Rare Diseases of the Salivary Glands and of Facial Nerve

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ABSTRACT

Salivary gland diseases are rare. In the European Union (EU), a disease is considered to be rare if not more than 5 of 10 000 people are affected. According to estimates, about 4 million people in Germany suffer from rare diseases. It are 30 million inn the EU [1]. In the present article, most of the described diseases of the salivary glands and of the facial nerve fall into this category. They form a very heterogeneous group and their treatment mainly takes place in specialized centers. Still, it is essential for otolaryngologists to identify and to diagnose these diseases in order to initiate the adequate therapeutic steps. This manuscript is a compilation of rare congenital and acquired salivary gland disorders and of rare facial nerve disorders. The etiologies of inflammatory diseases, autoimmune disorders, and tumors are taken into account. For the single topics, the current literature – if available – was evaluated and turned into summarized facts. In this context, the development of new processes, diagnostics, imaging, and therapy are considered. Genetic backgrounds of salivary gland tumors and the trends in the treatment of tumor lesions of the facial nerve are picked up. Furthermore, also rare diseases of the salivary glands in childhood are described. Some of them can occur in adults as well, but differ regarding their frequency and symptoms. Due to the rarity of these diseases, it is recommended to treat them in centers with special expertise. Finally, the difficulties of initiating trials and the problems of establishing disease registries concerning salivary gland disorders are discussed. This is highly relevant because these pathologies are relatively rare.

ABBREVIATIONS

AECG	American-European Consensus Group
AIDS	Acquired Immune Deficiency Syndrome
AV	Arteriovenous
CT	Computed tomography
HIV	Human immunodeficiency virus
MALT	Mucosa-associated lymphatic tissue
MRI	Magnetic resonance imaging
N	Nerve
PCR	Polymerase chain reaction

General Remarks

This review does not include publications that deal with frequently occurring diseases of the salivary glands. Even if disorders of the salivary glands are rare in view of the entirety of all diseases of the head and neck, the following chapters will consider only the rare ones of the rare. The discussion of all diseases of the salivary glands would be beyond the scope of this article.

Contents

1. Historic Facts

At the occasion of the 100th Anniversary of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC) it must not be forgotten to throw a glance at the history of diseases of the salivary glands and the facial nerve. The first descriptions of salivary glands date to more than 4000 years ago. The earliest description of salivary glands and in particular of saliva is found in ancient Mesopotamia on clay tablets of the Syrian king named Assurbanipal around 2500 B.C. The inscription refers to belladonna which was applied as effective medication against sialorrhea [2, 3]. Hippocrates (460–370 B.C.) mentioned diseases of the salivary glands such as "purulent and non-purulent mumps" that he differentiated from epidemic mumps [4]. Galeno de Pérgamo (129/130–200/216

A.C.) describes the facial nerve as the nerve having ramifications and connections: "qui inter se conjungantur". He describes the salivary glands as "a sponge that would clean the blood, eliminating impurities" [5]. Al Zahrawi (936–1013 A.C.) describes a ranula as frog-like structure: "it is a tumor similar to a frog generated by pure expectoration or by expectoration mixed with black material" [6]. Afterwards, there is the long dark period of the Middle Ages. Only in the 16th century, again reports about the salivary glands are mentioned. The term of "salivary gland" originates from that time. Probably, it was first mentioned in 1543 by Andreas Vesalius [7]. Thomas Wharton (1614–1673) described the submandibular duct in his "Adenographia" of 1656 as a very important structure. He argues that "the objective of the glands was to extract the necessary fluids from lymph and transport them to the 7nerves" [3, 8].

In April 1660, the Danish anatomist Niels Steenson or Nicolaus Stenonis (his Latin name; 1638–1686) discovered the parotid duct [9]. The German surgeon Lorenz Heister described the first parotidectomy in 1765 as well as the treatment of ranulae and sialoliths in the floor of the mouth [10]. Since the beginning of the 19th century, it has been requested to preserve the facial nerve during parotid surgery [11]. In 1825, Johann Ferdinand Heyfelder, Professor in Erlangen, was the first to describe the preservation of the facial nerve during parotidectomy to maintain its function. All other former surgeons had failed up to then. Afterwards, on January 24, 1847, he described the first anesthesia in Germany with the use of diethyl ether. He performed surgeries on 100 patients in his department, among them 2 parotidectomies with diethyl ether [12]. Theodor Billroth (1829–1894) and Rudolph Virchow (1821–1902) described the pleomorphic adenoma [13]. The division of the parotid gland into a superficial and a deep part that are separated by the facial nerve was first described in 1947 by Hamilton Bailey. Also his appeal was groundbreaking that the strategy of enucleations should be left that had been performed up to then because of the fear of postoperative facial paresis: He assumed that malignant cells that had been covered during an intracapsular enucleation or cells that remain in the interior of a capsular part that has not been completely removed made up 90 % of the recurrences. His work lays the foundation for extracapsular dissection of parotid tumors that is nowadays applied and for the lateral parotidectomy [14]. The technique of lateral parotidectomy was improved by Henry Samuel Shucksmith in 1951. He recommended to expose first the main trunk of the facial nerve at the foramen stylomastoideum and to prepare the single branches in anterograde direction. This was and is up to now one of the main techniques of parotidectomy [15]. Various other surgeons such as Blair, McEvedy, Watkin, Patey, Thackray, Hobsley, and Maynard from England as well as Sobin, Seifert, Küttner, and Miehlke from Germany have significantly promoted the knowledge of our times [13].

With regard to this history of thousands of years, the "only" 100 years of DGHNO-KHC are rather young. However, the development in these 100 years concerning the diseases of the salivary glands and the facial nerve was as fast as never before. Most diseases of salivary glands and lesions of the facial nerve known today as well as the rare diseases mentioned in this article have been described within these last 100 years. Since 1921 when the Society of German Oto-Rhino-Laryngologists, as it was called at that time, was founded, important contributions have been made to the knowledge that were discussed and improved on numerous annual meetings and publications.

2 Rare Diseases of the Salivary Glands

2.1 Identification of diseases of the salivary glands

Besides patient history, clinical findings, and laboratory diagnostics, especially the imaging plays an important role for the identification of rare lesions.

2.1.1 Ultrasound

The most thorough examination that is easily available is ultrasound. Reliable assessment of the findings of rare diseases strongly depends on the clinical and sonographic experience of the examiner. While the identification of tumor structures or stone formation is relatively easy, the differentiation of sialadenitis and sialadenosis represents a challenge even for experienced examiners. Acute and chronic sialadenitis are different with regard to their parenchymal pattern. In cases of acute disease, this pattern is loose, anechoic and shows a dilated duct structure indicating an accumulation of pus. Depending on the duration and extent of the inflammatory process, chronic cases rather show a dense parenchyma with inhomogeneous texture as result of scarring fibrosis. Sometimes, small cystic areas become apparent corresponding to ductal ectasia. Ultrasound may not clearly differentiate between the different pathogenetic types of acute and chronic sialadenitis. In contrast, the rare disease of sialadenosis either shows regular echoic swelling of all glands or very specific alterations as for example in Sjögren's disease or sarcoidosis (see below) [16].

2.1.2 CT scan and MRI

In comparison to ultrasound, MRI and CT scans have the advantage that they better display the extent and invasion of neighboring structures. They are very suitable for the diagnosis of tumors. Imaging of salivary gland tumors is helpful to define the entity. However, the accuracy of merely morphologic procedures (ultrasound, CT scan, MRI) is limited if no lymph node enlargement is present and depends from the examiner's experience [17]. CT scans allow better diagnosis in cases of inflammations, bone infiltration, and vascular involvement. In tumor processes, MRI should be preferred because it better describes the extent of infiltration and tumor demarcation [18]. Tumor borders and the presence of cystic areas may give hints to differentiate between high- and low-grade tumors [19].

2.2 Rare pediatric diseases of the salivary glands

Salivary gland diseases in childhood occur very rarely. Exceptional conditions are virally induced diseases and chronic juvenile parotitis that will not be dealt with in this manuscript. Especially in children, it is a major challenge to identify these rare salivary gland diseases in order to introduce adequate therapy.

In pediatric patients, salivary gland diseases generally express in an unspecific way with painful or painless swelling, altered salivary flow, or facial paresis. Beside the clinical examination, mainly ultrasound is performed. Due to the low penetration depth, transducers with 7.5–12 MHz are suitable to diagnose inflammations,

sialoliths, tumors, and lymph nodes. The vascularization may be determined by color Doppler sonography which is helpful for hemangiomas and arteriovenous (AV) malformations [20]. MRI and CT scans are only applied in cases of tumorous masses or specific indications. Also the indication for biopsy is reduced in children because it usually has to be performed under general anesthesia. However, biopsy taking would have the advantage that the tumor dignity can be determined and on the other hand that material for microbiological assessment or identification of pathogens may be gained [20]. In the context of general anesthesia, it must be taken into consideration to perform complete extirpation of the tumorous mass.

Extremely rarely observed are congenital diseases of the salivary glands. The incidence of parotid aplasia amounts to 1:5000 live births [21], aplasia of the submandibular gland has been reported only in about 40 cases [22]. They may occur as single lesions or in combination with other malformations of the face. In cases of Treacher Collins syndrome, 29 % of the patients had a salivary gland dysplasia and 19 % a salivary gland aplasia. More than half of these patients have missing parotid secretion. But only in 35 % of the cases, this fact leads to xerostomia because the minor salivary glands possibly compensate the secretion. In healthy individuals, the minor salivary glands contribute less to the overall salivary volume, but due to their secretion they play a crucial role in the humidification of the oral mucosa. The minor salivary glands themselves have not been investigated in this study [23]. In cases of lacrimo-auriculo-dento-digital syndrome, malformations of different appearance are found. The children present with deafness, dental anomalies and malformation of the extremities, or the development of extreme caries because of xerostomia [24]. Also ranulae as benign tumors of the sublingual gland may occur at birth in rare cases [25]. Another rare congenital tumor is the sialoblastoma, also known as embryoma. This tumor should be completely resected because it has an aggressive growth pattern and tends to be recurrent [26].

Neoplasms of the salivary glands in childhood are considered as being rare with 5 % of all salivary gland tumors. However, they make up 39 % of all salivary gland lesions diagnosed in pediatric patients [27], 68 % of them are benign and 32 % are malignant. The most frequently observed benign tumor is the pleomorphic adenoma (> 90 %) [28]. It mainly develops in the parotid gland (85 %), sometimes also in the submandibular gland (11.7 %) and the sublingual gland (3.2 %) or the minor salivary glands [27]. Similar to adults, therapy consists of surgical removal. Malignant tumors comprise mucoepidermoid carcinomas in more than 50 % of the cases, more rarely acinar cell carcinomas and adenoidcystic carcinomas are observed [29]. Hereby, therapy is different from the one of adults. Radiotherapy is recommended only in exceptional cases because of the rate of secondarily radio-induced tumors amounts to about 60 % [30]. Nonetheless, Thariat et al. and Kupferman et al. recommend adjuvant radiotherapy for high-grade tumors and tumors in advanced stages (T4N +) [31, 32].

Two third of all pediatric tumors are hemangiomas, about 80 % of them are located in the parotid gland, 18 % in the submandibular region, and 2 % are associated with the minor salivary glands [33]. Histologically, the difference is made between true hemangiomas (e. g. juvenile capillary hemangiomas) and AV malformations and lymphangiomas [34].

