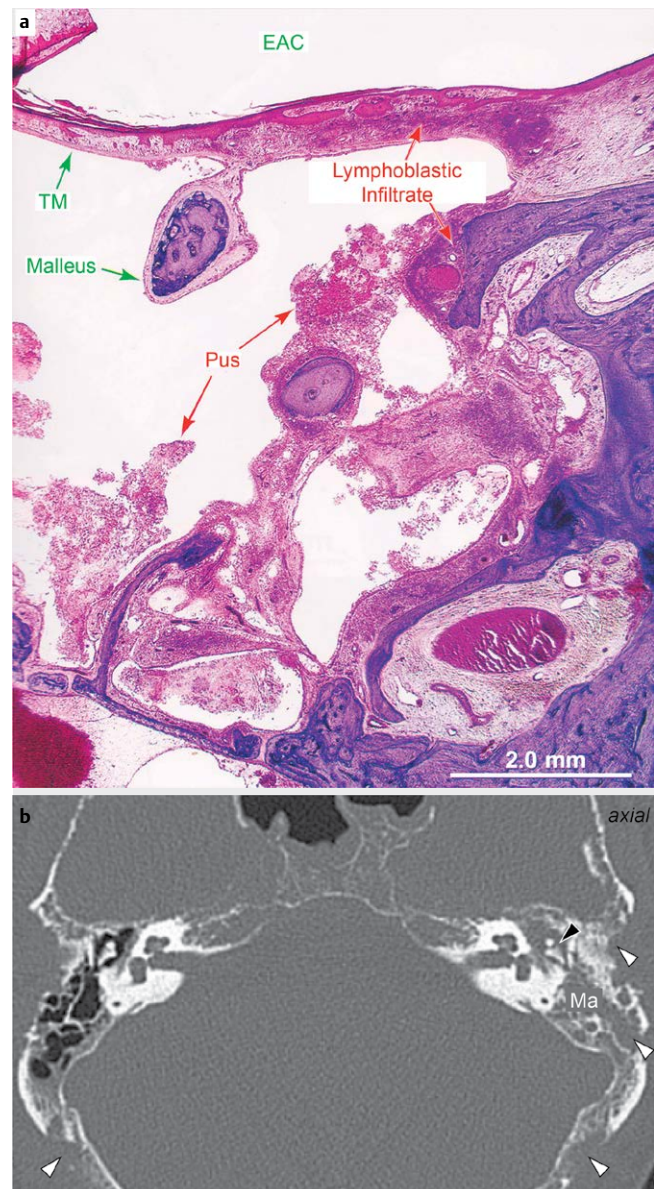
5.1.2 Myeloma of the temporal bone

Myeloma of the temporal bone corresponds to B-cell non-Hodgkin lymphoma (category 2) and can affect all bones of the body, predominantly the spine and long tubular bones. It usually occurs between the age of 40 and 60. The temporal bone usually is affected in the terminal stage only. Histologically, the bone is replaced by plasma cells (myeloma cells). The symptoms may also resemble acute otitis media [132], but are usually overshadowed by the disease's manifestation at other sites.

Diseases of the blood and haematopoietic system may lead to an initial manifestation in the middle ear and mastoid and resemble acute otitis media or skin ulcer due to otorrhoea and mastoid swelling [156]. Due to the possible aggressive course of the disease, an early diagnosis and initiation of chemotherapy is necessary.

5.2 Malignant epithelial neoplasms

Malignant epithelial neoplasms of the ear originate in the auricle in 60 %, in the auditory canal in 28 %, and in the middle ear or mastoid in 12 % [133]. The incidence ranges from 1:4 000 to 1:20 000. Malignant epithelial neoplasms occurring in the middle ear have a worse prognosis than those occurring in the ear canal or pinna [133, 134]. Two thirds of malignant epithelial neoplasms of the auricle are basal cell carcinomas, one third are squamous cell carcinomas. In the middle ear, the distribution is reversed with two-thirds squamous cell carcinomas and only one-third basal cell carcinomas. There are almost exclusively case reports reporting on the occurrence of malignant melanoma in the middle ear. In 11 % of cases, lymphogenic metastasis is already evident at initial diagnosis [133]. Malignant melanoma has an extremely poor prognosis with a metastasis rate of around 50 % [135]. Possible symptoms include otorrhoea, hearing loss and pain [135]. In addition, facial paresis, dizziness and mastoid erythema or swelling may occur [133, 136]. Radiation has been reported to be a risk factor for the occurrence of malignant epithelial tumours of the middle ear [137–140]. The diagnosis is confirmed by biopsy or excision. Therapy usually consists of surgical resection. In cases of middle ear involvement, an additional subtotal petrosectomy has to be performed.



► **Fig. 9** **a** Acute lymphocytic leukaemia in an axial histopathological section of the right temporal bone of a 9-year-old boy. Clinically, there was otalgia, a hyperperfused right tympanic membrane and mastoid swelling. The histopathological section showed lymphoblastic infiltrates, oedematous thickening and hypervascularisation of the tympanic membrane and the middle ear mucosa. Furthermore, pus was found in the middle ear. EAC: external auditory canal. TM: tympanic membrane. Figure and legend modified after [48]. **b** Axial CT of the temporal bone of a 55-year-old male adult with B-cell chronic lymphocytic leukaemia (B-CLL). Bony destruction of the calvarial bone and left mastoid (white arrowheads) with complete obstruction of the aerated mastoid cells is seen. **Ma**: mastoid; black arrowhead: incudo-malleal joint.

5.3 Glandular neoplasms

The leading symptoms of benign glandular neoplasms include painless swelling and hearing loss; malignant neoplasms may cause otorrhoea and nerve paresis. Four entities of glandular neoplasms

are distinguished according to Dehner and Chen [141]. Murphy et al. described carcinoid of the middle ear in 1980 [142].

5.3.1 Adenoma

Adenomas can originate from the apocrine glands of the auditory canal, usually the ceruminous glands. This is why the term ceruminoma was formerly used. However, other glandular tissues such as the hair follicles or sebaceous glands are also possible origins of adenomas. Glands have a two-layered structure and consist of an oxyphilic layer on the inside and a myoepithelial layer on the outside. Consequently, glandular neoplasms may have a pleomorphic cell population of basal myoepithelial cells (which express cytokeratin types 5 and 6, S100 and the tumour protein p63) and luminal ceruminous cells, which express cytokeratin type 7 [143]. If the adenomas originate from the middle ear epithelium, light microscopy shows a mucus formed by the tumour in the cytoplasm or in the glandular lumen [144]. There are histological similarities of adenomas to mixed tumours or adenoid cystic carcinomas. An adenoma can be distinguished from carcinoma by the absence of bone erosion. Clinically, there is a mass in the middle ear or auditory canal, which has a slowly progressive growth that may be associated with a slow hearing loss. Rarely, facial paresis [145] or a pulse-synchronous ringing in the ears may occur [146].

5.3.2 Pleomorphic adenoma

Pleomorphic adenoma may occur in the outer ear canal and may initially be clinically apparent by swelling of the outer ear canal. It may arise from the ceruminous glands or, in rare cases, from ectopic salivary gland tissue [147–152]. Pleomorphic adenoma is histologically characterized by a heterogeneous histological pattern with myxoid portions in 90 %, pseudocartilaginous portions in 50 % and squamous portions in 25 % of cases [153].

5.3.3 Adenoid cystic carcinoma

Adenoid cystic carcinoma is a malignancy arising from the apocrine, seromucinous ceruminous gland tissue or salivary gland tissue that may occur in the ear canal. Symptoms include pain and swelling with a slow growth tendency. The carcinoma is prone to recurrence after surgical removal and to distant metastases. The recurrence rate is reported to be 41 % within an average interval of eight years [154]. Histology shows a "Swiss cheese pattern", which is characterized by cylinders with hollow centres and with embedded acidophilic mucous material. Differential diagnosis includes basal cell carcinoma, ceruminoma, mucoepidermoid carcinoma and adenocarcinoma [155].

5.3.4 Adenocarcinomas

Adenocarcinomas develop from glandular atypia of the ceruminous glands [156, 157] or sebaceous glands [158, 159] of the external auditory canal or middle ear epithelium [160–162]. Metastases of adenocarcinoma must be considered as a differential diagnosis.

5.3.5 Carcinoid of the middle ear

The carcinoid of the middle ear was first described in 1980 by Murphy et al [142]. The tumour originates from the neuroendocrine cells (so-called Kulchitsky cells), that are abundantly present in the

pancreas, lungs and gastrointestinal tract and synthesize peptide hormones. Carcinoid of the middle ear most frequently affects adults, predominantly females [163]. Symptoms include conductive hearing loss and swelling or masses in the middle ear. A recurrence rate of 22 % has been reported. Metastases occur in up to 9 % of cases [163]. Histology shows a similar appearance as an adenoma. It is discussed that both adenoma and carcinoid of the middle ear are the same type of tumour with different degrees of glandular and neuroendocrine differentiation [164, 165].

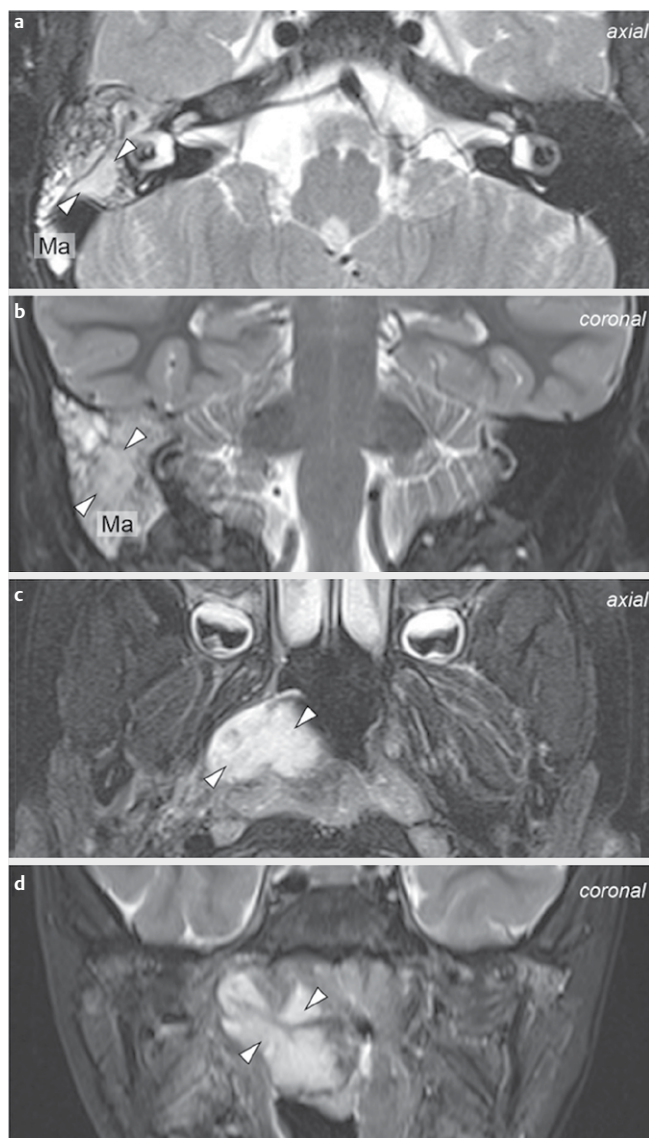
5.4 Sarcomas

5.4.1 Osteogenic sarcoma

Osteogenic sarcoma is the most common malignant neoplasm of bone and occurs in approximately 75 % of patients between the ages of 10 and 25. It may occur in children as part of retinoblastoma, Li-Fraumeni syndrome, Rothmund-Thomson syndrome or Werners syndrome [166]. In older adults, an association with Paget's disease or radiation has been described [167]. Osteogenic sarcoma originates from mesenchymal stem cells, that can differentiate into bone, connective tissue or cartilage. It is characterized by a malignant sarcomatous stroma with formation of osteoid (soft, non-mineralized bone) and bone. In 90 % of cases, the metaphyses of the long tubular bones are affected [168]. Occurrence in the temporal bone is very rare [138, 169–176]. The existing case reports suggest an association with radiation (e. g. nasopharyngeal carcinoma or paraganglioma). The prognosis of tumours induced by radiation is poor [138]. Symptoms include a slowly growing retroauricular swelling of a bony consistency that is displaceable towards the skin [174]. If present, this swelling may be painful and associated with otorrhoea [173].

5.4.2 Rhabdomyosarcoma

Rhabdomyosarcoma commonly affects children. It may manifest in the orbit, oral cavity, nose, pharynx or middle ear (► **Fig. 10**) [177, 178]. It usually occurs in the first decade of life, mainly below the age of five years [179]. If the middle ear is affected, the disease is almost always fatal [180, 181]. In addition to an extension into the mastoid tip and the middle cranial fossa, growth along the Fallopian canal and the internal auditory canal into the posterior cranial fossa is possible [182, 183]. Depending on the origin of rhabdomyosarcoma, histology reveals rhabdomyoblasts or striated muscle and positive immunostaining for muscle-specific proteins such as actin, myosin, desmin and myoglobin is found. Electron microscopy shows myofilaments, Z-bands, desmin filaments. Four histological subgroups exist (embryonic, alveolar, botryoid, spindle cell). Symptoms include bloody otorrhoea, which may be erroneously interpreted as a sign of acute otitis media, and facial nerve palsy, which usually occurs in the later stages. Therapy usually consists of polychemotherapy, which should be carried out in certified oncological centres. In Germany, therapy is carried out after registration in the "Soft Tissue Sarcoma Registry" (SoTiSaR) according to the recommendation of the study centre. Surgical therapy is indicated only in exceptional cases and after assessment by a surgical reference centre for rhabdomyosarcomas. Surgery needs to be indicated with care under consideration of all possible functional deficits [179, 184, 185].



► **Fig. 10** T2-weighted fat-suppressed MRI images of a 5-year-old boy with an embryonal rhabdomyosarcoma of the right mastoid and epipharynx. A hyperintense signalling of the tumour (white arrowheads) with complete obstruction of the aerated mastoid cells is shown (Ma, a, b). The tumour (white arrowheads, c, d) extends into the epipharynx via the petrous apex.