A rare type of purulent acute sialadenitis is the neonatal purulent parotitis that develops directly after birth. Up to now, only few cases have been described in case reports. The clinical appearance with swelling and reddening corresponds to other purulent parotitis. It is associated with dehydration and low birth weight, ductal obstruction, and structural anomalies of the parotid gland. Most frequently observed pathogens are Staphylococcus aureus, gram-negative Streptococcus and rarely anaerobes [35].

Pneumoparotitis is a rare, painful disease in the context of which affected children and adolescents blow air into Stenon's duct which occurs in the context of playing wind instruments or psychological disorders [36]. The diagnosis is made by ultrasound where numerous echoic reflexions are visible. The treatment consists of symptomatic therapy with glandular massage, sialogogue, and analgesics as well as psychotherapy, if needed [37].

In comparison to infection with tuberculous mycobacteria, that may affect numerous lymph nodes in the parotid gland, the infection with atypic mycobacteria is relatively rare. Since the incidence increases worldwide, it will be mentioned here [38]. The typical clinical symptoms are unilateral, rather solid swellings of the intraglandular lymph nodes. Cutaneous fistulas are possible and may persist even for months or years. The diagnostics include microbiological identification of the pathogens by means of culture and PCR. Therapy may consist of surgical excision of the affected lymph nodes or drug therapy. Mahadevan et al. favor surgical treatment because pharmacotherapy (clarithromycin and rifabutin or ethambutol) have to be applied for several weeks and thus represent a compliance risk [39]. The healing rates are better of 30 % for surgical therapy compared to pharmacotherapy [40]. After years, the lesions may be self-limiting which, however, is associated with poor esthetic results [41].

Regarding differential diagnosis, also other granulomatous diseases of the salivary glands must be taken into consideration. Those are for example sarcoidosis, cat-scratch disease, Kikuchi lymphadenitis, or actinomycosis. The differentiation is made by means of identification of the pathogens and histology. Actinomycosis is caused by gram-positive anaerobe bacteria, often by trauma or also dental treatment. The salivary glands may also be affected in cases of mainly painless necrotizing inflammation leading to fistula development. The therapy of choice consists of penicillin application [20].

In rare cases, also autoimmune diseases may affect the salivary glands in children. The main appearance is the juvenile Sjögren's syndrome. Girls are affected six times more frequently than boys. The diagnosis is made based on the AECG criteria [42]. Hence, at least 4 of the following criteria should be fulfilled: ocular symptoms, oral symptoms, positive Schirmer's test, lymphocytic infiltration, involvement of the salivary glands (reduced salivary flow, sialectasia), or auto-antibodies (SSA, SSB). Further findings might be increased amylase, renal tubular acidosis, leukopenia, ANAs, positive rheumatoid factors, and hypergammaglobulinemia [20]. Ultrasound reveals an enlarged parotid gland with anechoic cloud-like structural change, similar to adults [43]. Biopsy of the minor salivary gland of the lower lip has a sensitivity of 78–84 % and a specificity of 82–100 %, open parotid biopsy has only 78 % and 86 %, respectively [44, 45]. The therapy of children is symptom-based [44].

2.3 Rare inflammatory diseases

Acute and chronic sialadenitis can often be identified already by exact history taking and clinical examination. For accurate differentiation, further examinations by means of ultrasound, MRI/CT scan if needed, blood count, serology, and/or biopsy are needed.

2.3.1 Infectious diseases

2.3.1.1 Infection with tuberculous and non-tuberculous mycobacteria

Mycobacterial sialadenitis with primary or secondary manifestation in the lymph nodes of the parotid gland rarely occurs in Western Europe and is more frequently found in developing countries. However, the increasing globalization and refugee movements lead to an increased incidence also in Germany. The parotid gland is affected in 70 %. If the submandibular gland is affected, also active pulmonary tuberculosis may be suspected. As origin, an ascending infection of the tonsils or teeth is assumed [46]. Furthermore, hematogenic infection or an infection via cervical lymph nodes is discussed [47]. In cases of unilateral, diffusely enlarged parotid gland revealed by ultrasound with prominent intraglanular lymph nodes, this differential diagnosis must be taken into account. CT scans describe an asymmetric lymphadenopathy with necrotic areas and ring-shaped contrast enhancement into the subcutaneous fatty tissue. The definitive evidence is always performed by microbiology as culture and the identification of acid-resistant rods and by means of PCR. The material may be gained by means of fine needle aspiration cytology. The sensitivity and specificity amount to 81–100 and 94–100 %, respectively [48].

The difference is made between acute and chronic types. The acute infection presents as painful with short-term history and abscess-like formations in the gland. The chronic infection which is more frequently observed is characterized by a unilateral solid swelling. In this context, lymphoma or other tumorous lesions have to be excluded [49, 50].

The therapy is performed with pharmaceutics that have to be applied for several months. In cases of infection with atypical mycobacteria, surgical therapy is favored, similar to pediatric disease [39, 40].

2.3.1.2 HIV

During the former HIV pandemic when no antiviral therapy was available, 50 % of the HIV-positive patients and 80 % of the patients suffering from AIDS had an involvement of the salivary glands in the sense of swelling [51]. After introduction of antiretroviral therapy, the incidence of HIV-associated salivary gland diseases as expression of an immune reconstitution was even increasing [52]. The swellings concern in particular the parotid gland and are found on both sides in 40 % of the cases. Patients report about accompanying Sjögren-like symptoms with xerostomia and dry eyes [53, 54]. In the meantime, the incidence of HIV-related swellings of the parotid gland decreased in western countries due to the increased application of highly active antiviral therapy [55]. In contrast, they are still frequently observed in African countries. A South-African monocenter investigation reports about 168 cases within a period of 8 years [56] which shows that a very high total number can be expected for entire Africa. Histomorphologically, lymphatic infiltration with invasion of CD8 T cells occurs [57]. Epithelium encapsulated in intraglandular lymph nodes leads to the development of characteristic lymphoepithelial cysts in particular in the parotid gland. The cysts are clearly visible in ultrasound. The result is the appearance of the gland infiltrated by cysts that is pathognomonic for HIV infection. The most important differential diagnosis is Sjögren's syndrome where also lymphoepithelial cysts may be detected. CT scan and MRI may also reveal unspecific cystic lesions [58]. The definitive diagnosis is made by serology.

Swelling of the salivary glands of AIDS patients may also be caused by accompanying hepatitis C or mumps infection. Beside the direct glandular affection, also HIV-associated malignancy may occur that manifests mainly in the parotid gland. These are the Kaposi sarcoma and malignant lymphoma of the intraglandular lymph nodes [53].

2.3.1.3 Hepatitis C

Hepatitis C is not only characterized by chronic liver lesion but it is also associated with numerous extrahepatic manifestations. At the salivary glands sialadenitis comparable to Sjögren's disease may develop [59]. A French study performed by Haddad could show already in 1992 that 57 % of hepatitis C positive patients had sialadenitis grade 3 to 4 [60]. The difference regarding Sjögren's syndrome consists of the condition that xerostomia and xerophthalmia are less severely developed. The predominance of the female gender and the evidence of anti-SSA antibodies are missing. However, the virus can be identified in the saliva in 83 % of the cases [61]. Doeffel-Hantz et al. describe improved sicca symptoms after treatment with interferon alpha and ribavirin [62]. Similar to Sjögren's syndrome, the development of B cell Non-Hodgkin lymphoma is a complication such as in HCV infection [63]. In most cases, only one salivary gland is involved, mostly the parotid gland, rarely also the submandibular gland or the minor salivary glands [64]. In this context, otolaryngologists have to examine the affected gland by means of ultrasound and confirm the diagnosis by surgery.

Overall, hepatitis C sialadenitis should be excluded especially in male patients suffering from symptoms similar to Sjögren's syndrome. If the diagnosis is confirmed, the ENT specialist has to perform adequate follow-up in order to early detect the development of lymphomas.

2.3.1.4 Actinomycosis

Actinomycosis is a mixed infection with anaerobic and aerobic actinomycetes, in particular Actinomyces israelii [65]. The neck and face are most frequently affected. A merely submandibular or parotid manifestation is rare. It appears as solid swelling with multiple fistulas. Generally, the course is slowly progressive and painless. However, there are also acute types with fever [66]. Differential diagnosis must exclude atypical mycobacteriosis from actinomycosis that is also associated with fistula-like tumorous mass. Further differential diagnoses are neoplasms and granulomatous lesions. Predisposing factors are dental infections, dental treatments, or oral injuries that lead to a release of the pathogen ascending into the parotid or submandibular gland. To make this possible, a massive increase of the bacterium that is also present in the normal oral flora has to develop. An increased anaerobic accompanying flora enhances the relatively low invasion of the actinomycetes by enzy-

matic effects and toxin formation and thus may trigger a florid infection [67]. The diagnostics are based on the clinical appearance and the microbiological identification of pathogens. For this purpose, fine needle aspiration cytology or biopsy are most suitable. It is important for microbiological examination to mention the suspected diagnoses because often the culture provides a negative result since strict anaerobic culture conditions are not generally available [68]. Therapy consists of surgery and application of antibiotics. Abscess formations and necroses are removed surgically. The application of antibiotics such as penicillin or cephalosporin has to be performed over 3–12 months [69].

2.3.1.5 Cat-scratch disease

Strictly speaking, the cat-scratch disease does not involve the salivary glands but the periparotid and submandibular lymph nodes from which the infection passes on to the salivary glands [46]. The incidence amounts to 0.77–0.86 per 100 000 people [70]. Since the disease remains often asymptomatic in humans, the actual spread of the infection in the population is estimated higher. Nonetheless, the disease also bears important risks; in the literature more than 100 encephalitic complications have been described [71, 72]. The pathogenic agent is the bacterium *Bartonella henselae* which could only be associated with the disease in the 1990ies [73]. The disease is transferred by kitten. Older cats have already undergone the infection and are no longer contagious [74]. According to an investigation performed by Dalton et al., the most frequently observed symptoms of cat-scratch disease are regional lymph node swelling (85 %), fever (54 %) as well as general feeling of illness (45 %). Within 1–3 weeks, papulomatous to pustular efflorescence develops from the skin scratches [75]. In cases of positive history, the disease is confirmed by antibodies, by identification of pathogens via PCR, or histology. Experienced cytologists also detect the disease cytologically by means of Warthin-Starry silver staining. In immunocompetent patients, spontaneous healing may be awaited. If the inflammation leads to abscesses, surgical intervention is recommended in combination with the application of a macrolide or tetracycline [76].

2.3.2 Chronic non-infectious diseases

Chronic diseases are less frequently observed than acute salivary gland diseases. One key origin of all chronic, non-infectious sialadenitis might be a reduced salivary secretion rate with subsequent stasis. This mainly affects the parotid gland. In the course of the disease, ductal ectasias and destruction of the acini are observed in combination with lymphocytic infiltration. Up to 80 % of the patients develop xerostomia. It is crucial to exclude common obstructive diseases such as stones and stenoses [46].

2.3.2.1 Autoimmune diseases

2.3.2.1.1 Sjögren's syndrome

With a prevalence of 0.3 to 1 per 1000 people Sjögren's syndrome is not really rare [77] but it will be discussed here because of its importance and the described pathologies that are associated with this disease. The ratio of females to males amounts to 9:1. 80 % of the patients complain about the 3 leading symptoms of xerostomia and xerophthalmia, fatigue, and joint pains which lead to a significant impairment of the quality of life [78]. A primary and a secondary type are mentioned. The term of secondary or associated disease is applied when the disease occurs in combination with other pathologies that may also affect the salivary glands such as for example IgG4-associated disease, lupus, or HIV and hepatitis C infections. The major diagnostic challenge concerns the fact that dryness of the mucosa, pains in the joints and tiredness appear very frequently in the general population without having a disease status. The term of Sjögren's syndrome is only applied when also immunological findings (presence of serum anti-SSA antibodies or focal lymphatic sialadenitis after biopsy of labial salivary glands) can be confirmed [79]. The criteria that have recently been established by the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) for classification also apply for the diagnosis of Sjögren's syndrome (▶ **Table 1**) [42, 80].