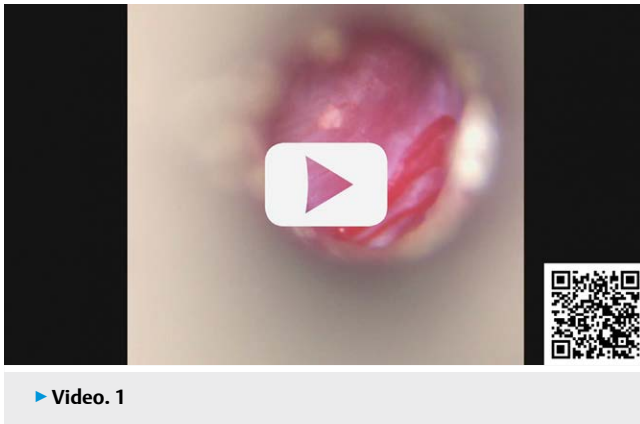
5.4.3 Chondrosarcoma

Cartilage neoplasms account for up to 33 % of bone tumours. They are difficult to distinguish from chondromas [186]. Chondrosarcomas usually affect adults between the age of 25 and 50 years. Chondrosarcomas show a slow growth and an equal gender distribution. The clinical appearance is characterized by early pulmonary metastasis, rapid growth and osteolytic lesions as signs of malignancy [187, 188]. Involvement of the temporal bone is very rare and most likely occurs in the mastoid tip and clivus [189–191]. Symptoms include diplopia, headache, hearing loss, balance disorders, visual changes and hypaesthesia of the facial skin. Manifestation in the auditory canal is also possible [189, 192].

5.5 Paragangliomas of the temporal bone (tympano-jugular paragangliomas)

The first description of vascular paragangliomas (formerly called “glomus tumours”; glomus = autonomic ganglion = paraganglion) was made 1941 by Guild [193]. Paragangliomas are the most common neoplasms of the middle ear [194] and originate from the parasympathetic ganglion cells. Two types of paragangliomas are described, “chromaffin” (epinephrine-producing) and non-“chromaffin” (non-epinephrine-producing) types [195]. Paragangliomas usually occur sporadically; a few are associated with hereditary syndromes, typically multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome or neurofibromatosis type 1 [196, 197]. In rare cases, they occur as multiple tumours [194, 198]. Hereditary paragangliomas are caused by germline mutations affecting the mitochondrial succinate dehydrogenase complex. Compared to sporadic paragangliomas, hereditary paragangliomas are more likely to occur as multiple tumours, to manifest at a younger age and to be associated with neuroendocrine tumours. As a consequence, genetic diagnosis is recommended in patients that present with paragangliomas [199]. The most common clinical manifestation combination consists of paraganglioma of the middle ear (tumour of the glomus tympanicum in the mesotympanum) and the ipsilateral carotid bifurcation (tumour of the glomus caroticum). Paragangliomas usually occur in middle-aged patients and women are affected more frequently than men [200]. The classification of tympano-jugular follows the classification according to Fisch [201]. Paraganglioma of the middle ear (Fisch type A) originates in the glomus tympanicum and is confined to the middle ear. Paragangliomas of the jugular fossa (originating from the glomus jugulare) but also paragangliomas of the vagal nerve (originating from the glomus vagale) may destroy the temporal bone. Fisch type D paragangliomas extend intracranially.

Symptoms include hearing loss in 91–100 % of cases [202, 203], pulsatile tinnitus in the ear in about 52 % of cases, otalgia in about 28 %, and vertigo in about 25 % of cases [203]. Clinical examination classically reveals a reddish pulsating mass behind the second and third tympanic quadrant (► **Video. 1**). Differential diagnoses include an elevated bulb of the jugular vein, an abnormal course of the internal carotid artery, a schwannoma in the jugular foramen, or plasmocytoma, meningioma or neurofibroma [204]. Paragangliomas of the jugular fossa can lead to lesions of the lower cranial nerves caused by compression. When growing into the aerated mastoid cells, an infiltration of the infralabyrinthine space may occur even before bone destruction is visible in radiological imaging [205]. Subsequently, bony destruction of the cochlea and vestibular labyrinth may occur [205]. The incidence of malignant paraganglioma is estimated to be approximately 1:4 000 000 people [206, 207]. Distant metastases in the context of malignant paragangliomas are rare and occur in up to 4 % of the cases. They may be present in the lungs, liver or lymph nodes [208]. Paragangliomas of the middle ear typically receive their vascular supply from the inferior tympanic artery and the ascending pharyngeal artery. Large tumours receive additional blood supply from the vertebral artery [209]. Diagnostics include MRI and angiography. T1-weighted MRI typically shows a so-called salt-and-pepper pattern due to the different flow velocities within a richly vascularized tumour (► **Fig. 11**) [210]. Functional imaging using radiotracers has a high



sensitivity concerning the identification of paragangliomas [211]. It is indicated in patients under the age of 40 years, in cases of positive genetic testing, if there is a positive family history of paragangliomas or in cases of particularly large paragangliomas in order to exclude a multilocal occurrence or metastasis [212]. The therapy depends on the tumour size, the affected structures, the age at diagnosis, the hormone expression and other concomitant diseases. An indication for surgery usually is given in smaller tumours in which surgical resection can be carried out with function preservation. It is accompanied by prior embolization. In cases of inoperability, old age or severe concomitant diseases that increase the risk of surgery and postoperative morbidity, radiotherapy with good long-term results is available as an alternative [213–215]. In cases of multiple tumours or metastatic growth, radioreceptor therapy may also be indicated [216].

5.6 Metastases

Metastases occurring in the middle ear and mastoid may have their primary in the breast, kidney, lung, stomach, larynx, prostate, thyroid, cervix, liver, brain or skin [217, 218]. Since metastases in the middle ear usually occur late in the course of the disease, the symptoms are often overshadowed by the symptoms of the primary tumour or by other metastases. Temporal bone metastases resemble the histology of the primary tumour, but are often less differentiated [48]. Metastases may have osteolytic properties or stimulate bone proliferation. They usually grow destructively at the beginning but may also present with bone-repairing properties (e. g. mammary and prostate). Most commonly, temporal bone metastases occur in the petrous bone [217, 219]. Symptoms depend on the site of occurrence and size. Conductive hearing loss and pain may occur when the external auditory canal, middle ear, mastoid and auditory tube are affected. Meningeal carcinomatosis is a special form of carcinomatosis that spreads into the subarachnoid space and the internal auditory canal and may consequently affect the cranial nerves and the inner ear.

5.7 Benign blood and lymphatic neoplasms

Haemangiomas and lymphangiomas are embryonic tumours. Lymphangiomas as well as haemangiomas of the temporal bone, especially involving the middle ear, are extremely rare [220, 221]. Sym-

ptoms of middle ear involvement may include conductive hearing loss and paralysis of the facial nerve [221].

5.8 Teratoma

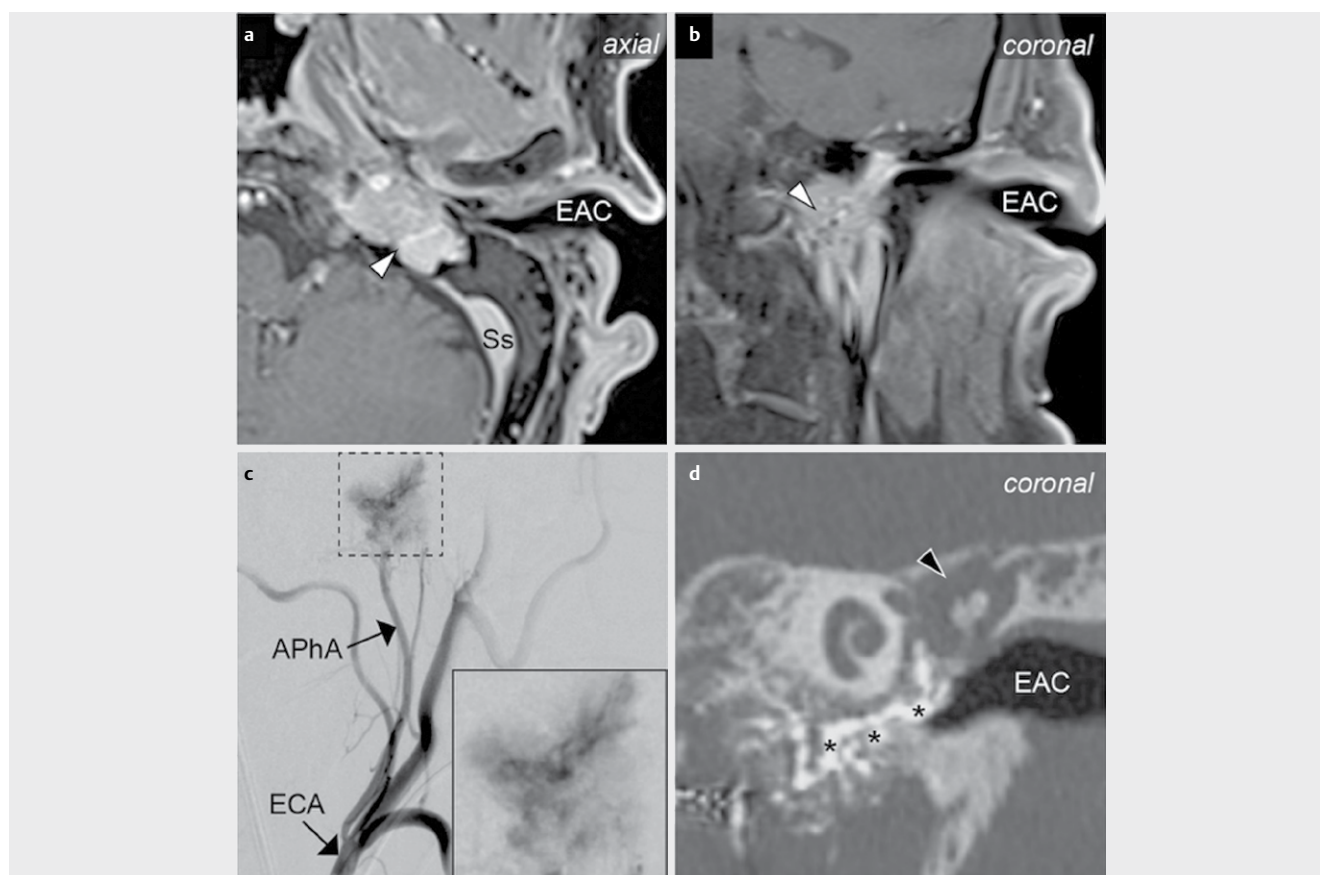
Teratoma is tissue of ectodermal, mesodermal and endodermal origin without function and clear structure with occurrence in locations not intended for it. Usually the ovaries, testes, retroperitoneum or mediastinum are affected. Occurrence at the base of the skull and rarely in the temporal bone has been described [48, 222, 223].

5.9 Tumours of the internal auditory canal, the inner ear, the cerebellopontine angle and the pyramidal tip

Tumours of the cerebellopontine angle account for around 10 % of all intracranial tumours. Nearly 90 % of all cerebellopontine angle tumours are vestibular schwannomas and meningiomas. Other cerebellopontine angle tumours include epidermoid cysts, arachnoid cysts, lipomas, schwannomas of other cranial nerves, metastases, vascular lesions (e. g. paragangliomas or haemangiomas) and cholesterol granulomas [224–226]. Cerebellopontine angle tumours cause symptoms by the compression of neurovascular structures. Typical manifestations include unilateral hearing loss, vertigo and tinnitus. Depending on the size and dignity, they may also cause facial pain, facial nerve paresis, vocal cord paralysis, dysphagia, diplopia or brainstem compression [224].

5.9.1 Vestibular schwannoma

Vestibular schwannoma is a benign tumour that originates from the nerve sheath of one of the two vestibular nerves or, in rare cases, from the cochlear nerve [227]. The nerve of origin of the vestibular schwannoma can be determined by vestibular five-receptor diagnostics, consisting of a stimulation of the three semicircular canals by using video head impulse test or caloric stimulation of the lateral semicircular canals as well as derivation of ocular and cervical vestibular evoked myogenic potentials [228]. Further, functional diagnostics include subjective (pure tone audiogram, speech audiogram) and objective (brainstem audiometry, otoacoustic emissions) audiometry. If there is an asymmetry in the pure-tone audiogram of ≥ 20 dB in two adjacent frequencies or unilateral tinnitus or an asymmetry ≥ 15 dB in two adjacent frequencies between 2 and 8 kHz, radiologic imaging by contrast MRI is recommended [229]. High-resolution radiological imaging allows an early detection even of small tumours (► Fig. 12). Vestibular schwannomas comprise 80 % of tumours in the cerebellopontine angle, making them the most common tumour entity in the posterior fossa in adults [230]. Treatment options include surgery, observation (especially of small or large stationary tumours) and radiotherapy. Treatment decisions are individualized and follow an interdisciplinary approach: In asymptomatic vestibular schwannomas, the treatment concept usually consists of regular radiological imaging following fixed intervals together with clinical controls of symptom progress ("wait and control", "wait and scan", "wait and test and scan", "watchful waiting") [231]. Growth rates of between 1 and 2 mm per year up to growth rates of 17 mm per year are reported in the literature [232, 233]. Treatment is indicated in case of growth (> 3 mm/year [234]), brainstem contact or brainstem compression, and the occurrence of disabling vertigo. Further indications for



► **Fig. 11** Paraganglioma of the left tympanic glomus. **a, b** Contrast-enhanced T1-weighted MRI image with fat suppression showing the paraganglioma (white arrowhead) obliterating the tympanic cavity. **b** Contrast-enhanced T1-weighted MRI image after contrast agent administration. The vessels present as the pathognomonic hypointense "salt-and-pepper" pattern of paraganglioma with flow interruptions due to high vascularity (white arrowhead). **c** Selective angiography shows the paraganglioma as a typical "tumour blush" (dashed box, enlarged view as inset bottom right) with vascular inflow from the ascending pharyngeal artery (APhA) from the stromal area of the external carotid artery (ECA). **d** Coronal CT of the temporal bone after successful embolization with liquid histoacryl (asterisks). **EAC:** external auditory canal; **Ss:** sigmoid sinus.

treatment are deterioration of hearing, balance or facial nerve function. The occurrence of intralabyrinthine schwannomas (intracochlear and/or intravestibular), on the other hand, is much more uncommon and is reported in only up to 10 % of vestibular schwannomas [52, 235–237]. While vestibular disorders are the most common initial symptomatology of vestibular schwannomas of the cerebellopontine angle, intralabyrinthine schwannomas are of particular importance in the differential diagnosis of sudden hearing loss [237]. In the case of transmodiolar or transmacular growths, they are particularly challenging due to the necessary trade-off between complete resection versus possible hearing rehabilitation using a cochlear implant [238].