In addition to these criteria, an experienced examiner may detect inhomogeneous glandular swellings in sonography penetrated by numerous anechoic tumorous masses that correspond on one hand to cystic ductal enlargement and on the other hand to intraglandular lymph nodes. Overall, a cloud-like structure appears [16]. Unfortunately, ultrasound has not been included in these classification criteria due to historic-geographic reasons. However, the integration of ultrasound as diagnostic measure is currently taken into consideration [80].

▶ **Table 1** ACR-EULAR classification criteria of 2017 for primary Sjögren's syndrome.

		Score
Labial salivary gland with focal lymphatic sialadenitis in the histology and a score of ≥ 1	A score resulting from the number of mononuclear cell infiltrates and consists of ≥ 50 inflammatory cells per 4 mm² of minor lower lip salivary glands that have been gained by biopsy	3
Presence of anti-SSA antibodies	Measured in the serum. Positive serological results for anti-SSB/La antibodies in absence of anti-SSA/Ro antibodies are not specific and represent no criterion for diagnosis	3
SICCA eye color value of ≥ 5	A score (0–12) that is ophthalmologically evaluated by means of fluorescein and lissamin green staining	1
Schirmer test of ≤ 5 mm per 5 min	Measurement of the tear production by inserting filter paper on the conjunctiva of the lower lid. The liquid quantity on the paper is assessed.	[1]
Unstimulated total saliva flow of ≤ 0.1 ml per min	Collection of saliva in a tube for at least 5 minutes after the patient has swallowed.	1
Total		9

ACR-EULAR = American College of Rheumatology – European League against Rheumatism. The diagnosis of Sjögren's syndrome is made as of a score of 4. These criteria apply for patients who have at least one symptom of xerophthalmia or xerostomia or systemic manifestations.

Unfortunately, according to the criteria of the American-European Consensus Group, sialendoscopy has not been included as recommended examination to assess the involvement of the salivary glands in Sjögren's syndrome. Also here, there are historic reasons for its exclusion: the revised AECG criteria were established in 2002 while sialendoscopy is a relatively new procedure and at that time it had not been globally distributed. This technique allows endoscopic transluminal visualization and provides a mechanism for diagnostics and treatment. Inflammatory as well as obstructive pathologies in the context of the ductal system can be detected. This contributes to the identification of ductal anomalies in Sjögren's syndrome [81].

Pathophysiology is currently based on a viral activation of the mucosal epithelium leading to the production of autoantibodies which leads to the production of interferon alpha. The increased expression of genes that are related to interferon (type I or type II) can be confirmed in the salivary glands [82, 83].

The treatment of the disease is performed symptomatically with anticholinergics (pilocarpine), cyclosporine eye drops, analgesics, and by dentists for prophylaxis and treatment of caries that has been triggered by xerostomia. Up to now, no benefit of specific immunotherapy could be confirmed [84].

ENT specialists play a crucial role in the follow-up of these patients because patients with Sjögren's syndrome have a 15–20 fold risk to acquire B cell lymphoma. These are mainly Non-Hodgkin lymphomas. It is important for ENT specialists to know that lymphomas often develop in the organ where Sjögren's syndrome became active for the first time, i. e. frequently in the salivary glands. Hence, these are generally mucosa-associated lymphatic tissue (MALT) lymphomas [85]. Risk factors for the development of MALT lymphomas are recurrent swellings of the parotid gland, splenomegaly, purpura, positive rheumatoid factors, cryoglobulinemia, reduced C4 and CD4 T cell levels, germ cell mutations, increased mononuclear cell infiltrates in the lower lip biopsy. Patients with this risk profile should undergo controls every 6 months [79]. Here a very close cooperation between rheumatologists and ENT specialists is required because imaging of the salivary glands by means of ultrasound and MRI if required. Strict ultrasound characteristics, however, have not yet been described. In cases of salivary gland manifestation, the ENT specialist confirms the diagnosis by targeted lymph node resection in preserving extracapsular technique.

2.3.2.1.2 IgG4-associated sialadenitis in the form of Mikulicz's syndrome and Küttner's tumor

IgG4-associated diseases rank second regarding the manifestation in the head and neck after pancreas and some pseudotumoral diseases of unknown pathogenesis. In the last ten years, Mikulicz's syndrome and Küttner's tumor were classified as IgG4-associated diseases [86]. The identification of IgG4-positive plasma cells in the context of Mikulicz's syndrome as well as Küttner's tumor led to renewed interest in these diseases and to reclassification of inflammatory salivary gland diseases based on immunological analyses [87].

The salivary gland disease identified in 1896 by Küttner [88] usually concerns one or both submandibular glands that present clinically as solid tumor-like masses with tendency to nodular swelling that may easily be confused with malignant tumors. The disease is often associated with microlithiasis. Histological cuts show the preservation of the lobular architecture, severe lymphoplasmatic inflammation, large irregular lymphoid follicles with increased germ centers and acinar atrophy without conspicuous lymphoepithelial lesions. Characteristically, a severe cellular interlobular fibrosis is observed due to activated fibroblasts and an infiltration of lymphocytes and IgG4-positively stained plasma cells [87].

Also the description of Mikulicz's syndrome originates from the end of the 19th century performed by Freiherr von Mikulicz-Radecki [89]. He was the first to describe an idiopathic, bilateral, painless, symmetric, and persisting swelling of the lacrimal glands, the parotid glands, and the submandibular glands. Since Mikulicz's syndrome and Sjögren's syndrome are histologically similar, Mikulicz's syndrome was considered as subtype of Sjögren's syndrome for a long time. In the context of hematoxylin eosin staining, salivary gland tissue showed an infiltration of mononuclear cells and lymphoid follicles around the ductal and acinar cells in Mikulicz's syndrome. The differentiation of Sjögren's syndrome was only possibly by the detection of numerous IgG4-positive plasma cells in the neighborhood of acinar and ductal cells in Mikulicz's syndrome in contrast to Sjögren's syndrome [90]. The presence of IgG4-positive plasma in the inflammatory infiltration of salivary gland tissue allows the assumption that Mikulicz's syndrome and also Küttner's tumor are only 2 different phenotypes of an IgG4-associated disease [81]. Thus the terms of Mikulicz's syndrome and Küttner's tumor must be considered as historical.

Currently, it is assumed that IgG4-associated disease mainly concerns males of mean age who have persisting swellings of the parotid gland and/or the submandibular glands on one or both sides. Clinically, only 30 % of the cases suffer from xerostomia. Frequent accompanying symptoms (in 70 % of the cases) are the involvement of lacrimal ducts, sinonasal disorders, and cervical lymphadenopathy [91].

Ultrasound is the primary imaging procedure for diagnosis. The disorder formerly known as Küttner's tumor often reveals a nodular pattern with dilated ducts and microlithiasis [87]. The diagnosis is made by histology of a biopsy of the major salivary glands [81]. Laboratory tests confirm the diagnosis and show increased IgG, IgG2, IgG4, and IgE levels. A serum IgG4 concentration of more than 135 mg/dl is considered as threshold for the diagnosis [92].

In the literature, only very few publications are available that deal with the treatment of IgG4-associated diseases. Most authors report about systemic steroid therapy as primary treatment. Prednisolone is the most frequently applied pharmaceutic. Long-term treatment with glucocorticoids seems to significantly improve the symptoms in the context of reduced saliva secretion which according to some trials even leads to the restoration of histological anomalies. The role of other immunosuppressant such as azathioprine or methotrexate is not yet clarified [81, 92, 93].

2.3.2.1.3 Sarcoidosis

Sarcoidosis is a multisystemic disease of unknown origin that is characterized by the formation of immunogranulomas in the affected organs. It is a disease that mainly affects 20–40-year-old people. According to the prevailing hypothesis, different, not yet identified antigens – either infectious or environmental – may trigger an excessive immune reaction with complaints in genetically prone hosts [94]. The lung is most frequently affected (90 %) [95], but theoreti-

cally the disease may concern every organ. The salivary glands are involved in 5–10 % of the cases [58]. Hereby, 3 clinical manifestations are observed: (1) The most frequent manifestation is accompanied by swellings of the major salivary glands and the histological confirmation of non-caseating granulomas. Also in the minor salivary glands, these granulomas are found. The patients suffer from xerostomia that is proportional to the extent of granulomatous infiltration. (2) In the second type, swellings of the salivary glands are absent. Nonetheless, the non-caseating granulomas are located at the hard palate in up to 38 % of the cases and in the lower lip in 58 % of the cases. (3) The third manifestation is Heerfordt syndrome with swelling of the parotid glands, uveitis, and facial palsy. These findings may appear with different severity and can occur also unilaterally [96, 97].

Because of numerous other origins of salivary gland swellings, the diagnosis is a real challenge. There are no specific laboratory tests and no characteristic imaging findings. The diagnosis is based only on the clinical appearance which is confirmed by the histological proof of non-caseating granulomas. Teymoortash and Werner [98] investigated 6 cases of parotid sarcoidosis with regard to their sonographic findings. All cases showed enlarged glands and otherwise unspecific multiple echogenic septa, echo-free foci, or anechoic areas in the glandular margins. The unspecifity of the findings could also be confirmed by other authors from German-speaking countries [99, 100]. Only in the context of Heerfordt syndrome, ultrasound revealed an echoic structure that is penetrated by numerous increased lymph nodes of according anechoic areas [16]. MRI shows a homogeneous enhancement in the T2 weighting.

Salivary gland biopsy reveals caseating granulomas, not least to exclude differential diagnoses such as neoplasms and other granulomatous diseases.

The treatment of parotid sarcoidosis is performed in an individualized way with drugs. Hereby, corticosteroids are mostly applied. The basic approach should be to find the lowest possible dose of cortisone. Some alternative pharmaceutics such as azathioprine, chloroquine, methotrexate, pentoxifylline, cyclophosphamide, tetracycline derivatives, and infliximab may be used in cases of refractory diseases or as corticoid-avoiding alternatives. Isolated alterations of the parotid gland may also be removed with preservation of the facial nerve. If no other symptoms of the disease are present, pharmacotherapy is not needed. In some patients, spontaneous healing is observed [101]. Due to the rarity of the salivary gland manifestation of sarcoidosis, only few data are available regarding the rate of spontaneous remissions. For most patients, the prognosis is considered as very favorable. The severest and most common complication of sarcoidosis is the development of pulmonary fibrosis in combination with pulmonary hypertonia [102]. So the treatment should always include internal medicine as interdisciplinary approach.

2.3.2.2 Kimura's disease

Kimura's disease occurs very rarely in Europe and America and is a chronic inflammatory disease with endemic character in Asia. It is characterized by severe lymphocytic and eosinophilic infiltration of the subcutaneous fatty tissue and manifests mainly in the area of the salivary glands [103]. The therapy consists either of surgical resection or a treatment attempt with corticosteroids. However, after both treatment approaches recurrences may occur [104].