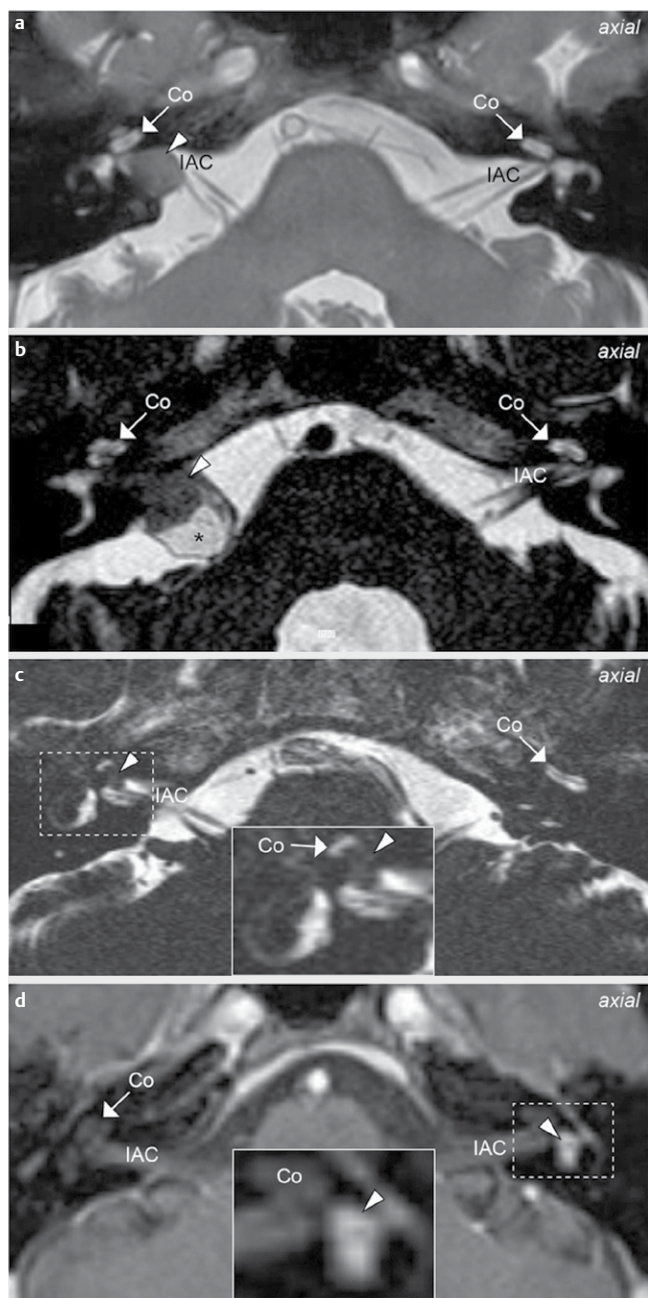
5.9.2 Meningioma

Meningiomas usually occur in a sporadic fashion, but may also be associated with hereditary syndromes, such as neurofibromatosis type II. They make up the second most common entity of cerebellopontine angle tumours, accounting for 3 % to 10 % [239]. Most meningiomas are benign and slow growing. Only around 1 % of meningiomas in the cerebellopontine angle become symptomatic. Meningiomas differ from vestibular schwannomas in pathogenesis

and radiological features [240, 241], but are hard to distinguish in terms of clinical presentation and audiological examination [224, 239].

5.9.3 Epidermoid cyst

Epidermoid cysts comprise approximately 5 % of cerebellopontine angle tumours. They develop from ectodermal inclusions scattered during embryogenesis. The cyst is lined with squamous epithelium and filled with lamellae of exfoliated corneal debris. Most epidermoid cysts are benign. Squamous cell carcinomas arising from epidermoid cysts are rarely reported [242, 243]. Epidermoid cysts have a higher rate of involvement of the facial nerve and trigeminal nerve compared with vestibular schwannomas. Other leading symptoms that contribute to the differential diagnosis may include hemifacial spasm, facial hypaesthesia or neuralgia [224, 239]. In addition, a distinction can be made on the basis of radiological imaging [241].



► **Fig. 12** Localization of vestibular schwannoma. **a** High T2-weighted MRI image of a 56-year-old patient with intrameatal vestibular schwannoma of the right side (white arrowhead). **b** Highly T2-weighted MRI image of a 68-year-old patient with intra- and extrameatal vestibular schwannoma of the right side (white arrowhead) with cystoid portion (star) with brainstem contact. **c** Strong T2-weighted MRI image of a 49-year-old patient with intracochlear schwannoma with transmodiolar growth of the right side (white arrowhead) (dashed box, enlarged view as inset at bottom centre). **d** T1-weighted MRI image after contrast agent administration of a 49-year-old patient with intravestibular schwannoma in the left vestibule with transition to the horizontal semicircular canal (white arrowhead) (dashed box, enlarged view as bottom centre inset). **Co**: cochlea; **IAC**: internal auditory canal.

6 Infectious Diseases

6.1 Tuberculosis

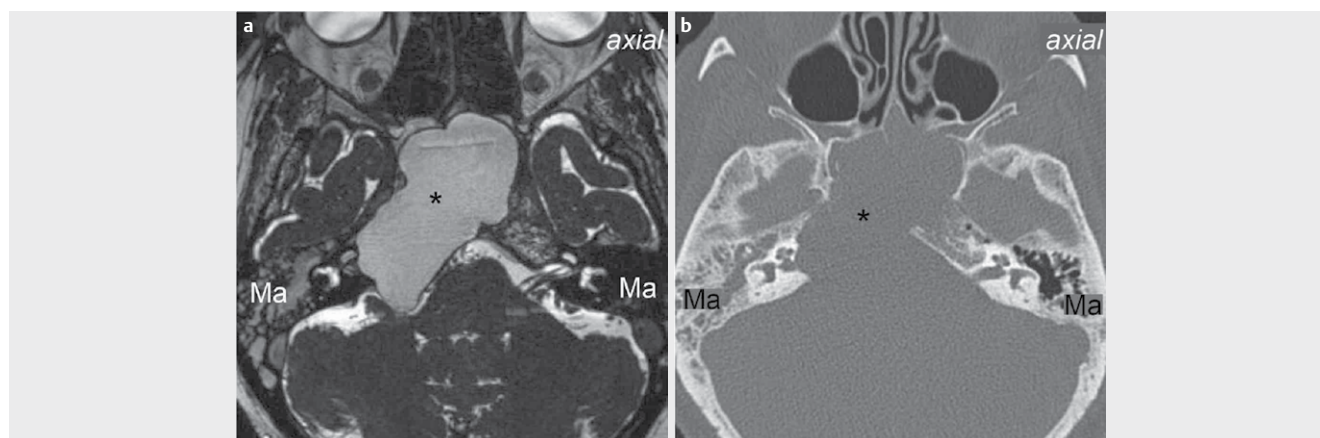
Ear manifestation of tuberculosis typically involves the occurrence of multiple tympanic membrane perforations, that may be bilateral. In up to 3 % worldwide, acute otitis media is caused by tuberculosis [244]. An association between the reactivation of tuberculosis and the HI virus is assumed [245]. The disease usually manifests with an oedematous swelling of the tympanic membrane and an infiltration by giant cells. Characteristic formations of tubercles from epithelioid cells, lymphoid cells and Langerhans cells are found. As a result, ulcerations and purulent exudates develop, followed by bone resorption. Treatment in the early stages consists of antibiotic or surgical treatment [246]. Frequently, under the clinical appearance of recurrent mastoiditis or persisting inflammation after surgery, surgical treatment is carried out and the microbiological diagnosis only follows postoperatively with retard [247]. Particularly in cases of prolonged otitis media and/or multiple tympanic membrane perforations, tuberculosis has to be considered. It is diagnosed by the microbiological detection of acid-fast bacilli from ear swabs or tissue biopsy.

6.2 Ootosyphilis

Syphilis (lues) is caused by *Treponema pallidum*, may occur congenital or acquired and may affect the audiovestibular system as part of neurosyphilis. The incidence of hearing loss, that mostly affects the inner ear, is between 18 % and 90 % in syphilis [248]. Immunosuppressed patients with HIV infection are particularly at risk for the occurrence of otosyphilis [249]. In addition to the typical meningo-neuro-labyrinthitis, osteitis of the temporal bone may also occur. This can also affect the ossicular chain [250]. Antibiotics and steroids are used for treatment.

6.3 Necrotizing (malignant) external otitis

Otitis externa necroticans is an aggressive osteomyelitis of the temporal bone and skull base. Its origin usually is the bony part of the external auditory canal. It is most commonly caused by *Pseudomonas aeruginosa*, but fungal colonisation is also increasingly important and may influence treatment decisions [251, 252]. The disease typically affects older adults, with diabetes mellitus as an important risk factor [253–255]. Histology reveals a transformation of bone into granulation tissue with fusion of the mastoid and temporal bone. The disease predominantly spreads along compact bone [256, 257]. If left untreated, the disease can lead to life-threatening complications such as mastoiditis, cranial nerve palsies, phlebitis or thrombosis of the sigmoid sinus or internal jugular vein, sepsis and osteomyelitis of the skull base. Therefore, in prolonged courses of otitis externa with a softened bone of the auditory canal and in patients with diabetes mellitus, radiological CT imaging and biopsy are indicated. In addition to the topical antiseptic and antibiotic treatment, treatment consists of systemic antibiotics, that should be administered in accordance with the ear smear for at least 4–6 weeks and, if necessary, extended with antifungal medication [258]. If there is no improvement with conservative therapy, surgical treatment may be necessary [255]. Hyperbaric oxygen therapy is another alternative therapy [259].



► **Fig. 13** Mucocoele involving the right petrous apex (asterisk) with cranial nerve involvement VII & VIII. **a** T2 weighted MRI of the mastoid. Hyperintense signalling of the mucocoele that extends into the sphenoid sinus with complete obstruction of the aerated mastoid cells. **b** CT of the temporal bone. Bone destruction of the petrous bone with loss of the bony border to the cerebellum is shown. **Ma:** Mastoid.

6.4 Cholera

The vibrio-bacteria family consists of more than 200 serogroups. The most common types are the cholera toxin-producing serogroups O1 and O139, which cause epidemic cholera followed by diarrhoea [260, 261]. A second group is characterized by self-limiting milder gastrointestinal infections, which may be associated with extraintestinal infections such as sepsis, wound infection, skin and soft tissue infections, peritonitis, meningitis, cholangitis and ear infections [262, 263]. The pathogen is primarily transmitted via unfiltered or insufficiently filtered drinking water and contaminated food. A few cases of otitis media or otitis externa caused by *Vibrio cholerae* non-O1/O139 have been reported in the literature [263]. Bathing in swimming pools, stagnant water or the Baltic Sea is considered a risk factor [263].

In summary, inflammation of the external auditory canal and middle ear warrants microbiological examination by smear and/or tissue biopsy to detect rare pathogens, especially in cases of prolonged disease courses.

7 Varia

7.1 Pneumatocoele of the temporal bone

Pneumatocoele of the temporal bone is a cystic cavity that increases in size, is filled with air and may communicate with the retroauricular skin or extradural cranial spaces beyond the borders of the temporal bone. Infections or trauma are discussed to be the causes [264]. Symptoms may include headache, dizziness as well as an increase of symptoms due to Valsalva manoeuvres [265]. The diagnosis is confirmed on temporal bone CT by the presence of septations within the pneumatocoele [266]. The therapy concept consists of careful evacuation and closure of the aerated mastoid cells [267].

7.2 Otogenic primary mucocoele of the mastoid

Mucocoeles are slow-growing cysts that result from distension of a hollow organ or cavity with mucus. Mucocoeles show signs of chronic sterile infection and have the ability to cause bony remodelling or reabsorption. Mucocoeles may be primary or secondary to chro-

nic inflammation, trauma, scarring from previous surgery or radiotherapy and, less common, to neoplasia [268–270]. Their occurrence in the mastoid (► **Fig. 13**) is very rare, with almost exclusively case reports in the literature [271–279]. In the case of bony erosions and destruction at the mucocoele margin, intra- and extracranial complications may occur [280]. Treatment of mucocoele includes marsupialisation, in which it is drained via natural drainage routes while the mucosa is spared. Surgical treatment is indicated for mucocoele in the mastoid, as it may extend with the risk of infection and intra- or extracranial complications [280]. Appropriate surgical treatment may include complete removal of the lesion by mastoidectomy to reduce the risk of recurrence [280].

7.3 Otogenic pneumocephalus

Otogenic pneumocephalus is characterized by air penetrating intracranially through a dural defect into the subarachnoid space, brain parenchyma or ventricular spaces. Symptoms include headache, otorrhoea, meningism and dizziness [281]. Possible causes described in the literature are trauma, complications of ear surgery, otitis media or cholesteatoma [282]. If caused by trauma, otogenic pneumocephalus may be accompanied by a cerebrospinal fluid fistula. If caused by otitis media or a cholesteatoma, the complication of an intracranial abscess may occur. Therapy consists of the combination of pressure relief and defect closure. In postoperative tension pneumocephalus, immediate needle aspiration should be performed. In persistent pneumocephalus, surgical revision closing the defect is indicated [282].