2.3.2.3 Rosai-Dorfman disease

Rosai-Dorfman disease is a rare histiocytic proliferative disorder of unknown genesis. If was first described by Rosai and Dorfman in 1969 [105]. Clinico-pathologically it presents as sinus histiocytosis with massive lymphadenopathy and increased salivary glands. In most cases, it is a painless cervical lymphadenopathy. The second most frequent manifestation outside the cervical lymph nodes are the major salivary glands [106]. The difficulty of diagnosing the disease consist of differentiating them from other glandular swellings. This may be performed by histology after biopsy. But also for pathologists, this disease is a challenge. The difference must be made between Rosai-Dorfman histiocytes, Langerhans cell histiocytes, and normal sinus histiocytes. The first two can only be identified by expression of the S100 protein in contrast to normal sinus histocytes. Langerhans cell histiocytes are CD1 negative [107]. Most patients are young (mean age of disease onset: 20.6 years). Males are slightly more frequently affected than females. In general, Rosai-Dorfman disease has a long-term clinical course that is characterized by alternating exacerbations and remissions. Finally, most patients experience complete remission unless a predisposition for other immunological diseases are present [108].

2.4 Rare sialadenoses

Sialadenoses are non-inflammatory, non-neoplasmatic, parenchymatous diseases of the salivary glands that are based on metabolic and secretory disorders of the glandular parenchyma [109]. They only receive little attention, however, they lead to important impairment of the quality of life and thus they will be discussed in the context of this article.

2.4.1 Endocrine sialadenoses

2.4.1.1 Diabetes mellitus

Several epidemiological trials could show that salivary secretory disorders are frequently observed in diabetes mellitus patients [110]. Both types of diabetes mellitus (I and II) are concerned [111, 112]. These salivary secretory disorders might be associated with a poor quality of life and increase the proneness to caries and oral infections in diabetes mellitus patients, especially in cases of dehydration and insufficient blood glucose controls [110]. Xerostomia as well as reduced basal and postprandial saliva secretion result [113]. Prolonged hyperglycemia that is characteristic for diabetes mellitus may not only cause systemic alterations but also change the function of the salivary glands as well as disturb the composition and volume of the secreted saliva [114].

2.4.1.2 Functional disorders of the thyroid gland

Only little literature and research is available regarding the effect of thyroid gland diseases on the salivary glands. Animal trials could reveal that hyperthyreosis leads to an increased size and number of tubuli in the submandibular gland of rats and a reduced prevalence of dental caries, whereas hypothyreosis leads to significant atrophy of the submandibular salivary glands together with increased dental caries [115]. Muralidharan et al. could show in an Indian cohort that hypothyreosis leads to reduced salivary secretion rates. The prevalence of hyposalivation was lower compared to di-

abetes mellitus. The salivary flow rates improved after treatment of hypothyreosis [116].

2.4.2 Metabolic sialadenoses

Malnutrition and eating disorders have an impact on the function and size of the salivary glands. Psoter et al. could reveal in Haitian children that early postnatal malnutrition leads to reduced basal and postprandial saliva flow even after years (n = 1017) [117]. Bulimic patients with anorexia nervosa often have salivary gland swellings. Since these patients often negate or do not spontaneously admit their eating disorder, history taking is difficult and in some cases, the bilateral swellings of the major salivary glands is the only visibly symptom [118]. The origin of the glandular swellings is unclear, trophic stimulation of the glands due to a pancreatic stimulus is assumed or an enzymatic secretory disorder that is associated with a dysfunction of the autonomous neural system [119, 120]. In cases of unclear, non-inflammatory bilateral salivary gland swellings, also bulimic eating disorder has to be taken into consideration. The swellings of the salivary glands are verified by ultrasound or MRI. Blood values such as reduced serum potassium content, increased bicarbonate and amylase may give further hints. The treatment consists of psychotherapy and accompanying pilocarpine, if required. The bilateral lateral parotidectomy for esthetic and psychological reasons is controversially discussed [121].

2.4.3 Drug-related sialadenoses

The salivary glands are controlled by the autonomous neural system, mainly the parasympathetic part. The function of the salivary glands can be impaired by a multitude of drugs that cause xerostomia, sialorrhea, or glandular swellings and pains. While xerostomia and sialorrhea are frequently observed side effects of drugs, the authors will discuss here the rarer painful glandular swellings. ▶ **Table 2** lists drugs that may cause glandular swellings. It is assumed that it is the case of hypersensitivity reactions [122].

2.5 Rare obstructive diseases

Obstructive sialadenitis makes up about half of all benign glandular diseases. In 80–90 %, the obstructions concern the submandibular gland and in 5–10 % the parotid gland. Possible causes are sialolithiasis, stenoses, mucosal retentions, polyps, foreign bodies, external compression, or anatomical variations of the ductal systems. The most frequent origin with 60 % of all obstructions is sialolithiasis [123]. The incidence amounts to about 6:100,000. In the following chapters, rare obstructive diseases that are not related to sialoliths will be described.

▶ **Table 2** Medication with painful side effects of salivary gland swelling.

Catecholamin inhalates	Naproxen
Cholrhexidin	Nifedipin
Cimetidin	Pheytoin
Clonidin	Ranitidin
Jodine	Sulfanomide
Methyldopa	Trimipramin

2.5.1 Stenoses and strictures of the salivary duct

10–15 % of all obstructive diseases are stenoses. They lead to obstruction with reduced salivary flow, infection of the ascending duct, and the development of mucous or fibrinous plaques. Ductal wall alterations, in particular strictures, are the consequence. Strictures often concern the parotid ducts and typically occur in the 4th, 5th, and 6th decade of life, especially in females. They develop secondarily after eosinophilic inflammation of the salivary glands and occur alone or as multiple findings [124]. In the obstructed ducts, mucous and fibrin accumulate. Mucous may be the organic matrix for later stone formation. Stenoses and strictures cannot be easily differentiated from sialolithiasis. They also lead to swellings of the major salivary glands and often the diagnosis cannot be made by usual radiological means or even high-resolution ultrasound [125]. By means of ultrasound indirect signs of a stricture can be detected that consists of ductal enlargement without indication of sialolithiasis. If correctly performed, ultrasound is cost-effective, rapid, non-invasive, and highly-predictive diagnostic tool. The quality of the diagnosis, however, depends on the experience of the examiner. Alternatively, sialography has been established in many centers as gold standard with high success rates [126–128]. The main advantage of sialography compared to ultrasound is that the number and also the length of the strictures can be determined appropriately. In comparison to ultrasound, however, it is an invasive procedure that is associated with radiation exposure, possible allergic reactions because of the application of contrast agents, and additional costs. An alternative to conventional sialography is MR sialography. With this measure, stenoses may be visualized and the condition of the glandular function is revealed [129]. This technique is based on the principles of MR hydrography where strongly T2-weighted (T2W) pulse sequences are used in order to display a static liquid. The advantage of MR hydrography is its non-invasive nature. The salivary flow is stimulated by means of citric acid. Neither contrast agent nor radiation exposure nor an experienced examiner are required. The disadvantage is the lower spatial resolution [130]. If adequately performed, ultrasound as well as sialography are valuable instruments for the diagnosis of ductal stenoses and strictures of the major salivary glands [131].

Since the implementation of sialendoscopy in the early 1990ies [132], it was established as diagnostic and therapeutic gold standard of salivary gland diseases [133–135]. Sialendoscopy may confirm the diagnosis and characterize the disorder. During the same session, also the treatment may be performed. Koch et al. describe that endoscopically controlled anti-inflammatory treatment improved the symptoms of parotid strictures and the progress of the disease in 17.9 % of their patients. In their patient cohort, the interventional sialendoscopy was effective in 75.8 % regarding the dilatation of the strictures of Stenon's duct; and 56.4 % of all patients were successfully treated in the single-mode procedure [131]. If the treatment fails, surgical procedure is recommended. In cases of distal stenoses, a dilated neoostium should be created by reinserting Stenon's duct and suturing it with the buccal mucosa. An additional stent can be helpful for temporary splinting. Thus, parotidectomy is reserved for only few cases (< 6 %) as ultima ratio [131,136].

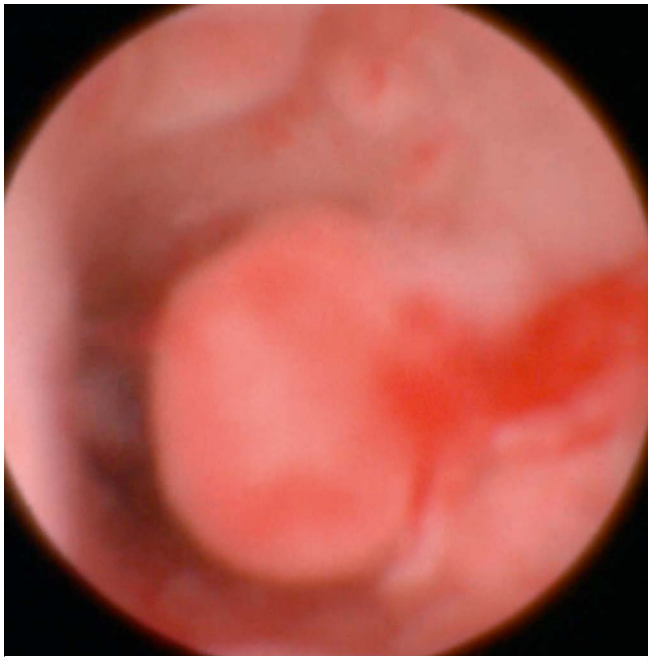
Due to the rare occurrence, there are only very few extensive reports about the diagnosis and treatment of submandibular ste-

noses [124, 137, 138]. Because of the long course of the duct in the floor of the mouth, the length and extent of the stenosis play a crucial role regarding the choice of the treatment method [124, 138]. Regarding stenoses in the distal part of the duct, the transoral slotting and marsupialization are the method of choice. In more centrally and posthiliary located stenoses, the interventional sialendoscopy is a very important method. Based on endoscopic procedures, freedom of symptoms may be achieved in 80–90 % of the patients [126, 139]. In patients with accompanying inflammatory reactions, the intraductal rinsing with cortisone can be successfully applied [137]. In single cases, treatment success was also described for sialography-controlled balloon dilatation. This procedure has the disadvantage that only indirect visualization of the stenosis is possible, radiation exposure occurs and the risk of reaction on contrast agent exists [140]. Submandibulectomy is thus reserved only to diffuse and extensive stenoses or to cases where conservative treatment options have failed [137, 139].

2.5.2 Inflammations of the salivary duct and other rare obstructions

Inflammations of the salivary duct (sialodochitis) are a particular and early type of ductal stenosis. They make up about 5–10 % of all obstructions. Edematous alterations of the wall structure are found. The ductal system is obstructed by serous mucous and plaques. In the secretion of the inflamed glands, a clearly increased number of eosinophilic cells is observed [125]. Sialodochitis mainly affects the parotid gland. The therapy of choice is the mechanical removal of mucous and plaques via an endoscopic intervention. In this context, the additional intraductal application of cortisone is essential [131, 134].

Obstructions caused by anatomical variations or foreign bodies occur in only 1–5 % of all cases. They may include severe kinks, sail-like retractions of the duct system or polyps of the ductal wall (▶ **Fig. 1**). Also these pathologies lead to salivary congestion with subsequent recurrent inflammations [141]. Here, the endoscopic interventional treatment provides the possibility to extract the obstructing structures [142, 143].



▶ **Fig. 1** Sialendoscopic view into Stenon's duct with a large mucosal polyp originating from the lateral wall.

2.6 Rare salivary gland tumors

2.6.1 Benign tumors

Benign tumors of the salivary glands have an incidence of about 6:100 000 people. The most frequently occurring benignomas are pleomorphic adenomas (70–94 %) and Warthin's tumor (25 %) [144]. In the following paragraphs, rare but clinically relevant lesions will be discussed.