7.4 Spontaneous (meningo)encephalocele

A thinned tegmen tympani is considered a risk factor for the development of spontaneous encephalocele, which may be associated with CSF leaks. The possible mechanisms for thinning or erosion of the tegmen tympani include congenital defects, chronic middle ear disease, intracranial hypertension, trauma and obesity [283–285]. The symptomatology of spontaneous encephalocele may consist of conductive hearing loss, vertigo, oto-liquorrhoea or aural fullness [285–287]. The diagnosis is confirmed by the combination of CT and MRI and, if necessary, additionally by the detec-

tion of β 2-transferrin or β -trace protein [20]. Clinical examination may reveal a tympanic effusion. A treatment indication exists in particular in cases of CSF leak. Therapy consists of surgical closure of the defect with reinforcement of the dura and tegmen tympani. Depending on the size of the defect a transmastoid approach to the middle cranial fossa, a transtemporal approach (middle cranial fossa approach) or a combined approach may be performed [286, 287].

7.5 Ectopic brain tissue

Another rare differential diagnosis for soft tissue in the middle ear is the presence of ectopic brain tissue. Individual case reports mention manifestations in the nose, tongue, orbit [288–290] or the mastoid [291–294]. Histopathology shows evidence of brain tissue. Ectopic brain tissue may be distinguished from an encephalocele radiologically or clinically, and intraoperatively by an intact dura [294–296].

7.6 Idiopathic or spontaneous hematotympanum

The origin of idiopathic or spontaneous hematotympanum is not completely understood. It is considered to be a variant of acute otitis media [297]. Clinically, it presents with a blackish-blue tympanic membrane. The coloration of the haemolyzed blood results from recurrent bleeding in the middle ear, combined with a drainage disturbance via the Eustachian tube [297]. The bleeding is thought to originate from cholesterol granulomas, that may be a consequence of otitis media [48]. Surgical removal of the granulomas with tympanic drainage is described to be an effective therapy [298, 299].

7.7 Gorham-Stout syndrome

Gorham-Stout syndrome is a spontaneously occurring osteolysis. It is based on local proliferation of small blood and lymph vessels with subsequent progressive destruction and resorption of the bone. The symptoms depend on the manifestation site. The most common symptom is local pain. If the temporal bone is affected, deafness may occur [300]. The diagnosis is made on clinical, radiological and histological findings and by excluding the potential differential diagnoses [300, 301]. Treatment options include radiotherapy, bisphosphonates and interferon- α 2b [302]. Surgical intervention may be required due to CSF leaks or medullary compression [303].

7.8 Cholesterol granuloma

Cholesterol granuloma is an inflammatory reaction to blood degradation products and presents as a cyst with a thick fibrous lining filled with brownish-yellow fluid. It can occur in the middle ear, mastoid and petrous apex and is considered to be the most common benign lesion of the petrous apex [304]. Occurrence in the mastoid and middle ear is reported to be much less common [304]. Poor pneumatization or haemorrhage in the mastoid are considered to be the predisposing factors [305]. Cholesterol granulomas in the middle ear and lateral skull base are often asymptomatic, but may lead to cephalgia, hearing loss or, with increasing size, to cranial nerve deficits [306]. MRI shows high signal intensity in T1 and T2 sequences. CT offers information about the displacement of bony structures or

bony destruction [304]. Therapy consists of either regular follow-up or surgical resection in symptomatic cases [307–309].

7.9 Giant cell granuloma

Giant cell granuloma is a reactive process triggered by trauma or inflammation [310, 311]. It is a rare bony lesion of the head and neck that manifests predominantly in the maxilla and mandible. The description of a manifestation in the mastoid is rare and consists exclusively of case reports [312, 313]. Symptomatology depends on the structures involved and may include conductive hearing loss, tinnitus, vertigo, local swelling or weakness of the facial nerve [314]. Treatment options include curettage, surgical excision and radiotherapy [315, 316]. Complete surgical resection is mandatory due to high recurrence rates followed after incomplete resection [317].

8 CONCLUSION

Rare diseases of the middle ear and lateral skull base may resemble common otolaryngologic diseases, which harbours the risk of delayed diagnosis or misdiagnosis. In a case of otitis media that does not respond to antibiotic treatment, aural smear, especially for mycobacteria, needs to be performed to exclude rare infections [318]. In case of pulmonary involvement and simultaneous otorrhoea or multiple perforations of the tympanic membrane, an ear manifestation of tuberculosis should be considered. The concomitant diseases of the patient can be indicative. Especially in immunosuppressed patients with HIV infection, rare bacterial infections such as otosyphilis may occur. Furthermore, the risk of necrotizing (malignant) external otitis in elderly patients with diabetes mellitus has to be considered. In cases of protracted, recurrent or bilateral otitis, autoimmune disorders such as granulomatosis with polyangiitis may be the underlying condition. In cases of middle ear and mastoid diseases without a response to antibiotics, a biopsy is obligatory to exclude malignancies or diseases of the haematopoietic system as well as autoimmune disorders. It is supplemented by appropriate serologic investigations. Systemic causes such as histiocytosis or vasculitis should be considered, especially in cases of bilateral destructive ear disease detected in CT-imaging associated with increased erythrocyte sedimentation rate and without other indications of infection, or in cases of long-term granulation tissue after tympanomastoid surgery with persistent otorrhoea and skin lesions. Asymmetric hearing or balance disorders as well as deficits of the caudal cranial nerves may indicate neurological disease patterns or be the initial manifestation of neoplasms and lesions of the temporal bone. A unilateral tinnitus occurs as the first symptom in 1 to 5 % of cases in vestibular schwannoma and a pulse-synchronous tinnitus may indicate a paraganglioma or a vascular anomaly. Therefore, these symptoms should be investigated by radiologic imaging even in the absence of conspicuous tympanic membrane findings.

In the case of petrous bone lesions, the differential diagnosis includes metastasis and rare bone or cartilage tumours. For this reason, the imaging of choice usually consists of a high-resolution CT of the temporal bone. For further diagnosis, an MRI may be added. One exception is vestibular schwannoma, where the initial imaging should consist of contrast MRI. A biopsy can be performed via various access routes and confirms the diagnosis [319]. Close interdisciplinary cooperation and specific questions with information on the clinical symptoms need to be communicated with the examining histopathologists, human geneticists or molecular pathologists.

A detailed diagnosis is necessary prior to any surgical intervention. In particular if there are indications of malformations, radiological imaging is mandatory to identify anatomical variants of the temporal bone and to avoid surgical complications such as haemorrhages, CSF fistulas or injuries to the facial nerve.

For quality control in patient care and in surgical interventions, knowledge of rare diseases is an essential component and must be available to assess complicated protracted disease courses. In addition to making physicians aware of rare differential diagnoses, recording of patient data in designated registers may be helpful. Making use of cumulative data storage, the conduction of studies that go beyond case reports is enabled and further information about the individual diseases may be gained. As a consequence, an improvement of treatment options can be achieved [320–322]. Only a careful collecting and documentation of all necessary diagnostic criteria such as anamnesis, clinical findings, imaging, laboratory and results of microbiological, histological and, with increasing importance, molecular pathological and genetic examinations enable a reliable diagnosis and an adequate treatment.

9 Acknowledgements

Special thanks are due to Professor Dr. Robert Mlynski for his numerous comments and suggestions on the manuscript and for providing the image material for ► **Figs. 1,3,4a–c, ► 5,9b** and ► **13**. Special thanks are also due to Dr. David Bächinger for his critical review of the manuscript and for his constructive support in preparing the figures. Professor Dr. Sönke Langner, Institute for Diagnostic and Interventional Radiology, Paediatric and Neuroradiology, is thanked for the image material of ► **Figs. 6,10** and ► **11** and PD Dr. Marcus Frank, Institute for Electron Microscopy University Medical Center Rostock, for the electron microscopic images of ► **Fig. 2**.

Conflict of interest

The authors declare that they have no conflict of interest.

Literature

- [1] Jahrsdoerfer RA, Yeakley JW, Aguilar EA, Cole RR, Gray LC. Grading system for the selection of patients with congenital aural atresia. *Am J Otol* 1992; 13: 6–12
- [2] Jahrsdoerfer RA. Congenital atresia of the ear. *Laryngoscope* 1978; 88: 9: 1–48
- [3] Weerda H. Classification of congenital deformities of the auricle. *Facial Plast Surg* 1988; 5: 385–388
- [4] Patterson ME, Linthicum FHJ. Congenital hearing impairment. *Otolaryngol Clin North Am* 1970; 3: 201–219
- [5] Gerhardt HJ, Otto HD. [Stapedial malformation]. *Acta Otolaryngol* 1970; 70: 35–44
- [6] Teunissen EB, Cremers WR. Classification of congenital middle ear anomalies. Report on 144 ears. *Ann Otol Rhinol Laryngol* 1993; 102: 606–612
- [7] Fu Y, Dai P, Zhang T. The location of the mastoid portion of the facial nerve in patients with congenital aural atresia. *Eur Arch Otorhinolaryngol* 2014; 271: 1451–1455
- [8] Mündnich K, Terrahe K. Missbildungen des Ohres. In: Berendes J, Link R, Zöllner F, Editors. *Ohr I, Band 5: Stuttgart*; 1979: p 1–49
- [9] Chang SO, Min YG, Kim CS, Koh TY. Surgical management of congenital aural atresia. *Laryngoscope* 1994; 104: 606–611
- [10] Gorlin R, Pindborg J, Cohen M. Oculoauriculovertebral dysplasia. In: *Syndromes of the Head and Neck*. 2nd ed. New York: 1976: p 546–552
- [11] Phelps PD, Poswillo D, Lloyd GA. The ear deformities in mandibulofacial dysostosis (Treacher Collins syndrome). *Clin Otolaryngol Allied Sci* 1981; 6: 15–28
- [12] Jahrsdoerfer RA, Aguilar EA, Yeakley JW, Cole RR. Treacher Collins syndrome: An otologic challenge. *Ann Otol Rhinol Laryngol* 1989; 98: 807–812
- [13] Boggering B. [Oto-vertebral syndrome]. *Fortschr Med* 1975; 93: 1452–1455
- [14] Frenzel H. Hearing rehabilitation in congenital middle ear malformation. *Adv Otorhinolaryngol* 2018; 81: 32–42
- [15] Mlynski R, Schwager K. Funktionelle Rekonstruktion bei Ohrfehlbildungen. In: Bumm K, Editor. *Korrektur und Rekonstruktion der Ohrmuschel*. 1st ed. Saarbrücken 2016: p 275–291
- [16] Beutner D, Delb W, Frenzel H, Hoppe U, Hüttenbrink KB, Mlynski R et al. Guideline “Implantable hearing aids”-short version : German S2k guideline of the Working Group of German-Speaking Audiologists, Neurotologists and Otolologists (ADANO), of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHN) in colla. *HNO*. 2018; 66: 71–76
- [17] Thompson H, Ohazama A, Sharpe PT, Tucker AS. The origin of the stapes and relationship to the otic capsule and oval window. *Dev Dyn* 2012; 241: 1396–1404
- [18] Herther C, Schindler RA. Mondini's dysplasia with recurrent meningitis. *Laryngoscope*. 1985; 95: 655–658
- [19] Tandon S, Singh S, Sharma S, Lahiri AK. Use of Intrathecal Fluorescein in Recurrent Meningitis after Cochlear Implantation. Vol. 28: *Iranian Journal of Otorhinolaryngology*. Iran 2016; p 221–226
- [20] Weiss NM, Andus I, Schneider A, Langner S, Schroder S, Schraven SP et al. Intrathecal Application of a Fluorescent Dye for the Identification of Cerebrospinal Fluid Leaks in Cochlear Malformation. *J Vis Exp*. 2020;
- [21] Frenzel H, Sprinzl G, Widmann G, Petersen D, Wollenberg B, Mohr C. Grading system for the selection of patients with congenital aural atresia for active middle ear implants. *Neuroradiology*. 2013; 55: 895–911