2.6.1.1 Basal cell adenomas

Basal cell adenomas are rare benign monomorphic salivary gland tumors and mainly occur in the parotid gland. The differentiation regarding basal cell adenocarcinoma is difficult. The basal cell adenoma represents 54 % of all monomorphic adenomas and 1–3 % of the tumors of the major salivary glands. The age of disease onset is higher with 50–70 years compared to most benign tumors. Histologically, 4 types are differentiated, solid, trabecular, tubular, and membranous lesions. Clinically, the tumors present as smoothly delimited, well movable, and elastic masses. The therapy consists of surgical removal in the sense of lateral or in rare cases also complete parotidectomy. Malignant degenerations are very rare [145, 146]. Recurrences of basal cell adenomas are rare except the membranous subtype for which reports exists that it re-appears in up to 25 % of the cases [147].

2.6.1.2 Lipomas

Lipomas of the salivary glands are rare (< 0.5 %) and usually concern the parotid gland. They are well circumscribed and are called sialolipomas when they have an intratumoral ductal component. The oncocytic lipoadenoma seems to be a characteristic subtype of sialolipoma with oncocytes and sebaceous residues. They show a high signal intensity on T1-weighted MRI while the signal on T2-weighted images decreases. The treatment consists of simple resection. Up to now, recurrences have not been reported [148].

2.6.1.3 Oncocytomas and nodular hyperplasias

Oncocytomas are mainly tumors that develop in women of middle age and older. The parotid gland is the most frequently observed location (80 %). Oncocytomas may also develop in numerous other organs. The tumors are slowly growing and sometimes develop on both sides. The term of oncocytoma is based on the histological layered structure of oncocytes. Pathogenetically, a mitochondrial dysfunction is found that leads to degeneration of the epithelial glandular cells. Malignant degeneration to oncocytic carcinoma is possible. The treatment consists of surgical resection.

Since 2017, the nodular oncocytic hyperplasia is an independent lesion related with oncocytomas. In contrast to the oncocytoma, these lesions do not present as solitary delineable mass but as lesion consisting of multiple oncocytic nodules. Often they are

diagnosed accidentally and there is no tendency regarding malignant degeneration [149, 150].

2.6.1.4 Sclerotic polycystic adenomas

Sclerotic polycystic adenosis is a rare disease of the salivary glands with histological characteristics that are similar to fibrinous-cystic changes of the mammary gland. The lesion often develops bilaterally in the parotid glands. Clinically, a well delimited mass with nodular structure is found. Mainly women of higher ages are affected. Pathologically, this disease may be confused with pleomorphic adenoma or invasive carcinoma. Recurrences were described in up to 19 % and may develop even more than 20 years later. Probably, incomplete resection or multifocal occurrence is responsible for recurrent lesions. Up to now, no hint for malignant degeneration is reported [146, 149].

2.6.1.5 Mesenchymal tumors

Primary benign soft tissue tumors of the head and neck are relatively rare. Most of them are not characteristic for this region even if they occur frequently but rarely in the head and neck and especially in the salivary glands [151]. Most reported cases were case reports or small case series. They include leiomyomas, rhabdomyomas, or myoepitheliomas.

Leiomyomas belong to the benign mesenchymal tumors. They consist of smooth muscle cells and mainly occur in the uterus. The head and neck region is concerned in 8–13 % whereas the salivary glands are affected in less than 1 % of the cases [152–154]. Leiomyomas grow slowly and have a low degeneration rate. Thus, a complete resection should be intended only in cases of according clinical appearance and after weighing the surgical risks [152].

Rhabdomyomas are benign mesenchymal tumors with skeletal muscle differentiation. Topographically, the difference is made between cardiac and extracardiac types. The extracardiac rhabdomyomas are classified into adult, fetal, and genital subtypes. Adult extracardiac rhabdomyomas may also affect the head and neck area. They occur predominantly in older people with a predilection in males [155]. Manifestations in the area of the minor salivary glands, the sublingual gland, and the submandibular gland have been described [156–159]. Due to the high local recurrence rate (up to 42 %), a complete excision is recommended. Malignant degeneration has not been reported up to now [160].

Benign myoepitheliomas are a rare type of salivary gland tumors that completely consists of myoepithelial cells [161]. They make up less than 1 % of all salivary gland tumors and are most frequently found in the parotid gland (40 %) and the minor salivary glands of the hard palate (21 %). Malignant transformation is rare, and is often preceded by longer clinical courses with several recurrences of the benign type. In contrast to benign lesions, the malignant type has an infiltrative growth pattern [151]. The prognosis for myoepitheliomas of the salivary glands is favorable. The treatment consists of surgical resection. Due to the high local recurrence rate, patients undergo regular follow-up [161].

2.6.1.6 Vascular formations in the area of the parotid gland

Rarely, swellings in the area of the parotid gland may be caused by vascular formations such as aneurysm or pseudo-aneurysm of the external carotid artery or its branches. In older patients, the origin is mostly arteriosclerosis. In younger people, the most frequent origin is a trauma, more rarely also connective tissue diseases or vasculitis [162]. In cases of pseudo-aneurysm, nearly exclusively traumatic lesions are responsible [163]. Clinically, they are often confused with parotid tumors. Imaging by means of sonography or ultrasound reveals an inconspicuous gland displaced externally, mostly caused by a medially located mass. In the literature, case reports of aneurysms and pseudo-aneurysms of the internal and external carotid arteries and their branches are described that become apparent due to a unilateral swelling in the jaw angle [162, 164–166]. Interestingly, also 2 cases have been reported where aneurysm of the superficial temporal artery after parotidectomy has developed [167, 168]. Aneurysms with involvement of the external carotid artery and their off-branching vessels are rare and make up 0.4–4 % of all aneurysms [165]. Sonographically, a highly vascularized mass is revealed. In the Doppler sonography, the partly thrombosed aneurysm shows a two-color image due to circulating blood in the aneurysm. The blood flows in direction of the transducer and away from it. Thus the red and blue color coding are directly adjacent in the area of the aneurysm ("yin-yang sign"). Further imaging consist of CT scan, MRI, or angiography [167]. Differential diagnostics have to take into account kinking and coiling of the internal carotid artery, lymphadenopathy, glomus tumors, neurinomas, or lymphangiomas [162]. Also arteriovenous fistulas must be excluded by differential diagnosis and may occur together with aneurysms or pseudoaneurysms [169]. Therapeutically, wait-and-see strategy is applied in older asymptomatic patients. Further treatment options are the embolization or the surgical removal. Since a swelling in the area of the parotid gland mostly leads the patients to seek advice of ENT specialists, otolaryngologists should be aware of the manifold possible origins that partly also include these life-threatening diseases.

2.6.1.7 Metastatic pleomorphic adenoma

Metastatic pleomorphic adenomas occur after several local recurrences of pleomorphic adenomas and typically extend to the lung and the bones. The phenomenon has already been described in the 1940ies. It may be assumed that metastasis develops due to hematological tumor dissemination with repeated resections in the area. The metastases may develop even up to 22 years later. 20 % of the patients die of this disease [170].

Because of the infiltrative and metastatic growth it was formerly classified as malignant tumor. The current reclassification of the WHO is primarily based on the histological appearance and secondarily on the biological behavior. Histologically, the metastatic pleomorphic adenoma corresponds "only" to pleomorphic adenoma and has to be differentiated histologically from a carcinoma ex pleomorphic adenoma [171]. Thus, it was excluded from the category of malignant neoplasm and classified as benign epithelial tumor [171, 172]. It is necessary to wait if this classification can be confirmed with consideration of the aggressive nature of the tumor.

2.6.2 Malignant tumors

Despite their extreme rarity, salivary gland neoplasm have a high variety that is unparalleled in comparison to other organs. Based on the "Surveillance, Epidemiology, and End Results" (SEER) regis-

try, a slight increase of primary salivary gland carcinomas of 1.1 to 1.3 per 100 000 people is observed with regard to the epidemiology from 1975 to 2015. The ratio of males and females amounts to 1.6:1. The incidence increases after the 50th year of life to more than 7 cases per 100 000 people at the age of 70 years [173]. In the clinical practice, the following 5 carcinomas have a certain incidence: mucoepidermoid carcinomas (20 %), adenoidcystic carcinomas (16 %), carcinoma ex pleomorphic adenoma (12 %), acinar carcinoma (10 %) [174, 175]. These carcinomas will be considered in this article only with regard to their molecular genetics and transforming significance. In the following, those rare salivary gland carcinomas have been selected from the multitude of salivary gland tumors that have a relevant clinical importance.

2.6.2.1 Epithelial-myoepithelial carcinoma

The epithelial-myoepithelial carcinoma is a rare malignancy of the salivary glands and makes up about 1 % of all salivary gland carcinomas [176]. The entity is significant because it may easily be confused with the highly malignant adenoid cystic carcinoma. Both carcinomas show a biphasic pattern with clear myoepithelial cells that include salivary ducts with an epithelial lining. However, they are clearly different with regard to their growth pattern and their prognosis. The classic epithelial-myoepithelial carcinoma is a low-grade carcinoma with good prognosis while the prognosis for adenoid cystic carcinoma is poor. Rarely, intermediate or high-grade carcinomas develop. The difference to the more aggressive adenoid cystic carcinoma is only possible by molecular genetics by means of the identification of a MYB-NIF fusion that occurs only in adenoid cystic carcinoma. Clinically, the epithelial-myoepithelial carcinoma appears most frequently in the parotid gland. Regional and distant metastatic rates are low. The disease-specific survival amounts to more than 90 % for low-grade epithelial-myoepithelial carcinomas [177]. Currently, no standard treatment scheme is available. The surgical resection is the therapy of choice. Some authors describe an adjuvant radiotherapy with 60 Gy/30 fractions for intermediate or high-grade variants [178–180].

2.6.2.2 Adenocarcinomas not otherwise specified (NOS)

Until 2005, the adenocarcinoma NOS was one of the most frequent salivary gland malignancies [181]. Currently it occurs more rarely because many tumors with cribriform to micropapillary differentiation and often positivity for androgen receptors and for HER2/neu are now classified as salivary duct carcinomas. Due to the progress in molecular genetics (see below), nowadays several tumors can be correctly classified and are excluded from the NOS category. On the other hand, the current classification classifies entities that were independent up to then such as cystadenocarcinoma, mucinous adenocarcinoma, and intestinal adenocarcinoma as adenocarcinomas NOS [149]. The survival mainly depends on the histological grading. In comparison to low-grade carcinomas, high-grade adenocarcinomas NOS have a poor prognosis with a very high rate of lymph node metastases (> 40 %) and distant metastases (> 40 %). Hereby, a postoperative radiotherapy with 64–66 Gy, 2Gy/d after surgical resection improved the survival rate [182].

2.6.2.3 Salivary duct carcinomas

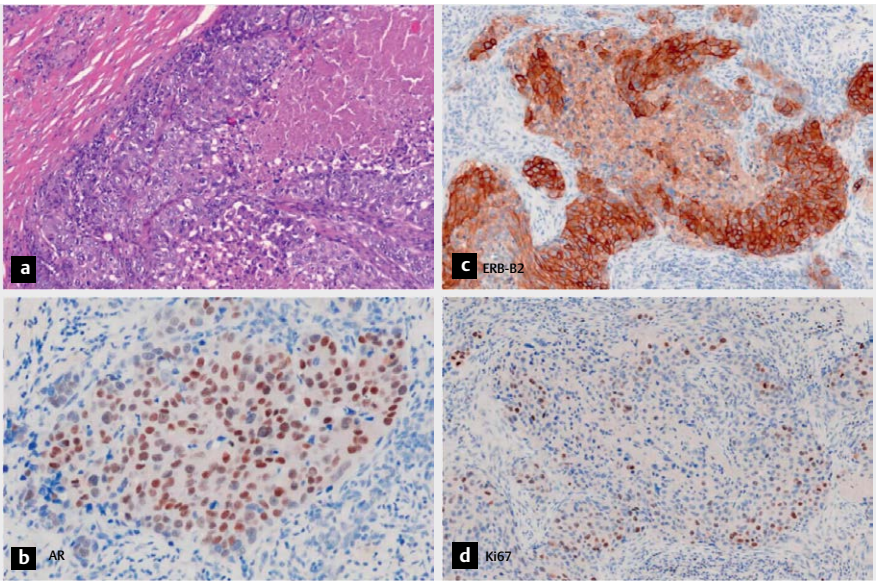
Salivary duct carcinomas are considered as highly aggressive tumors among salivary gland carcinomas because most patients do not live longer than 3 years after diagnosis [183]. It is a rare carcinoma which was first described as salivary gland malignoma in 1968 by Kleinsasser that is histologically similar to lactiferous duct carcinoma of the breast [184]. The incidence amounts to 1.8–6 % of all salivary gland carcinomas [185, 186]. The majority expresses androgen receptors. The identification of these receptors can be crucial for the differentiation with other tumor entities [187]. It occurs more frequently in the parotid gland than in the submandibular or minor salivary glands. Early regional lymph node metastasis, the development of distant metastases as well as a high recurrence rate are characteristic. This also explains the aggressive treatment approach with tumor resection in the sense of complete parotidectomy and frequent resection of the facial nerve (40–73 %) in order to achieve an oncologically perfect R0 situation [181, 188]. Since the risk of occult metastasis amounts to 24 %, elective neck dissection is recommended also in cN0 necks [189]. In most described case series, adjuvant irradiation is performed. Beside the identification of androgen receptors, also the HER2/neu receptor expression is an independent prognostic factor for a reduced disease-specific and distant-metastases-free survival (▶ **Fig. 2**). Hence, beside radiotherapy also initial treatment schemes with target therapy or antiandrogen therapy adapted to the receptor status should be evaluated [190].

2.6.2.4 (Mamma-analogous) secretory carcinomas

In 2010, Skalova et al. were the first to describe the secretory carcinoma [191]. In 2017, it was officially included in the WHO classification [192]. Comparable to the salivary duct carcinoma, also this carcinoma is similar to mamma carcinomas (secretory juvenile mamma carcinoma). Formerly, these carcinomas were classified as acinar cell carcinomas or adenocarcinomas NOS. The secretory mamma carcinoma and the secretory salivary gland carcinoma both have the ETV6-NTRK3 gene fusion. Regarding this similarity and in order to standardize the nomenclature beyond the organ locations, the official term for this entity also in the salivary glands is now simply “secretory carcinoma” [171]. Typically, secretory carcinomas are rather indolent such as the acinar cell carcinoma. However, a slightly higher lymph node metastatic rate (up to 25 %) can be observed compared to true acinar cell carcinoma [193]. The prognostic characteristics include the tumor stage and the high-grade transformation (see below). The increasing application of selective tyrosine kinase inhibitors might be therapeutically relevant for advanced stages of secretory carcinomas [194].

2.6.2.5 High-grade transforming tumors

High-grade transformation is the preferred terminology (in contrast to de-differentiation) for the progress of a usually low-grade carcinoma to a high-grade carcinoma [195]. The tumors for which this phenomenon is well characterized includes acinar cell carcinomas, adenoid cystic carcinomas, rarely mucoepidermoid carcinomas, epithelial-myoepithelial carcinomas, secretory carcinomas, and polymorphic (formerly: low-grade) adenocarcinoma. This was the reason to no longer use the term of “low-grade” in the context of polymorphic adenocarcinoma. Tumors with high-grade trans-



▶ **Fig. 2** Salivary duct carcinoma. Courtesy of Prof. Alexander Marx, University Hospital of Mannheim. **a** HE staining with typical commedo necrosis (original amplification x25). **b** salivary duct carcinoma with nuclear expression of the androgen receptor (IHC; original amplification x150). **c** ERB-B2 (= HER2/neu) expression with characteristic complete membrane pattern (IHC; original amplification x200). **d** Ki67 staining (IHC; original amplification x150).

formation can mimic salivary duct carcinomas, and in fact most non-apocrine androgen receptor-negative salivary duct carcinomas are actually unidentified high-grade transformations of another tumor type [196].

2.6.2.6 Translocations and gene fusions

Due to the increasing clinical significance, the new paradigm of translocations and gene fusions that often occur in salivary gland tumors will be intensively discussed. ▶ **Table 3** gives an overview. In many cases, molecular changes, especially fusion genes, are important to find the diagnosis. In this way, the suffix of "not otherwise specified" could be effectively removed from several adenocarcinomas and the salivary gland tumor could be classified in the correct entity. Thus, the group of adenocarcinomas NOS is continuously decreasing.

The mucoepidermoid carcinoma has the clinically most relevant translocation in which the genes *MAML2* and *CRTC1* or *CRTC3* are involved. The presence of a *MAML2* translocation is prognostically most relevant because it correlates with the prognosis and the tumor stage. Tumors with this translocation are less aggressive and mostly low-malignant. This may play an important role for the decision in favor or against adjuvant therapy after surgical tumor resection [197].

In the context of secretory carcinoma, it was possible to differentiate them from acinar cell carcinoma or adenocarcinoma NOS by the discovery of t(12;15)(p13;q25) chromosomal translocaton with ETV6-NTRK3 fusion. Furthermore, the ETV6-NTRK3 fusion codes for a tyrosine kinase that might be used as therapeutic approach [198].

Also several hyaline clear cell carcinomas have formerly been classified as adenocarcinomas NOS. Most clear cell carcinomas have a t(12;22)(q13;q12) chromosomal translocation which leads to the fusion of EWSR1 and ATF1 genes. Thus, this entity can be more easily be classified. This is of high clinical relevance because clear cell carcinomas tend more frequently to the development of bone and nerve infiltrations compared to other salivary gland carcinomas [199].

▶ **Table 3** Most important genomic alteration in salivary gland tumors.

Pleomorphic adenoma	PLAG 1 fusion
	HMGA2 fusion
Carcinoma ex pleomorphic adenoma	PLAG1 fusion
	HMGA2 fusion
Adenoid cystic carcinoma	MYB-NIFB
Mucoepidermoid carcinoma	CRTC1-MAML2
	CRTC2-MAML2
Salivary duct carcinoma	TP53 mutation
	ERB2 amplification
	PIK3CA mutation
Clear cell carcinoma	EWSR1-ATF1
Secretory carcinoma	ETV6-NTRK3

The adenoid cystic carcinoma is characterized by slow highly infiltrative growth with a tendency to perineural invasion and by the t(6;9)(q22–23;p23–24) translocation with MYB-NIFB fusion. It could not be consistently shown that the MYB status correlates with the prognosis or other clinically-pathological characteristics but the detection is considered as strong marker in the routinely performed diagnostics of salivary gland tumors for which the differential diagnosis of adenoid cystic carcinoma must be taken into account [200, 201].

Similar to ductal breast cancer, also the salivary duct carcinoma is characterized by the nearly uniform expression of the androgen receptor. The identification of the androgen receptor expression contributes to the differential diagnosis with regard to other high-grade carcinomas. Additional frequently occurring molecular alterations are mutations in TP53, PIC3CA, and HRAS. Another similarity to ductal breast cancer includes HER2 (ERBB2) gene amplification that only occurs in up to 20–30 %. Both receptor expressions (androgen and HER2 receptor) gain in importance due to the targeted application of antibodies (target therapy with bicalutamide or trastuzumab). The treatment with an anti-HER2 therapy in combination with an antiandrogen therapy and radio(chemo)therapy led to proven tumor reduction in some patients. In single studies, for example paclitaxel and/or carboplatin were tested in combination with trastuzumab [202, 203]. It is doubted if the reduction of the tumor load was due to the application of chemotherapy in addition to target therapy. Complete remission, however, is also very rare after anti-HER2 therapy. There are hints that additional mutations reduce the effectiveness of the HER2 blockage [202, 204, 205].

2.7 Current trial situation in the context of salivary glands

Since salivary gland diseases are rare entities, trial conduction with adequate numbers of cases is very limited. There are many monocentric studies that are mainly retrospective or have only small case numbers in a prospective approach. Investigations in a multicenter setting would be desirable. In the US National Library of Medicine, currently 285 trials are listed on the topic of salivary glands, among them 66 as multicenter trials. Among the 7 German trials mentioned, none has a multicenter approach. In recent times, oncological salivary gland trials come more and more to the fore. Already regarding the topic of salivary gland oncology, 115 trials are listed. The major part deals with antibody therapy or chemotherapy (81). Hot topics of the trials on malignant salivary gland tumors are the identification of high-risk patients [206], the application of target therapies, and checkpoint inhibitors as well as gene panel analyses. Most promising is the application of the HER2 antibody trastuzumab, either as pure form or as conjugate. Overall response rates of up to 90 % and partly even complete responses could be described [206]. Even if many salivary gland carcinomas are androgen receptor positive, first results of target therapy with an antiandrogen are not very promising (NCT02749903) [207]. Further trials as for example the multicenter EORTC phase 2 study about the effectiveness and safety of chemotherapy (cisplatin + doxorubicin/carboplatin + paclitaxel) versus antiandrogen therapy (bicalutamide + triptorelin) in patients with recurrent and/or metastatic androgen receptor-positive salivary duct carcinoma (EORTC-1206-HN-CG; NCT01969578 [208]) are still in the recruiting phase. Gene panel analyses on salivary gland carcinomas are still in an initial stage so that applicable target structures may be identified but currently this is only possible with significant efforts that do not justify the clinical cost-benefit effect [209]. Checkpoint inhibitors achieve very good response rates in squamous cell carcinomas of the head and neck. In salivary gland carcinomas, the results are rather disillusioning (NCT03132038 [210], NCT03087019 [211], NCT03172624) [212].

2.8 Salivary gland registry

Beside the conduction of trials and meta-analyses, the collection of cases in registries is another possibility, to create large disease cohorts. In his article on the quality of therapy of salivary gland diseases, Guntinas-Lichius emphasizes the existing problems of establishing salivary gland registries and at the same time he describes the enormous chances that are associated with such registries. He illustrates that for example statements on recurrence rates and malignant transformations of pleomorphic adenomas or the incidence of sialoliths could be validly defined due to Dutch and Danish registries because the investigations refer to several thousands of cases (!) [213]. The history of German disease registries is not even 100 years old. The oldest German registry is the cancer registry of Hamburg founded in 1926. It was originally started by the city physician Sieveking for follow-up and supervision and was the first cancer registry of the world. Further regionally limited (cancer) registries followed [214]. Large national disease registries are established in the USA (SEER, NCDB), in Scandinavian countries, and in the Netherlands. Also salivary gland diseases are collected there. More than 100 trials on salivary gland tumors with immense numbers of cases could be developed from the SEER and NCDB data alone. It was possible only with the national structure of the registry to analyze a very high number of cases of such a rare tumor. The investigations could show that this carcinoma that was originally considered having a favorable prognosis may belong to an aggressive subtype (G3, N+, T3/4) for which the 5-year survival is reduced to less than 20 % from otherwise more than 90 % [215]. German pioneers of disease registries were pediatricians. Just for chronic diseases and malformations, more than 20 national registries exist [216]. Furthermore, there are cancer registries. Thus it is apparent that also German ENT departments should be able to establish registry structures that are essential to further develop the therapy of salivary gland diseases.