- [22] Schuknecht H. Gavin Livingstone Memorial Lecture. Anatomical variants and anomalies of surgical significance. *J Laryngol Otol* 1971; 85: 1238–1241
- [23] Hogg ID, Stephens CB, Arnold GE. Theoretical anomalies of the stapedial artery. *Ann Otol Rhinol Laryngol* 1972; 81: 860–870
- [24] Lyu A-R, Park SJ, Kim D, Lee HY, Park Y-H. Radiologic features of vascular pulsatile tinnitus - suggestion of optimal diagnostic image workup modalities. *Acta Otolaryngol* 2018; 138: 128–134
- [25] Hofmann E, Behr R, Neumann-Haefelin T, Schwager K. Pulsatile tinnitus: imaging and differential diagnosis. *Dtsch Arztebl Int* 2013; 110: 451–458
- [26] Friedmann DR, Eubig J, McGill M, Babb JS, Pramanik BK, Lalwani AK. Development of the jugular bulb: a radiologic study. *Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc [and] Eur Acad. Otol Neurotol* 2011; 32: 1389–1395
- [27] Merchant SN, Rosowski JJ. Conductive hearing loss caused by third-window lesions of the inner ear. *Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc [and] Eur Acad. Otol Neurotol* 2008; 29: 282–289
- [28] Sayit AT, Gunbey HP, Fethallah B, Gunbey E, Karabulut E. Radiological and audiometric evaluation of high jugular bulb and dehiscent high jugular bulb. *J Laryngol Otol* 2016; 130: 1059–1063
- [29] Koo YH, Lee JY, Lee JD, Hong HS. Dehiscent high-riding jugular bulb presenting as conductive hearing loss: A case report. *Medicine (Baltimore)* 2018; 97: e11067
- [30] Friedmann DR, Le BT, Pramanik BK, Lalwani AK. Clinical spectrum of patients with erosion of the inner ear by jugular bulb abnormalities. *Laryngoscope*. 2010; 120: 365–372
- [31] Maroldi R, Farina D, Palvarini L, Marconi A, Gadola E, Menni K et al. Computed tomography and magnetic resonance imaging of pathologic conditions of the middle ear. *Eur J Radiol* 2001; 40: 78–93
- [32] Kaftan S, Sarach V, Kahle G. [Vascular structure in the middle ear. Aberrant course of the internal carotid artery in the left tympanic membrane]. *HNO* 2002; 50: 864–865
- [33] Heimlich F, Dörfler A, Wallner F. [An aberrant course of the internal carotid artery through the middle ear]. *HNO*. 1999; 47: 986–989
- [34] Sun W, Germans MR, Sebök M, Fierstra J, Kulcsar Z, Keller A et al. Outcome comparison between surgically treated brain arteriovenous malformation hemorrhage and spontaneous intracerebral hemorrhage. *World Neurosurg* 2020; 139: e807–e811
- [35] Mohr JP, Overbey JR, Hartmann A, Kummer von R, Al-Shahi Salman R, Kim H et al. Medical management with interventional therapy versus medical management alone for unruptured brain arteriovenous malformations (ARUBA): final follow-up of a multicentre, non-blinded, randomised controlled trial. *Lancet Neurol* 2020; 19: 573–581
- [36] Zipfel GJ, Shah MN, Refai D, Dacey RGJ, Derdeyn CP. Cranial dural arteriovenous fistulas: modification of angiographic classification scales based on new natural history data. *Neurosurg Focus* 2009; 26: E14
- [37] Paget J. On a form of chronic inflammation of bones (osteitis deformans). *Med Chir Trans* 1877; 60: 37–64
- [38] Paget J.. Additional cases of osteitis deformans. *Med Chir Trans* 1882; 65: 225–236
- [39] Mills BG, Singer FR, Weiner LP, Holst PA. Immunohistological demonstration of respiratory syncytial virus antigens in Paget disease of bone. *Proc Natl Acad Sci USA* 1981; 78: 1209–1213
- [40] Siris ES. Seeking the elusive etiology of Paget disease: A progress report. Vol. 11, *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*. United States. 1996; p 1599–1601
- [41] Eekhoff EWM, Karperien M, Houtsma D, Zwinderman AH, Dragoiescu C, Kneppers ALJ et al. Familial Paget's disease in The Netherlands: Occurrence, identification of new mutations in the sequestosome 1 gene, and their clinical associations. *Arthritis Rheum* 2004; 50: 1650–1654
- [42] Koller F. Über die Heredität der ostitis deformans. *Helv Med Acta* 1946; 13: 389–400
- [43] Schmorl G. Über ostitis deformans Paget. *Virchows Arch* 1932; 283: 694–751
- [44] Bozorg Grayeli A. Progressive hearing loss with stapes fixation [Internet]. 2006; Available from https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=3235
- [45] Lindsay JR, Suga F. Paget's disease and sensori-neural deafness: temporal bone histopathology of Paget's disease. *Laryngoscope*. 1976; 86: 1029–1042
- [46] Nager GT. Paget's disease of the temporal bone. *Ann Otol Rhinol Laryngol* 1975; 84: 4: 1–32
- [47] Waltner JG. Stapedectomy in Paget's disease. Histological and clinical studies. *Arch Otolaryngol* 1965; 82: 355–358
- [48] McKenna MJ, Merchant SN. 15. Disorders of Bone. In: Merchant SN, Nadol JBJ, Editors *Schuknechts's Pathology of the ear*. 3rd ed. 2010: p 715–774
- [49] Khetarpal U, Schuknecht HF. In search of pathologic correlates for hearing loss and vertigo in Paget's disease. A clinical and histopathologic study of 26 temporal bones. *Ann Otol Rhinol Laryngol Suppl* 1990; 145: 1–16
- [50] Monsell EM. The mechanism of hearing loss in Paget's disease of bone. *Laryngoscope*. 2004; 114: 598–606
- [51] Monsell EM, Bone HG, Cody DD, Jacobson GP, Newman CW, Patel SC et al. Hearing loss in Paget's disease of bone: Evidence of auditory nerve integrity. *Am J Otol* 1995; 16: 27–33
- [52] Długaczek J. Seltene Erkrankungen des vestibulären Labyrinths: von Zebras, Chamäleons und Wölfen im Schafspelz (accepted for publication). *Laryngorhinootologie*.. 2021;
- [53] Applebaum EL, Clemis JD. Temporal bone histopathology of Paget's disease with sensorineural hearing loss and narrowing of the internal auditory canal. *Laryngoscope*. 1977; 87: 1753–1759
- [54] Kösling S, Plontke SK, Bartel S. Imaging of otosclerosis. *Rofo*.. 2020;
- [55] Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet* 1979; 16: 101–116
- [56] Sillence DO, Rimoin DL, Danks DM. Clinical variability in osteogenesis imperfecta-variable expressivity or genetic heterogeneity. *Birth Defects Orig Artic Ser* 1979; 15: 113–129
- [57] Armstrong BW. Stapes surgery in patients with osteogenesis imperfecta. *Ann Otol Rhinol Laryngol* 1984; 93: 634–635
- [58] Garretsen TJ, Cremers CW. Stapes surgery in osteogenesis imperfecta: analysis of postoperative hearing loss. *Ann Otol Rhinol Laryngol* 1991; 100: 120–130
- [59] Patterson CN, Stone HB 3rd. Stapedectomy in Van der Hoeve's syndrome. *Laryngoscope*. 1970; 80: 544–558
- [60] Opheim O. Loss of hearing following the syndrome of Van der Hoeve-de Kleyn. *Acta Otolaryngol* 1968; 65: 337–344
- [61] Sinder BP, Novak S, Wee NKY, Basile M, Maye P, Matthews BG et al. Engraftment of skeletal progenitor cells by bone-directed transplantation improves osteogenesis imperfecta murine bone phenotype. *Stem Cells* 2020; 38: 530–541
- [62] Lee LR, Peacock L, Ginn SL, Cantrill LC, Cheng TL, Little DG et al. Bone Marrow Transplantation for Treatment of the Col1a2(+/G610C) Osteogenesis Imperfecta Mouse Model. *Calcif Tissue Int* 2019; 104: 426–436

- [63] Gotherstrom C, Westgren M, Shaw SWS, Astrom E, Biswas A, Byers PH et al. Pre- and postnatal transplantation of fetal mesenchymal stem cells in osteogenesis imperfecta: a two-center experience. *Stem Cells Transl Med* 2014; 3: 255–264
- [64] Perosky JE, Khoury BM, Jenks TN, Ward FS, Cortright K, Meyer B et al. Single dose of bisphosphonate preserves gains in bone mass following cessation of sclerostin antibody in *Btl/+* osteogenesis imperfecta model. *Bone*. 2016; 93: 79–85
- [65] Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. *N Engl J Med* 2016; 375: 1532–1543
- [66] Bacon S, Crowley R. Developments in rare bone diseases and mineral disorders. *Ther Adv Chronic Dis* 2018; 9: 51–60
- [67] Weil A. Pubertas praecox und Knochenbrüchigkeit. In: *Pubertas praecox und Knochenbrüchigkeit*. 1st ed. Klin: Wschr.; 1922: p 2114–2115
- [68] Albright F, Butler A, Hampton A, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. *N Engl J Med* 1937; 216: 727–746
- [69] Marie PJ. Cellular and molecular basis of fibrous dysplasia. *Histol Histopathol* 2001; 16: 981–988
- [70] Weinstein LSG(s)alpha mutations in fibrous dysplasia and McCune-Albright syndrome. *J Bone Miner Res* 2006; 21P120–4
- [71] Cheng MH, Chen YR. Malignant fibrous histiocytoma degeneration in a patient with facial fibrous dysplasia. *Ann Plast Surg* 1997; 39: 638–642
- [72] Van Rossem C, Pauwels P, Somville J, Camerlinck M, Bogaerts P, Van Schil PE. Sarcomatous degeneration in fibrous dysplasia of the rib cage. *Ann Thorac Surg* 2013; 96: e89–e90
- [73] Yabut SMJ, Kenan S, Sissons HA, Lewis MM. Malignant transformation of fibrous dysplasia. A case report and review of the literature. *Clin Orthop Relat Res* 1988; 228: 281–289
- [74] Hartley I, Zhadina M, Collins MT, Boyce AM. Fibrous Dysplasia of Bone and McCune-Albright Syndrome: A Bench to Bedside Review. *Calcif Tissue Int* 2019; 104: 517–529
- [75] Pritchard JE. Fibrous dysplasia of the bones. *Am J Med Sci* 1951; 222: 313–332
- [76] Cleiren E, Benichou O, Van Hul E, Gram J, Bollerslev J, Singer FR et al. Albers-Schonberg disease (autosomal dominant osteopetrosis, type II) results from mutations in the *CLCN7* chloride channel gene. *Hum Mol Genet* 2001; 10: 2861–2867
- [77] de Vernejoul MC, Benichou O. Human osteopetrosis and other sclerosing disorders: recent genetic developments. *Calcif Tissue Int* 2001; 69: 1–6
- [78] Stark Z, Savarirayan R.. Osteopetrosis. *Orphanet J Rare Dis* 2009; 4: 5
- [79] Myers EN, Stool S. The temporal bone in osteopetrosis. *Arch Otolaryngol* 1969; 89: 460–469
- [80] Wong ML, Balkany TJ, Reeves J, Jafek BW. Head and neck manifestations of malignant osteopetrosis. *Otolaryngology*.. 1978; 86: ORL-585-594
- [81] Dozier TS, Duncan IM, Klein AJ, Lambert PR, Key LJ. Otologic manifestations of malignant osteopetrosis. *Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc [and] Eur Acad. Otol Neurotol* 2005; 26: 762–766
- [82] Coccia PF, Krivit W, Cervenka J, Clawson C, Kersey JH, Kim TH et al. Successful bone-marrow transplantation for infantile malignant osteopetrosis. *N Engl J Med* 1980; 302: 701–708
- [83] Hamersma H. Osteopetrosis (Marble bone disease) of the temporal bone. *Laryngoscope*. 1970; 80: 1518–1539
- [84] Jones MD, Mulcahy ND. Osteopathia striata, osteopetrosis, and impaired hearing. A case report. *Arch Otolaryngol* 1968; 87: 116–118
- [85] Milroy CM, Michaels L. Temporal bone pathology of adult-type osteopetrosis. *Arch Otolaryngol Head Neck Surg* 1990; 116: 79–84
- [86] Yarrington CTJ, Sprinkle PM. Facial palsy in osteopetrosis. Relief by endotemporal decompression. *JAMA*. 1967; 202: 549
- [87] Hamersma H, Hofmeyr L. Too much bone: the middle ear in sclerosing bone dysplasias. *Adv Otorhinolaryngol* 2007; 65: 61–67
- [88] Schmitz L, Favara BE. Nosology and pathology of Langerhans cell histiocytosis. *Hematol Oncol Clin North Am* 1998; 12: 221–246
- [89] Valladeau J, Ravel O, Dezutter-Dambuyant C, Moore K, Kleijmeer M, Liu Y et al. Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. *Immunity*. 2000; 12: 71–81
- [90] Greenberger JS, Crocker AC, Vawter G, Jaffe N, Cassady JR. Results of treatment of 127 patients with systemic histiocytosis. *Medicine (Baltimore)* 1981; 60: 311–338
- [91] Smith DG, Nesbit MEJ, D'Angio GJ, Levitt SH. Histiocytosis X. role of radiation therapy in management with special reference to dose levels employed. *Radiology*. 1973; 106: 419–422
- [92] Sims DG. Histiocytosis X. follow-up of 43 cases. *Arch Dis Child* 1977; 52: 433–440
- [93] Arcenci RJ, Brenner MK, Pritchard J. Controversies and new approaches to treatment of Langerhans cell histiocytosis. *Hematol Oncol Clin North Am* 1998; 12: 339–357
- [94] McCaffrey TV, McDonald TJ. Histiocytosis X of the ear and temporal bone: review of 22 cases. *Laryngoscope*. 1979; 89: 1735–1742
- [95] Tos M. A survey of Hand-Schuller-Christian's disease in otolaryngology. *Acta Otolaryngol* 1966; 62: 217–228
- [96] Schuknecht HF, Perlman HB. Hand-Schuller-Christian disease and eosinophilic granuloma of the skull. *Ann Otol Rhinol Laryngol* 1948; 57: 643–676
- [97] Dingley AR. Eosinophil granuloma of the temporal bone. *J Laryngol Otol* 1952; 66: 285–287
- [98] Falkenburg LW, Littleton TR, Hunt RR, Horwitz M. Bilateral eosinophilic granulomas of the mastoid processes. Report of a case in a two-year-old boy, with review. *AMA Arch Otolaryngol* 1959; 70: 292–296
- [99] Martin TH. Solitary eosinophilic granuloma of the temporal bone. A case report. *Laryngoscope*. 1969; 79: 2165–2171
- [100] Sweet RM, Kornblut AD, Hyams VJ. Eosinophilic granuloma in the temporal bone. *Laryngoscope*. 1979; 89: 1545–1552
- [101] Cunningham MJ, Curtin HD, Jaffe R, Stool SE. Otologic manifestations of Langerhans' cell histiocytosis. *Arch Otolaryngol Head Neck Surg* 1989; 115: 807–813
- [102] Chisolm JJ. Otorhinologic aspects of Hand-Schuller-Christian's disease. *Laryngoscope*. 1954; 64: 486–496
- [103] Levy R, Sarfaty SM, Schindel J. Eosinophilic granuloma of the temporal bone. Two cases with bilateral involvement. *Arch Otolaryngol* 1980; 106: 167–171
- [104] Hudson WR, Kenan PD. Otologic manifestations of histiocytosis X. *Laryngoscope*. 1969; 79: 678–693
- [105] Schuknecht HF. Histiocytosis X. *Otolaryngol Head Neck Surg* (1979) 1980; 88: 544–7
- [106] Levine S, Stone J. Pathogenesis of Wegener's granulomatosis and related vasculitides. 2007;p www.uptodate.com version 15.3
- [107] Calonijs IH, Christensen CK. Hearing impairment and facial palsy as initial signs of Wegener's granulomatosis. *J Laryngol Otol* 1980; 94: 649–657

- [108] Karmody CS. Wegener's granulomatosis: presentation as an otologic problem. *Otolaryngology*. 1978; 86: ORL-573-584
- [109] Kornblut AD, Wolff SM, deFries HO, Fauci AS. Wegener's granulomatosis. *Otolaryngol Clin North Am* 1982; 15: 673-683
- [110] Blatt I, Lawrence M. otologic manifestations of fatal granulomatosis of respiratory tract: Lethal midline granuloma - Wegener's granulomatosis. *Arch Otolaryngol* 1961; 73: 639-643
- [111] Ohtani I, Baba Y, Suzuki C, Sakuma H, Kano M. Temporal bone pathology in Wegener's granulomatosis. *Fukushima J Med Sci* 2000; 46: 31-39
- [112] McDonald TJ, DeRemee RA. Wegener's granulomatosis. *Laryngoscope*. 1983; 93: 220-231
- [113] Amirraghi N, Robertson S, Iyer A. Primary otological manifestations of granulomatosis with polyangiitis: A case series. *J Laryngol Otol* 2015; 129: 179-182
- [114] Bacciu A, Bacciu S, Mercante G, Ingegnoli F, Grasselli C, Vaglio A et al. Ear, nose and throat manifestations of Churg-Strauss syndrome. *Acta Otolaryngol* 2006; 126: 503-509
- [115] Rahne T, Plontke S, Keyßer G. Vasculitis and the ear: A literature review. *Curr Opin Rheumatol* 2020; 32: 47-52
- [116] Ishiyama A, Canalis RF. Otological manifestations of Churg-Strauss syndrome. *Laryngoscope*. 2001; 111: 1619-1624
- [117] Jaksch-Wartenhorst. Polychondropathia. *Wien Arch* 1923; 6: 93-100
- [118] Herman JH, Dennis MV. Immunopathologic studies in relapsing polychondritis. *J Clin Invest* 1973; 52: 549-558
- [119] Michet CJ. Etiology and pathogenesis of relapsing polychondritis [Internet]. 2020; Available from <https://www.uptodate.com/contents/etiology-and-pathogenesis-of-relapsing-polychondritis>
- [120] Bachor E, Blevins NH, Karmody C, Kuhn T. Otologic manifestations of relapsing polychondritis. Review of literature and report of nine cases. *Auris Nasus Larynx* 2006; 33: 135-141
- [121] McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. *Medicine (Baltimore)* 1976; 55: 193-215
- [122] Hoffman RA, Horten B. Rheumatoid nodule of the temporal bone. *J Laryngol Otol* 1989; 103: 768-770
- [123] Gussen R. Atypical ossicle joint lesions in rheumatoid arthritis with sicca syndrome (Sjogren syndrome). *Arch Otolaryngol* 1977; 103: 284-286
- [124] Castillo Bustamante M, Gandhi D, Kozin E, Remenschneider A. Otopathological changes of the middle and inner ear in rheumatoid arthritis. In Boston. 2019;
- [125] Swerdlow S, Campo E, Harris N. World Health Organization Classification of Tumors of Haematopoietic and Lymphoid Tissues. IARC Press; 2008
- [126] Freedman A, Friedberg J, Aster J. Classification of the hematopoietic neoplasms [Internet]. 2020; Available from: www.uptodate.com
- [127] Zechner G, Altmann F. The temporal bone in leukemia. *Histological studies*. *Ann Otol Rhinol Laryngol* 1969; 78: 375-387
- [128] Schuknecht HF, Igarashi M, Chasin WD. Inner Ear Hemorrhage in Leukemia. A Case Report. *Laryngoscope*. 1965; 75: 662-668
- [129] Hallpike CS, Harrison MS. Clinical and pathological observations of a case of leukaemia with deafness and vertigo. *J Laryngol Otol* 1950; 64: 427-430
- [130] Druss JG. Aural manifestations of leukemia. *Arch Otolaryngol* 1945; 42: 267-274
- [131] Thompson DH, Ross DG, Reid JW. Granulocytic sarcoma (chloroma) initially seen as acute mastoiditis. *Arch Otolaryngol* 1982; 108: 388-391
- [132] Li W, Schachern PA, Morizono T, Paparella MM. The temporal bone in multiple myeloma. *Laryngoscope*. 1994; 104: 675-680
- [133] LEWIS JS. Cancer of the ear: a report of 150 cases. *Laryngoscope*. 1960; 70: 551-579
- [134] Broders AC. Squamous-cell epithelioma of the skin: a study of 256 cases. *Ann Surg* 1921; 73: 141-160
- [135] Maxwell AK, Takeda H, Gubbels SP. Primary Middle Ear Mucosal Melanoma: Case Report and Comprehensive Literature Review of 21 Cases of Primary Middle Ear and Eustachian Tube Melanoma. *Ann Otol Rhinol Laryngol* 2018; 127: 856-863
- [136] Bradeley WH, Maxwell JH. Neoplasms of the middle ear and mastoid: report of fifty-four cases. *Laryngoscope*. 1954; 64: 533-556
- [137] Applebaum EL. Radiation-induced carcinoma of the temporal bone. *Otolaryngol Head Neck Surg* (1979) 1979; 87: 604-9
- [138] Lustig LR, Jackler RK, Lanser MJ. Radiation-induced tumors of the temporal bone. *Am J Otol* 1997; 18: 230-235
- [139] Ruben RJ, Thaler SU, Holzer N. Radiation induced carcinoma of the temporal bone. *Laryngoscope*. 1977; 87: 1613-1621
- [140] Beal DD, Lindsay JR, Ward PH. Radiation-Induced Carcinoma of the Mastoid. *Arch Otolaryngol* 1965; 81: 9-16
- [141] Dehner LP, Chen KT. Primary tumors of the external and middle ear. Benign and malignant glandular neoplasms. *Arch Otolaryngol* 1980; 106: 13-19
- [142] Murphy GF, Pilch BZ, Dickersin GR, Goodman ML, Nadol JB. Carcinoid tumor of the middle ear. *Am J Clin Pathol* 1980; 73: 816-823
- [143] Thompson LDR, Nelson BL, Barnes EL. Ceruminous adenomas: a clinicopathologic study of 41 cases with a review of the literature. *Am J Surg Pathol* 2004; 28: 308-318
- [144] Hyams VJ, Michaels L. Benign adenomatous neoplasm (adenoma) of the middle ear. *Clin Otolaryngol Allied Sci* 1976; 1: 17-26
- [145] Zahtz GD, Zielinski B, Abramson AL. Benign adenoma of the middle ear cavity causing facial paralysis. *Otolaryngol Head Neck Surg* 1981; 89: 624-627
- [146] Sudhoff H, Gehl H-B, Brasch F, Riemann R, Todt I. [A rare pathology of the petrous part of the temporal bone: adenoma of the middle ear]. *HNO* 2020; 68: 55-58
- [147] Smith HW, Duarte I. Mixed tumors of the external auditory canal. *Arch Otolaryngol* 1962; 75: 108-113
- [148] Baker BB, DeBlanc GB. Pleomorphic adenoma of the external auditory canal. *Ear Nose Throat J* 1977; 56: 81-83
- [149] Collins RJ, Yu HC. Pleomorphic adenoma of the external auditory canal. An immunohistochemical and ultrastructural study. *Cancer* 1989; 64: 870-875
- [150] Haraguchi H, Hentona H, Tanaka H, Komatuzaki A. Pleomorphic adenoma of the external auditory canal: a case report and review of the literature. *J Laryngol Otol* 1996; 110: 52-56
- [151] Tsukahara K, Suzuki M, Tokashiki R, Motohashi R, Iwaya K. Pleomorphic adenoma of the external auditory canal complicated by hearing loss secondary to chronic otitis media. *Auris Nasus Larynx* 2006; 33: 183-186
- [152] Markou K, Karasmanis I, Vlachtsis K, Petridis D, Nikolaou A, Vital V. Primary pleomorphic adenoma of the external ear canal. Report of a case and literature review. *Am J Otolaryngol* 2008; 29: 142-146
- [153] Mosby C. Pathology.. 4th ed. Anderson W editor 1961: 113-117. p
- [154] Dong F, Gidley PW, Ho T, Luna MA, Ginsberg LE, Sturgis EM. Adenoid cystic carcinoma of the external auditory canal. *Laryngoscope*. 2008; 118: 1591-1596
- [155] Furstenberg A. Primary adenocarcinoma of the middle ear and mastoid. *Ann Otol Rhinol Laryngol* 1924; 33: 677-689
- [156] Michel RG, Woodard BH, Shelburne JD, Bossen EH. Ceruminous gland adenocarcinoma: a light and electron microscopic study. *Cancer*. 1978; 41: 545-553

- [157] Jan J-C, Wang C-P, Kwan P-C, Wu S-H, Shu H-F. Ceruminous adenocarcinoma with extensive parotid, cervical, and distant metastases: case report and review of literature. *Arch Otolaryngol Head Neck Surg* 2008; 134: 663–666
- [158] Doble HP 2nd, Snyder GG 3rd, Carpenter RJ 3rd.. Sebaceous cell carcinoma of the external auditory canal. *Otolaryngol Head Neck Surg* 1981; 89: 685–688
- [159] Ray J, Worley GA, Schofield JB, Shotton JC, al-Ayoubi A. Rapidly invading sebaceous carcinoma of the external auditory canal. *J Laryngol Otol* 1999; 113: 578–580
- [160] Schuller DE, Conley JJ, Goodman JH, Clausen KP, Miller WJ. Primary adenocarcinoma of the middle ear. *Otolaryngol Head Neck Surg* 1983; 91: 280–283
- [161] Glasscock ME 3rd, McKennan KX, Levine SC, Jackson CG. Primary adenocarcinoma of the middle ear and temporal bone. *Arch Otolaryngol Head Neck Surg* 1987; 113: 822–824
- [162] Benecke JEJ, Noel FL, Carberry JN, House JW, Patterson M. Adenomatous tumors of the middle ear and mastoid. *Am J Otol* 1990; 11: 20–26
- [163] Ramsey MJ, Nadol JBJ, Pilch BZ, McKenna MJ. Carcinoid tumor of the middle ear: clinical features, recurrences, and metastases. *Laryngoscope* 2005; 115: 1660–1666
- [164] Devaney KO, Ferlito A, Rinaldo A. Epithelial tumors of the middle ear--are middle ear carcinoids really distinct from middle ear adenomas? *Acta Otolaryngol* 2003; 123: 678–682
- [165] Torske KR, Thompson LDR. Adenoma versus carcinoid tumor of the middle ear: a study of 48 cases and review of the literature. *Mod Pathol an Off J United States Can Acad Pathol Inc* 2002; 15: 543–555
- [166] Wang LL, Gebhardt MC, Rainusso N. Osteosarcoma: Epidemiology, pathogenesis, clinical presentation, diagnosis, and histology [Internet]. 2009;p www.uptodate.com version 17.2. Available from: <https://www.uptodate.com/contents/osteosarcoma-epidemiology-pathogenesis-clinical-presentation-diagnosis-and-histology>
Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. *Cancer* 2009; 115: 1531–43
- [167] Papagelopoulos PJ, Galanis EC, Vlastou C, Nikiforidis PA, Vlamis JA, Boscainos PJ et al. Current concepts in the evaluation and treatment of osteosarcoma. *Orthopedics* 2000; 23: 858–859
- [168] Naufal PM. Primary sarcomas of the temporal bone. *Arch Otolaryngol* 1973; 98: 44–50
- [169] Coventry MB, Dahlin DC. Osteogenic sarcoma; a critical analysis of 430 cases. *J Bone Joint Surg Am* 1957; 39-A: 741–57. discussion, 757–758
- [170] Gertner R, Podoshin L, Fradis M. Osteogenic sarcoma of the temporal bone. *J Laryngol Otol* 1983; 97: 627–631
- [171] Sataloff RT, Myers DL, Spiegel JR, Roberts BR, Telian S. Total temporal bone resection for osteogenic sarcoma. *Ear Nose Throat J* 1988; 67: 626–7. 630–2,passim.
- [172] Sharma SC, Handa KK, Panda N, Banerjee AK, Mann SB. Osteogenic sarcoma of the temporal bone. *Am J Otolaryngol* 1997; 18: 220–223
- [173] Seely DR, Gates GA. Parosteal osteogenic sarcoma of the mastoid bone. *Ann Otol Rhinol Laryngol* 1997; 106: 729–732
- [174] Goh YH, Chong VF, Low WK. Temporal bone tumours in patients irradiated for nasopharyngeal neoplasm. *J Laryngol Otol* 1999; 113: 222–228
- [175] Isikdogan A, Buyukcelik A, Ereku S, Pamir A. De novo osteogenic sarcoma of mastoid bone. *Sarcoma*. 2002; 6: 79–81
- [176] Wiener ES. Head and neck rhabdomyosarcoma. *Semin Pediatr Surg* 1994; 3: 203–206
- [177] Friedmann DR, Peng R, Fang Y, McMenomey SO, Roland JT, Waltzman SB. Effects of loss of residual hearing on speech performance with the CI422 and the Hybrid-L electrode. *Cochlear Implants Int* 2015; 16: 277–284
- [178] Durve DV, Kanegaonkar RG, Albert D, Levitt G. Paediatric rhabdomyosarcoma of the ear and temporal bone. *Clin Otolaryngol Allied Sci* 2004; 29: 32–37
- [179] Alexy Z. A case of rhabdomyosarcoma in the middle ear. *Monatsschr Ohrenheilkd Laryngorhinol* 1968; 102: 15–18
- [180] Jaffe BF, Fox JE, Batsakis JG. Rhabdomyosarcoma of the middle ear and mastoid. *Cancer*. 1971; 27: 29–37
- [181] Karatay S. Rhabdomyosarcoma of the middle ear. *Arch Otolaryngol* 1949; 50: 330–334
- [182] Myers EN, Stool S, Weltschew A. Rhabdomyosarcoma of the middle ear. *Ann Otol Rhinol Laryngol* 1968; 77: 949–958
- [183] Wiatrak BJ, Pensak ML. Rhabdomyosarcoma of the ear and temporal bone. *Laryngoscope*. 1989; 99: 1188–1192
- [184] Hawkins DS, Anderson JR, Paidas CN, Wharam MD, Qualman SJ, Pappo AS et al. Improved outcome for patients with middle ear rhabdomyosarcoma: a children's oncology group study. *J Clin Oncol* 2001; 19: 3073–3079
- [185] Reliability of histopathologic and radiologic grading of cartilaginous neoplasms in long bones *Bone J. Joint Surg Am* 2007; 89: 2113–2123
- [186] Lindbom A, Soderberg G, Spjut HJ. Primary chondrosarcoma of bone. *Acta radiol* 1961; 55: 81–96
- [187] O'Neal LW, Ackerman LV. Chondrosarcoma of bone. *Cancer*. 1952; 5: 551–577
- [188] Coltrera MD, Googe PB, Harrist TJ, Hyams VJ, Schiller AL, Goodman ML. Chondrosarcoma of the temporal bone. Diagnosis and treatment of 13 cases and review of the literature. *Cancer* 1986; 58: 2689–2696
- [189] Muckle RP, De la Cruz A, Lo WM. Petrous apex lesions. *Am J Otol* 1998; 19: 219–225
- [190] Oghalai JS, Buxbaum JL, Jackler RK, McDermott MW. Skull base chondrosarcoma originating from the petroclival junction. *Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc [and] Eur Acad. Otol Neurotol* 2005; 26: 1052–1060
- [191] Worley GA, Wareing MJ, Sergeant RJ. Myxoid chondrosarcoma of the external auditory meatus. *J Laryngol Otol* 1999; 113: 742–743
- [192] Guild S. A hitherto unrecognized structure, the glomus jugularis, in man. *Anat Rec* 1941; 79
- [193] Spector GJ, Maisel RH, Ogura JH. Glomus tumors in the middle ear. I. An analysis of 46 patients. *Laryngoscope*. 1973; 83: 1652–1672
- [194] Watzka M. Die Paraganglien. In: *Mikr Handbuch Anat Mensch*. 4th ed. 1943
- [195] van Baars FM, Cremers CW, van den Broek P, Veldman JE. Familial glomus tumors: clinical and genetic aspects. *Acta Otorhinolaryngol Belg* 1981; 35: 50–55
- [196] Baysal BE. Clinical and molecular progress in hereditary paraganglioma. *J Med Genet* 2008; 45: 689–694
- [197] Al-Mefty O, Teixeira A. Complex tumors of the glomus jugulare: criteria, treatment, and outcome. *J Neurosurg* 2002; 97: 1356–1366
- [198] Boedeker CC, Hensen EF, Neumann HPH, Maier W, van Nederveen FH, Suárez C et al. Genetics of hereditary head and neck paragangliomas. *Head Neck* 2014; 36: 907–916
- [199] Brown JS. Glomus jugulare tumors revisited: a ten-year statistical follow-up of 231 cases. *Laryngoscope*. 1985; 95: 284–288
- [200] Fisch U. Microsurgery of the skull base. In: *Microsurgery of the skull base*. Stuttgart: Thieme; 1988: p 149–153
- [201] McCabe BF, Fletcher M. Selection of therapy of glomus jugulare tumors. *Arch Otolaryngol* 1969; 89: 156–159