3 Rare Diseases of the Facial Nerve

The facial nerve is the 7th cranial nerve. The fact that the peripheral anatomical course of the facial nerve runs nearly through the entire ENT area makes it very important for otolaryngologists. It is a multifactorial nerve that contains motor, sensory, secretory, and sensitive fibers. On one hand, due to this ability of “multitasking” the facial nerve is the most important cranial nerve. On the other hand, it bears the risk that accordingly also multifactorial disturbances may occur.

3.1 Identification of rare diseases of the facial nerve

The primary diagnostics should first focus on the clinical appearance and functional testing. Direct diagnostics are not possible due to the long course hidden in the temporal bone. In some lesions, imaging must reveal indirect signs.

Displaying the facial nerve is difficult because of its soft part structure and its small diameter. Ultrasound may only describe it by means of high-resolution techniques. Lo et al. and Tawfik et al. could describe an enlarged diameter of the main trunk of the facial nerve in cases of idiopathic facial nerve palsy in comparison to regular findings [217, 218]. Wegscheider et al. succeeded in dis-

playing not only the main trunk but also the peripheral branches to the ocular orbicular muscle and major zygomatic muscle in cadaver dissections by means of high-resolution ultrasound. Depending on the part of the nerve, different transducers are recommended. A convex 6.6 MHz transducer is optimal for the main trunk. A linear 13 MHz transducer is appropriate for displaying the first bifurcation. With a linear 22 MHz transducer, the endings at the ocular orbicular muscle and the major zygomatic muscle can be described [219]

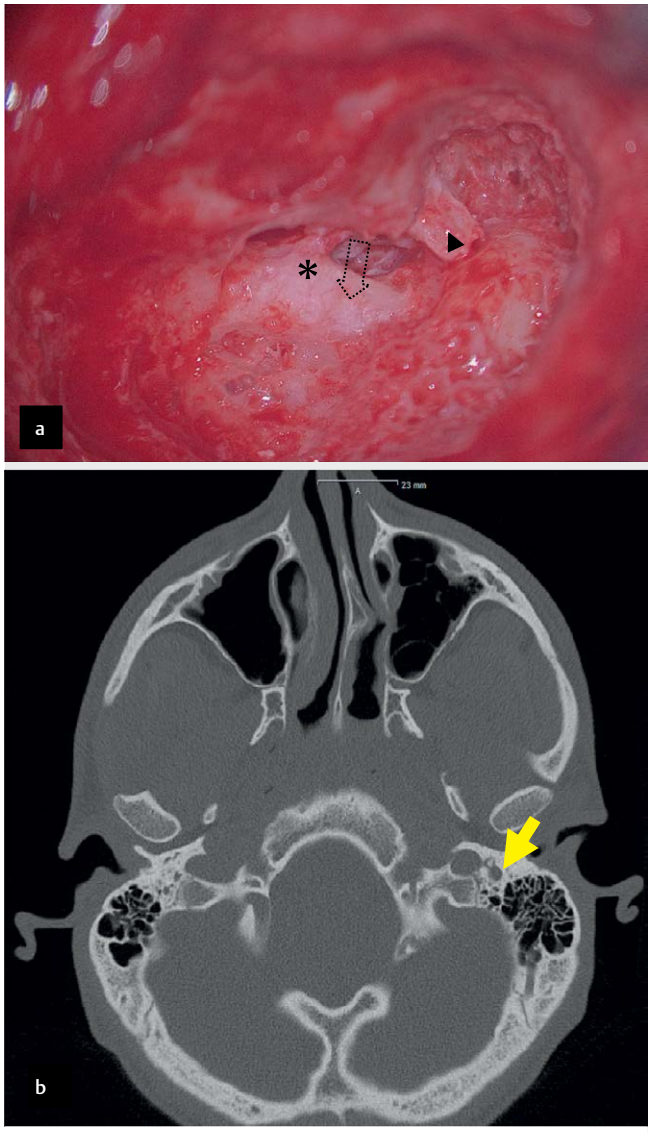
CT scan allows displaying the facial nerve via its bony canal in the area of the inner ear and the middle ear. MRI visualizes the intracranial parts [220] and the temporal bone segments [221]. Conventional MR techniques only allow limited assessment of the extracranial part of the facial nerve [222–224]. However, single reports could already show that also these parts can be made visible [223, 225]. The assessment of the intraparotideal course is difficult because the vascular structures in the parotid gland have a similar hypointensity on T2-weighted images [226]. Furthermore, currently many different MR protocols with different identification rates are applied. The best peripheral display of the facial nerve in MRI (3 Tesla) can be achieved by high-resolution protocols with a layer thickness of less than 1 mm and a diffusion-weighted sequence [227].

3.2 Anomalies of the facial nerve

Anomalies of the facial nerve are very rare and usually occur together with other malformations.

3.2.1 Anomalies of the facial nerve and dehiscence of the fallopian canal

The incidence of intraoperatively detected dehiscences of the fallopian canal varies between 6.0 and 33 % in the literature [228, 229]. Two third of the dehiscences are discovered during ear surgeries [230]. ▶ **Figure 3** shows an enlarged dehiscent facial nerve canal in a patient with middle ear dysplasia covering the round window. In cases of canal dehiscence, the facial nerve may be covered only by a thin membrane and herniate into the tympanic cavity. Here, it either runs over the oval niche or the promontory and may even have ramifications. The risk for accidental injury during middle ear surgery increases. Conductive hearing loss may be the only symptom. Most patients, however, have no clinical symptoms [231]. But the missing bony coverage of the facial nerve may lead to inflammatory nerve alterations. Thus, fallopian canal dehiscences can be associated with the occurrence of neuritis of the facial nerve and facial nerve palsy in acute as well as in chronic middle ear inflammations and cholesteatoma [232]. The origin of fallopian canal dehiscences is due to a malformation of the 2nd pharyngeal arch. In cases of malformation of the Reichert cartilage, as cartilage ring of the 2nd pharyngeal arch, an incomplete or missing closure of the facial nerve sulcus may result. This results in dehisecences or even absence of the bony canal in the middle ear. Apart from ontogenetic reasons, dehiscences may also appear as sequela of earlier surgeries, persisting inflammations, or tumors [230]. Therefore, the incidence of dehiscences at the time of cholesteatoma surgery in pediatric patients is lower than in non-pediatric patients [233].



▶ **Fig. 3** Transmastoid view on the enlarged facial nerve. **a** dehiscently and aberrantly running left facial nerve (star), detected during cochlear implant surgery. The arrow indicates the round window hidden by the facial nerve canal. Arrowhead: enlarged malleus-incus rudiment. **b** CT scan of the temporal bone with dilated facial nerve canal.

3.2.2 Anomalies of the facial nerve and auricular malformations

The development of the facial nerve is closely related to the development of the middle ear and the auricle. Auricular atresia and atresia of the external auditory canal occur in about 1:10 000–20 000 births as a consequence of aberrant development of the first and second pharyngeal arch [234] (see also the article on "Rare disease of the middle ear and the lateral skull base" by Nora M. Weiss). Due to a missing fusion of the ossification centers, the tympanic part of the facial nerve tends to run dehiscently in congenital auricular atresia. As sequela of the impaired development of the mastoid and the tympanic membrane, the vertical facial nerve segment lies in more anterior and lateral position and find its way to the stylomastoid foramen in a horizontal course. The second facial nerve knee

is found further lateral and may cover the access to the middle ear. Additionally, frequent crossing of the oval window and contact with the stapes superstructure occur. A malformed stapes is a warning for facial nerve anomaly. It is also possible that the facial nerve does not exit from the stylomastoid foramen but at the level of the jaw joint [235]. These anatomical variations significantly jeopardize the facial nerve in the context of middle ear interventions and surgeries of atresia. Therefore it is important to perform high-resolution CT scans before surgery so that the surgeon preoperatively appraises the position and course of the facial nerve and may plan the intervention accordingly. Nonetheless it must be taken into account that the assessment of CT scans does not always correspond to the intraoperative findings. In any case, always intraoperative monitoring of the facial nerve should be applied during ear surgeries of patients with auricular dystrophy. Due to the untypical course, the facial nerve may easily be confused with the chorda tympani, soft tissue, or scars.

3.3 Rare origins for a paresis of the peripheral facial nerve

The most frequently observed origins of peripheral facial nerve palsy are idiopathic (Bell's) palsy (that is no rare disease with an incidence of 30–40:100 000 people), followed by iatrogenic lesions caused by cerebellopontine angle and tumor surgeries. Also traumatic reasons (temporal bone fractures, facial injuries) occur rather frequently with 20 % of all peripheral origins [236]. Furthermore, viral (herpes zoster), bacterial (borrelia), and inflammatory lesions in the context of otitis media and mastoiditis are taken into account. Beside these diseases, there is a multitude of rare disorders that may lead to peripheral facial nerve palsy. The clinically most relevant ones will be discussed in this article.

3.3.1 Peripheral facial palsy in the context of systemic diseases

Often the correlation between facial nerve palsy and systemic diseases is not recognized and the facial palsy is classified as idiopathic. Therefore it is important to consider some systemic diseases in which the facial nerve might be involved.

Connective tissue diseases such as scleroderma may be associated with neurological lesions that can also affect cranial nerves. Mostly the trigeminus nerve is concerned but also affections of the facial nerve have been described. In a series of 10 scleroderma patients with cranial nerve palsy described by Treadsdall et al., the facial nerve was involved in 50 % [237]. Also the Melkersson-Rosenthal syndrome belongs to connective tissue diseases. It is characterized by the triad of lip swelling (cheilitis granulomatosa), fissured tongue (lingua plicata), and peripheral facial nerve palsy. It is an autosomal inherited disease of unclear etiology. The diagnosis is made clinically and by family history taking. The disease tends to recurrent episodes and may appear uni- or bilaterally. Up to now, no causal therapy is known. Most frequently, corticosteroids are applied [238].

In the context of a subacute subtype of sarcoidosis, Heerfordt-Waldenström syndrome, also a triad is observed consisting of facial nerve palsy, parotid glands swelling, and anterior uveitis. In the affected organs, granulomas are found. This type of sarcoidosis is usually self-limiting after 1–3 years. The mortality rate amounts to 1–5 % of the cases. The diagnosis is made clinically. The treatment depends on the degree of systemic impairment and is mostly performed by application of corticosteroids [239]. Also in the context of amyloidosis, the peripheral nerve system is involved. In cases of light chain amyloidosis, the cranial nerve deficits, also isolated facial palsy, precede the diagnosis of amyloidosis. The peripheral facial nerve paresis may develop several months or years before systemic involvement. Actually, some authors suggest that light chain amyloidosis should be assumed if facial nerve palsy is associated with proteinuria or monoclonal gammopathy [240, 241].

3.3.2 Rare infectious peripheral facial palsy

Beside herpes zoster and herpes simplex infections and Lyme borreliosis as most common infectious origins of facial pareses [242], there are several other, rarer, in particular viral infections that will be discussed in the following paragraphs. Apart from infection with *Borrelia burgdorferi* (Lyme borreliosis), bacterially caused facial nerve palsy mainly occur as complication of acute otitis media or mastoiditis. Neurotropic viruses such as the human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and human herpes virus 6 can also cause paresis of the facial nerve [243].