- [202] ALFORD BR, GUILFORD FR. A comprehensive study of tumors of the glomus jugulare. *Laryngoscope*. 1962; 72: 765–805
- [203] Megerian CA, McKenna MJ, Nadol JBJ. Non-paraganglioma jugular foramen lesions masquerading as glomus jugulare tumors. *Am J Otol* 1995; 16: 94–98
- [204] House WF, Glasscock ME 3rd. Glomus tympanicum tumors. *Arch Otolaryngol* 1968; 87: 550–554
- [205] Welander J, Söderkvist P, Gimm O. Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas. *Endocr Relat Cancer* 2011; 18: R253–R276
- [206] Prades CA, Atassi B, Nazeer H. Metastatic Malignant Paraganglioma: A Case Report and Review of Literature. Vol. 8: *World journal of oncology* 2017; p 92–95
- [207] Brewis C, Bottrill ID, Wharton SB, Moffat DA. Metastases from glomus jugulare tumours. *J Laryngol Otol* 2000; 114: 17–23
- [208] Glasscock ME 3rd, Harris PF, Newsome G. Glomus tumors: diagnosis and treatment. *Laryngoscope*. 1974; 84: 2006–2032
- [209] Olsen WL, Dillon WP, Kelly WM, Norman D, Brant-Zawadzki M, Newton TH. MR imaging of paragangliomas. *AJR Am J Roentgenol* 1987; 148: 201–204
- [210] Itani M, Mhlanga J, Mariani-Costantini R. Imaging of Pheochromocytoma and Paraganglioma. [Internet]. *Paraganglioma: A Multidisciplinary Approach*. [Internet]. Brisbane (AU) Codon Publications; 2019 Jul 2. Chapter 3. 2019. Available from: www.ncbi.nlm.nih.gov/books/NBK543223/ doi: 10.15586/paraganglioma.2019.ch3
- [211] Taïeb D, Timmers HJ, Hindié E, Guillet BA, Neumann HP, Walz MK et al. EANM 2012 guidelines for radionuclide imaging of pheochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging* 2012; 39: 1977–1995
- [212] Reith W, Kettner M. [Diagnosis and treatment of glomus tumors of the skull base and neck]. *Radiologe*. 2019; 59: 1051–1057
- [213] Hafez RFA, Morgan MS, Fahmy OM, Hassan HT. Long-term effectiveness and safety of stereotactic gamma knife surgery as a primary sole treatment in the management of glomus jugulare tumor. *Clin Neurol Neurosurg* 2018; 168: 34–37
- [214] Patel NS, Carlson ML, Pollock BE, Driscoll CLW, Neff BA, Foote RL et al. Long-term tumor control following stereotactic radiosurgery for jugular paraganglioma using 3D volumetric segmentation. *J Neurosurg* 2018; 1–9
- [215] Taïeb D, Jha A, Treglia G, Pacak K. Molecular imaging and radionuclide therapy of pheochromocytoma and paraganglioma in the era of genomic characterization of disease subgroups *Endocr Relat Cancer* 2019; 26: R627–R652
- [216] Gloria-Cruz TI, Schachern PA, Paparella MM, Adams GL, Fulton SE. Metastases to temporal bones from primary nonsystemic malignant neoplasms. *Arch Otolaryngol Head Neck Surg* 2000; 126: 209–214
- [217] Schuknecht H. Temporal bone removal at autopsy. Preparation and uses. *Arch Otolaryngol* 1968; 87: 129–137
- [218] Belal AJ. Metastatic tumours of the temporal bone. A histopathological report. *J Laryngol Otol* 1985; 99: 839–846
- [219] Roubaud J-C, Leclerc J-C, Mornet E, Marianowski R. Haemangioma of the temporal bone. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2020;
- [220] Hirai R, Ikeda M, Kishi H, Nomura Y, Shigihara S. A case of middle-ear cavernous lymphangioma with facial palsy. *J Laryngol Otol* 2011; 125: 405–409
- [221] Carli J, Andre J. [Teratological type dysembryoplastic tumor of the temporomastoid region]. *Ann Otolaryngol* 1958; 75: 791–792
- [222] Navratil J.. Teratome der Paukenhöhle und der Tuba eustachii. *Acta Otolaryngol* 1965; 60: 360–366
- [223] Lalwani AKXIV Skull Base. In *Current Diagnosis & Treatment in Otolaryngology: Head & Neck Surgery*. 3rd ed McGraw-Hill Education; 2011: p 769–844
- [224] Dazert S, Aletsee C, Brors D, Mlynski R, Sudhoff H, Hildmann H et al. Rare tumors of the internal auditory canal. *Eur Arch oto-rhino-laryngology Off J Eur Fed Oto-Rhino-Laryngological Soc Affil with Ger Soc Oto-Rhino-Laryngology*. *Head Neck Surg* 2005; 262: 550–554
- [225] Scherl C. Seltene Erkrankungen im Kopf-Hals-Bereich Teil III: Speicheldrüsen und Nervus Facialis (accepted for publication). *Laryngorhinootologie*.. 2021
- [226] Roosli C, Linthicum FHJ, Cureoglu S, Merchant SN. What is the site of origin of cochleovestibular schwannomas? *Audiol Neurotol* 2012; 17: 121–125
- [227] Rahne T, Plöchl S, Plontke SK, Strauss C. Preoperative determination of nerve of origin in patients with vestibular schwannoma. *HNO*. 2018; 66: 16–21
- [228] Waterval J, Kania R, Somers T. EAONO Position Statement on Vestibular Schwannoma: Imaging Assessment. What are the Indications for Performing a Screening MRI Scan for a Potential Vestibular Schwannoma? *J Int Adv Otol* 2018; 14: 95–99
- [229] Hasso AN, Smith DS. The cerebellopontine angle. *Semin Ultrasound CT MR*. 1989; 10: 280–301
- [230] Somers T, Kania R, Waterval J, Van Havenbergh T. What is the Required Frequency of MRI Scanning in the Wait and Scan Management? *J Int Adv Otol* 2018; 14: 85–89
- [231] Sakamoto T, Fukuda S, Inuyama Y. Hearing loss and growth rate of acoustic neuromas in follow-up observation policy. *Auris Nasus Larynx* 2001; 28: S23–S27
- [232] Paldor I, Chen AS, Kaye AH. Growth rate of vestibular schwannoma. *J Clin Neurosci Off J Neurosurg Soc Australas* 2016; 32: 1–8
- [233] Kania R, Vérillaud B, Camous D, Hautefort C, Somers T, Waterval J et al. EAONO position statement on Vestibular Schwannoma: Imaging Assessment Question: How should growth of Vestibular Schwannoma be defined? *J Int Adv Otol* 2018; 14: 90–94
- [234] Tieleman A, Casselman JW, Somers T, Delanote J, Kuhweide R, Ghekiere J et al. Imaging of intralabyrinthine schwannomas: a retrospective study of 52 cases with emphasis on lesion growth. *AJNR Am J Neuroradiol* 2008; 29: 898–905
- [235] Schulz C, Eßer D, Rosahl S, Baljić I, Kösling S, Plontke SK. [Management of vestibular schwannomas]. *Laryngorhinootologie* 2018; 97: 875–896
- [236] Plontke SK, Rahne T, Pfister M, Götze G, Heider C, Pazaitis N et al. Intralabyrinthine schwannomas : Surgical management and hearing rehabilitation with cochlear implants. *HNO* 2017; 65: 136–148
- [237] Plontke SK, Caye-Thomasen P, Strauss C, Kösling S, Götze G, Siebolts U et al. [Management of transmodiolar and transmacular cochleovestibular schwannomas with and without cochlear implantation. German version]. *HNO* 2020; 68: 734–748
- [238] Lalwani AK. Meningiomas, epidermoids, and other nonacoustic tumors of the cerebellopontine angle. *Otolaryngol Clin North Am* 1992; 25: 707–728
- [239] Lalwani AK, Jackler RK. Preoperative differentiation between meningioma of the cerebellopontine angle and acoustic neuroma using MRI. *Otolaryngol neck Surg Off J Am Acad Otolaryngol Neck Surg* 1993; 109: 88–95
- [240] Renowden S. Imaging of the cerebellopontine angle. *Pract Neurol* 2014; 14: 299–309
- [241] Roh TH, Park YS, Park YG, Kim SH, Chang JH. Intracranial squamous cell carcinoma arising in a cerebellopontine angle epidermoid cyst: A case report and literature review. *Medicine (Baltimore)* 2017; 96: e9423
- [242] Faltaous AA, Leigh EC, Ray P, Wolbert TT. A Rare Transformation of Epidermoid Cyst into Squamous Cell Carcinoma: A Case Report with Literature Review. *Am J Case Rep* 2019; 20: 1141–1143
- [243] Turner A, Fraser J. Tuberculosis of the middle-ear cleft in children: A clinical and pathological study. *J Laryngol Rhinol Otol* 1915; 30: 209–247

- [244] Ognibene FP. Upper and lower airway manifestations of human immunodeficiency virus infection. *Ear Nose Throat J* 1990; 69: 424–431
- [245] Saunders NC, Albert DM. Tuberculous mastoiditis: when is surgery indicated? *Int J Pediatr Otorhinolaryngol* 2002; 65: 59–63
- [246] Jeanes AL, Friedmann I. Tuberculosis of the middle ear. *Tubercle*. 1960; 41: 109–116
- [247] Tamari MJ, Itkin P. Penicillin and syphilis of the ear. *Eye Ear Nose Throat Mon* 1951; 30: 358–366. *passim*
- [248] Smith M, Canalis R. Otolgic manifestations of AIDS: The otosyphilis connection. *Laryngoscope*. 1989; 99: 365–372
- [249] Nadol J. Hearing loss of aquired syphilis: Diagnosis confirmed by incudectomy. *Laryngoscope*. 1975; 85: 1888–1897
- [250] Peled C, El-Seid S, Bahat-Dinur A, Tzvi-Ran LR, Kraus M, Kaplan D. Necrotizing Otitis Externa-Analysis of 83 Cases: Clinical Findings and Course of Disease. *Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc [and] Eur Acad. Otol Neurotol* 2019; 40: 56–62
- [251] Abu Eta R, Gavriel H, Stephen K, Eviatar E, Yeheskel E. The significance of tissue biopsy for fungi in necrotizing otitis externa. *Eur Arch oto-rhino-laryngology Off J Eur Fed Oto-Rhino-Laryngological Soc Affil with Ger Soc Oto-Rhino-Laryngology - Head Neck Surg* 2018; 275: 2941–2945
- [252] Chandler JR. Malignant external otitis and facial paralysis. *Otolaryngol Clin North Am* 1974; 7: 375–383
- [253] Chandler JR. Malignant external otitis. *Laryngoscope*. 1968; 78: 1257–1294
- [254] Chandler JR. Malignant external otitis: further considerations. *Ann Otol Rhinol Laryngol* 1977; 86: 417–428
- [255] Nadol JB. Histopathology of *Pseudomonas* osteomyelitis of the temporal bone starting as malignant external otitis. *Am J Otolaryngol* 1980; 1: 359–371
- [256] Kohut RI, Lindsay JR. Necrotizing (“malignant”) external otitis histopathologic processes. *Ann Otol Rhinol Laryngol* 1979; 88: 714–720
- [257] Mahdyou P, Pulcini C, Cahide I, Raffaelli C, Savoldelli C, Castillo L et al. Necrotizing otitis externa: a systematic review. *Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc [and] Eur Acad. Otol Neurotol* 2013; 34: 620–629
- [258] Amaro CE, Espiney R, Radu L, Guerreiro F. Malignant (necrotizing) externa otitis: the experience of a single hyperbaric centre. *Eur Arch oto-rhino-laryngology Off J Eur Fed Oto-Rhino-Laryngological Soc Affil with Ger Soc Oto-Rhino-Laryngology. Head Neck Surg* 2019; 276: 1881–1887
- [259] Harris JB, LaRocque RC, Qadri F, Ryan ET, Calderwood SB. Cholera. *Lancet (London, England)* 2012; 379: 2466–2476
- [260] Pang B, Yan M, Cui Z, Ye X, Diao B, Ren Y et al. Genetic diversity of toxigenic and nontoxigenic *Vibrio cholerae* serogroups O1 and O139 revealed by array-based comparative genomic hybridization. *J Bacteriol* 2007; 189: 4837–4849
- [261] Zhang X, Lu Y, Qian H, Liu G, Mei Y, Jin F et al. Non-O1, Non-O139 *Vibrio cholerae* (NOVC) Bacteremia: Case Report and Literature Review, 2015–2019. Vol. 13, *Infection and drug resistance*. New Zealand: p 1009–1016
- [262] Kechker P, Senderovich Y, Ken-Dror S, Laviad-Shitrit S, Arakawa E, Halpern M. Otitis Media Caused by *V. cholerae* O100: A Case Report and Review of the Literature. *Front Microbiol* 2017; 8: 1619
- [263] Madeira JT, Summers GW. Epidural mastoid pneumatocoele. *Radiology*. 1977; 122: 727–728
- [264] Krisht KM, Eli IM, Palmer CA, Schmidt RH. Giant Spontaneous Epidural Pneumatocoele: Case Report and Review of the Literature. *World Neurosurg* 2015; 84: 2075.e7–12
- [265] Schilde S, Plontke S, Seiwert H, Kösling S. Abnormal mastoid pneumatization. *HNO*. 2019; 67: 876–880
- [266] Graf K. [Spontaneous giant pneumatocoele of the mastoid]. *Pract Otorhinolaryngol (Basel)* 1955; 17: 462–466
- [267] Keshet N, Abu-Tair J, Zaharia B, Abdalla-Aslan R, Aframian DJ, Zadik Y. Superficial oral mucocoeles in cancer patient after radiation therapy: An overlooked yet imperative phenomenon. Vol. 52: *Oral oncology*. England 2016; p e1–e2
- [268] Mnejja M, Hammami B, Achour I, Chakroun A, Charfeddine I, Frikha M et al. [Post-radiation mucocoele in two patients treated for nasopharyngeal cancer]. *Cancer Radiother* 2011; 15: 254–256
- [269] Mark IHW, Tan HKK. Sphenoid mucocoele after radiation for the treatment of nasopharyngeal carcinoma. *J Otolaryngol - head neck Surg = Le J d'oto-rhino-laryngologie Chir cervico-faciale* 2008; 37: E28–E31
- [270] Tonni D, Sessa M, Redaelli de Zinis LO. Primary mucocoele of the mastoid: An incidental finding. Vol. 8, *Clinical case reports*. England 2020; p 461–465
- [271] Karandikar A, Goh J, Loke SC, Yeo SB, Tan TY. Mucous retention cyst of temporal bone: a mimic of cholesteatoma on DW-MRI. *Am J Otolaryngol* 2013; 34: 753–754
- [272] Ata N, Erkilic S. Mucous retention cyst of mastoid bone mimicking cholesteatoma. *Ear Nose Throat J* 2017; 96: E41–E42
- [273] Waltner JC, Karatay S. Cysts of the mastoid bone. *Arch Otolaryngol* 1947; 46: 398–404
- [274] Richardson GS. A cyst of the mastoid; report of a case. *Ann Otol Rhinol Laryngol* 1956; 65: 214–217
- [275] Nomura Y, Takemoto K, Komatsuzaki A. The mastoid cyst. Report of a case. *Laryngoscope* 1971; 81: 438–446
- [276] Zimmerman BE, Proud GO. Primary cysts of the mastoid process. *Laryngoscope*. 1983; 93: 805–807
- [277] Kavanagh KT, Giltman LI, Babin RW. Erosive mucosal cysts of the temporal bone. A case report with review of the pathogenesis. *Am J Otol* 1986; 7: 270–274
- [278] Tan CY, Chong S, Shaw C-KL. Primary mastoid cyst. *J Laryngol Otol* 2013; 127: S48–S50
- [279] Hwang PH, Jackler RK. Facial nerve dysfunction associated with cystic lesions of the mastoid. *Otolaryngol Head Neck Surg* 1998; 119: 668–672
- [280] Mohammed ER, Profant M. Spontaneous otogenic pneumocephalus. *Acta Otolaryngol* 2011; 131: 670–674
- [281] Andrews JC, Canalis RF. Otogenic pneumocephalus. *Laryngoscope*. 1986; 96: 521–528
- [282] Sanna M, Fois P, Russo A, Falcioni M. Management of meningoencephalic herniation of the temporal bone: Personal experience and literature review. *Laryngoscope* 2009; 119: 1579–1585
- [283] Kenning TJ, Willcox TO, Artz GJ, Schiffmacher P, Farrell CJ, Evans JJ. Surgical management of temporal meningoencephaloceles, cerebrospinal fluid leaks, and intracranial hypertension: treatment paradigm and outcomes. *Neurosurg Focus* 2012; 32: E6
- [284] Kutz JWJ, Tolisano AM. Diagnosis and management of spontaneous cerebrospinal fluid fistula and encephaloceles. *Curr Opin Otolaryngol Head Neck Surg* 2019; 27: 369–375
- [285] Nelson RF, Roche JP, Gantz BJ, Hansen MR. Middle Cranial Fossa (MCF) Approach Without the Use of Lumbar Drain for the Management of Spontaneous Cerebral Spinal Fluid (CSF) Leaks. *Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc [and] Eur Acad. Otol Neurotol* 2016; 37: 1625–1629
- [286] Hernandez-Montero E, Caballero E, García-Ibanez L. Surgical management of middle cranial fossa bone defects: meningoencephalic herniation and cerebrospinal fluid leaks. *Am J Otolaryngol* 2020; 41: 102560

- [287] BLACK BK, SMITH DE. Nasal glioma; 2 cases with recurrence. *AMA Arch Neurol Psychiatry* 1950; 64: 614–630
- [288] Ofodile FA, Aghadiuno PU, Oyemade O, Adebajojo T. Heterotopic brain in the tongue. *Plast Reconstr Surg* 1982; 69: 120–124
- [289] Scheiner AJ, Frayer WC, Rorke LB, Heher K. Ectopic brain tissue in the orbit. *Eye (Lond)* 1999; 13: 251–254
- [290] Uğuz MZ, Arslanoğlu S, Terzi S, Etit D. Glial heterotopia of the middle ear. *J Laryngol Otol* 2007; 121: e4
- [291] McGregor DH, Cherian R, Kepes JJ, Kepes M. Case reports: heterotopic brain tissue of middle ear associated with cholesteatoma. *Am J Med Sci* 1994; 308: 180–183
- [292] Lee JJ, Kim KK, Park YK, Eah KY, Kim JR. Glial choristoma in the middle ear and mastoid bone: a case report. *J Korean Med Sci* 2004; 19: 155–158
- [293] Plontke SK, Preyer S, Pressler H, Munding PM, Plinkert PK. Glial lesion of the infratemporal fossa presenting as a soft tissue middle ear mass — rudimentary encephalocele or neural crest remnant? 2000; 56: 141–147
- [294] Abrahams JJ, Eklund JA. Diagnostic radiology of the cranial base. *Clin Plast Surg* 1995; 22: 373–405
- [295] Koch BL, Ball WSJ. Congenital malformations causing skull base changes. *Neuroimaging Clin N Am* 1994; 4: 479–498
- [296] Lalwani AK, Jackler RK. Spontaneous hemotympanum associated with chronic middle ear effusion. *Am J Otol* 1991; 12: 455–458
- [297] Maeta M, Saito R, Nakagawa F, Miyahara T. Surgical intervention in middle-ear cholesterol granuloma. *J Laryngol Otol* 2003; 117: 344–348
- [298] Paparella MM, Lim DJ. Pathogenesis and pathology of the “idiopathic” blue ear drum. *Arch Otolaryngol* 1967; 85: 249–258
- [299] Plontke S, Koitschev A, Ernemann U, Pressler H, Zimmermann R, Plasswilm L. [Massive Gorham-Stout osteolysis of the temporal bone and the craniocervical transition]. *HNO* 2002; 50: 354–357
- [300] Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone); its relation to hemangiomatosis. *J Bone Joint Surg Am* 1955; 37-A: 985–1004
- [301] Patel DV. Gorham’s disease or massive osteolysis. *Clin Med Res* 2005; 3: 65–74
- [302] Simon F, Luscan R, Khonsari RH, Toubiana J, Belhous K, James S et al. Management of Gorham Stout disease with skull-base defects: Case series of six children and literature review. *Int J Pediatr Otorhinolaryngol* 2019; 124: 152–156
- [303] Pace A, Iannella G, Riminucci M, Corsi A, Magliulo G. Tympano-Mastoid Cholesterol Granuloma: Case Report and Review of the Literature. *Clin Med Insights Case Rep* 2020; 13: 1179547620958728
- [304] Gore MR, Zanation AM, Ebert CS, Senior BA. Cholesterol granuloma of the petrous apex. *Otolaryngol Clin North Am* 2011; 44: 1043–1058
- [305] Olcott C, Strasnick B. A blue middle ear mass: Cholesterol granuloma mimicking a glomus tumor and endolymphatic sac tumor. *Am J Otolaryngol* 2017; 38: 100–102
- [306] Kohanski MA, Palmer JN, Adappa ND. Indications and endonasal treatment of petrous apex cholesterol granulomas. *Curr Opin Otolaryngol Head Neck Surg* 2019; 27: 54–58
- [307] Sanna M, Dispenza F, Mathur N, De Stefano A, De Donato G. Otoneurological management of petrous apex cholesterol granuloma. *Am J Otolaryngol* 2009; 30: 407–414
- [308] Raghavan D, Lee TC, Curtin HD. Cholesterol Granuloma of the Petrous Apex: A 5-Year Review of Radiology Reports with Follow-Up of Progression and Treatment. *J Neurol Surg B Skull Base* 2015; 76: 266–271
- [309] Boedeker CC, Kayser G, Ridder GJ, Maier W, Schipper J. Giant-cell reparative granuloma of the temporal bone: a case report and review of the literature. *Ear Nose Throat J* 2003; 82: 926–929. 933-934,936-937
- [310] Jaffe HL. Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibro-oseous) dysplasia of the jawbones. *Oral Surg Oral Med Oral Pathol* 1953; 6: 159–175
- [311] Dietz A, Duprez T, Lelotte J, Finet P, Wilms G. Letter to the editor giant cell reparative granuloma of the temporal bone. *Acta neurologica Belgica; Italy*: 2020
- [312] Bernard F, Troude L, Bouvier C, Roche P-H. “Giant cell reparative tumor: An exceptional differential diagnosis for a lytic lesion of the temporal bone”. *Neurochirurgie*. 2016; 62: 332–335
- [313] Menge M, Maier W, Feuerhake F, Kaminsky J, Pfeiffer J. Giant cell reparative granuloma of the temporal bone. *Acta Neurochir (Wien)* 2009; 151: 397–399
- [314] Ciappetta P, Salvati M, Bernardi C, Raco A, Di Lorenzo N. Giant cell reparative granuloma of the skull base mimicking an intracranial tumor. Case report and review of the literature. *Surg Neurol* 1990; 33: 52–56
- [315] Plontke SK-R, Adler C-P, Gawlowski J, Ernemann U, Fries SA, Plinkert PK. Recurrent giant cell reparative granuloma of the skull base and the paranasal sinuses presenting with acute one-sided blindness. Vol. 12, *Skull base : official journal of North American Skull Base Society ... [et al.]* 2002; p 9–17
- [316] Auclair PL, Cuenin P, Kratochvil FJ, Slater LJ, Ellis GL. A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. *Oral Surg Oral Med Oral Pathol* 1988; 66: 197–208
- [317] Cho Y-S, Lee H-S, Kim S-W, Chung K-H, Lee D-K, Koh W-J et al. Tuberculous otitis media: a clinical and radiologic analysis of 52 patients. *Laryngoscope*. 2006; 116: 921–927
- [318] Plontke SK, Kösling S, Schilde S, Wittlinger J, Kisser U. The infracochlear approach for diagnostic petrous apicotomy. *HNO*. 2019; 67: 791–795
- [319] Kleijwegt M, Ho V, Visser O, Godefroy W, van der Mey A. Real Incidence of Vestibular Schwannoma? Estimations From a National Registry. *Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc [and] Eur Acad. Otol Neurotol* 2016; 37: 1411–1417
- [320] Quigley C, Deady S, Hughes E, McElnea E, Zgaga L, Chetty S. National incidence of eyelid cancer in Ireland (2005-2015). *Eye (Lond)* 2019; 33: 1534–1539
- [321] Berner K, Zaikova O, Johannesen TB, Hall KS, Bruland ØS. Validity and completeness of the Scandinavian Sarcoma Group Central Register by comparison with a nationwide cohort of patients with osteosarcoma in Norway. Vol. 118, *Journal of surgical oncology*. United States 2018; p 246–247
- [322] Heller J, Kraus F, Scheich M, Mlynski R. Therapie der traumatischen Stapesverletzung. In: 80th Annual Meeting of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery 2009