Facial nerve palsy is the most frequent neuropathy of the head associated with HIV infection. Depending on the immuno-competence of the host, unilateral as well as bilateral paresis may develop at any time in the course of HIV infection via different pathogenic mechanisms. It is important that it may appear as first or single symptom of asymptomatic HIV infection and mimic the idiopathic type (Bell's palsy). Bell's palsy occurs more frequently and the correlation between facial nerve palsy and HIV infection is rarely mentioned in the literature. Therefore the correlation between facial palsy and HIV infection is often not recognized and early HIV infection is overlooked [244].

Regarding Epstein-Barr virus infection, the literature is limited to case reports about pediatric and adult patients. Similar to HIV infection, the paresis occurs uni- or bilaterally. The diagnosis is made by serology with increased anti VCA IgM antibodies without increase of the EBNA antibodies in primary infection. In unclear cases, in-situ hybridization may confirm the presence of EBV-specific RNA. The primary infection often occurs in children while adults may also observe virus reactivation. Hereby, also the levels of EBNA antibodies are increased [245]. Vogelnik and Matos describe 5 own and 4 reported pediatric cases where the facial nerve palsy was clinically associated with acute otitis media [246]. In all described cases, the prognosis was good. In the course, complete restitution could be achieved. The treatment was performed symptomatically. A benefit by application of antiviral therapy was not described.

The human herpes virus 6 as cause of the exanthema subitum in children is also considered as trigger of facial nerve palsy. It was detected in the liquor of children and adults with facial paresis. Human herpes 6 viruses have a strong affinity to the brain. It was also discovered post mortem in asymptomatic patients in the brain tissue. Nonetheless, encephalitic complications of facial palsy are possible and should be taken into account. The paresis may appear during primary infection or in the context of virus reactivation. In cases of primary infection, the paresis develops after the three days of fever. Up to now, the optimal treatment is unknown. Ganciclo-

vir and foscarnet may have an antiviral effect against the human herpes virus 6 and should be applied in the context of association with encephalitis [247, 248].

3.3.3 Peripheral facial palsy during pregnancy

The data on the incidence of facial nerve palsy during pregnancy are not clear. While some authors estimate the occurrence as frequent in the normal population [249], other authors mention an increased incidence especially in the 3rd three months [250]. Etiologically, some factors are discussed. Among them are preeclampsia, changed immune status, increased sensitivity against virus infections, and increased edema formation in particular in the last three months of pregnancy. With regard to therapy, it is not sure if the usually applied cortisone therapy is justified for pregnant women. According to the current opinion, the timely treatment with corticoids is recommended [251]. For pregnant women the same diagnostic and therapeutic principles apply. Glucocorticoid therapy should be performed in an inpatient setting in close collaboration with the obstetrics [252]. The application of antivirals could not confirm a therapeutic benefit up to now [253] and should absolutely not be applied during pregnancy.

3.3.4 Congenital peripheral facial palsy

Congenital facial nerve palsy only occurs in 0.8–18:10 000 births. Regarding an isolated congenital facial palsy, a perinatal trauma is assumed that is caused by the superficial extracranial course of the facial nerve. In addition to isolated congenital cases, there are several syndromes that include lesions of the facial nerve. Those are for example Möbius syndrome, Goldenhar syndrome, and CHARGE syndrome [254]. While a complete remission appears in 90 % of perinatal traumatic facial nerve lesion without therapy, the facial palsy remains part of the syndromic disease.

Patients with classic Möbius syndrome have a complete bilateral paresis of the facial and abducens nerve and a missing major pectoralis muscle. In patients with incomplete Möbius syndrome, a residual motor function on one side of the face is observed even if they show the clinical appearance of the syndrome. Beside the treatment of the anomalies of the extremities and the palate, the central objective of the treatment consists of achieving a rehabilitation of the facial nerve by means of a dynamic surgical intervention. The microneurovascular free muscle transplantation is the procedure of choice. Most appropriate is the gracilis muscle because it can be well accessed and does not leave a functional deficit [255].

Goldenhar syndrome is characterized by impaired development of the eyes, ears (with or without hearing loss), lips, tongue, palate, mandible, maxilla, and dental structures. Furthermore, anomalies of the inner organs, in the central nervous system, and the skeleton are observed. Therefore, the term of "hemifacial microsmia" should no longer be used. The spectrum of anomalies includes patients with nearly unnoticeable facial asymmetry up to highly extended facial defects with more or less severe facial nerve palsy. The treatment of patients with Goldenhar syndrome is complex and should be adapted to the extent and the severity of the obvious anomalies depending on the patients' age. Usually, therapy starts early and lasts for a long time [256].

CHARGE syndrome was first described by Hall et al. in 1979 in 17 children with multiple congenital anomalies, which became apparent initially by choanal atresia [257]. Beside choanal atresia, coloboma, heart disease, mental retardation, auricular deformities, and hearing loss/deafness, it is also associated with congential facial nerve palsy (see also the article on "Rare diseases of the inner ear" by Athanasia Warnecke). The therapy is characterized by numerous surgical interventions, starting with airway and nutrition management via heart surgeries, cochlear implantation up to dynamic facial nerve rehabilitation [258].

3.4 Facial hemispasm

Facial hemispasm is a rare disease with a prevalence of about 1:10 000 and a predominance of the female gender of 2:1 [259]. In 1875, Schultze reported probably about the first case of facial hemispasm in the literature when he described a 56-year-old man with unvoluntary left-sided facial movements that resulted from aneurysm of the vertebral artery [260]. The spasm may occur as primary or secondary symptom. The primary hemispasm of the facial nerve results from the compression of the facial nerve in its core area in the posterior cranial fossa by an aberrant vessel (superior, anterior, inferior cerebellar artery or vertebral artery). Secondary origins are manifold and comprise tumors, malformations, brain infarction, traumas, or demyelinizing diseases. Generally, the spasm concerns the upper part of the face and passes on to the lower parts in the course of the disease. Immediate simultaneous involvement of the upper and lower face is typical for secondary cases [261]. Bilateral diseases have been described but they are very rare (< 1 %) and also in these cases, the disease starts on one side and involves the other side after several months or years. In these cases, the contractions remain asymmetric whereas the side that is affected later has less severe manifestations. In primary types, the origin of arterial hypertonia is discussed that leads to the formation of ectopic vessels that possibly compress the core area of the facial nerve or trigger a parasympathetic stimulus in the posterior cranial fossa [259]. The diagnosis is made based on the clinical appearance. In order to exclude secondary origins, MRI should be performed. In any case, further electrophysiological diagnostics should be performed. Due to the low prevalence of the disease, only few controlled clinical trials have been conducted to find the best possible therapeutic modality. Because of the clinical effect, a treatment with botulinum toxin is considered as therapy of choice. The symptoms are effectively reduced and the quality of life is increased. The dose and the injection point depend on the clinical findings. Mostly only the ocular orbicular muscle and the platysmal part are treated. The treatment of the jaw angle is critical due to the risk of hanging corner of the mouth. Even if botulinum toxin is the most effective therapy, other options including drug-related therapy and microsurgical decompressions are also indicated in single cases. The applied medication includes anticonvulsant such as carbamazepine, clonazepam, gabapentin, pregabalin, baclofen, and others. The disadvantage of oral medication is the inconsistent effect and the sedating side effects [262]. As surgical procedures, the decompression according to Jannetta is considered as standard procedure. Hereby the pathological vessel-nerve contact is eliminated. If the indication is made carefully and critically, the success rates are very high with 80 up to more than 90 %

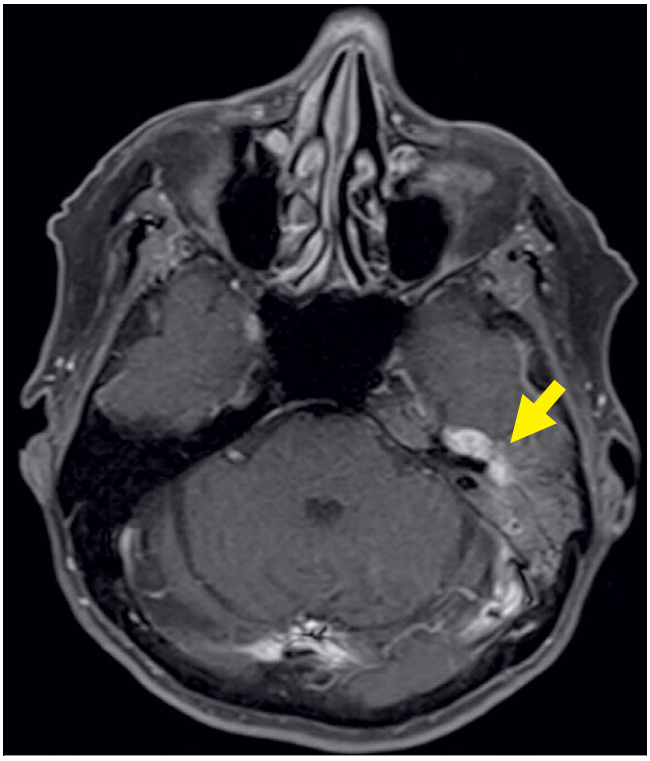
[263]. But also recurrences (25 %) and complications occur frequently (hearing loss 20 %, facial nerve palsy 2 %, liquor fistula 2 %). As a consequence, the surgical option is mainly reserved to those patients who either do not respond to botulinum toxin therapy or decide for persistent healing of their disease [259].

3.5 Rare tumors of the facial nerve

Primary tumors of the facial nerve are rare and represent a difficult challenge of treatment. In general, every tumor can be diagnosed by means of imaging procedures. The selection of the optimal treatment option is challenging because the literature is sparse and often inconsistent. However, it is clear that the treatment of facial nerve tumors has become more and more conservative in the course of the time.

3.5.1 Schwannomas

Schwannomas of the facial nerve are also called neurinomas and neurilemmomas. They are the most frequently occurring facial nerve tumors but nonetheless they are so rare that their actual incidence in the population is difficult to define. Saito and Baxter found 5 (0.83 %) incidental facial nerve schwannomas in 600 temporal bone preparations which of course is not representative for the general population but at least a certain estimate [264]. In the context of neurofibromatosis type II, they occur with an incidence of 58 % [265]. The lesion is a well encapsulated, slowly growing tumor that originates from Schwann cells of the facial nerve. Generally, each segment of the nerve may be affected. In most cases, the geniculate ganglion or the tympanic part are involved [266]. Many tumors are asymptomatic. The symptoms vary according to the tumor size and location. In up to 78.6 %, hearing loss develops, tinnitus appears in 7–51.8 % and vertigo in 46 % of the cases. Especially with relation to the facial nerve function, most patients have a slowly developing pareses or recurrent palsy over several months. Recurrent facial nerve palsy should always lead to the examination of facial nerve schwannoma [267, 268]. The merely clinical diagnosis is difficult to make due to the manifold symptoms. Ear microscopy is usually inconspicuous unless the tympanic segment is concerned. Then possibly a tumor may be visible behind the tympanic membrane [269]. MRI and CT scan may be helpful. In the thin-layer MRI with gadolinium, a contrast enhancing lesion may be found along the facial nerve in the temporal bone. If facial nerve segments or the ventral fraction in the area of the major petrosus nerve and the dorsal friction in the area of the tympanic course are affected, the typical image of sandglass is seen in MRI (▶ **Fig. 4**). CT scan typically shows an increased fallopian canal in comparison to the contralateral side [270]. The therapy is oriented at individual aspects. The major objective is the preservation of the facial nerve function. In the literature, numerous treatment methods are described that reach from conservative wait-and-see management via decompression, tumor debulking up to resection with facial nerve transplants. One of the main difficulties regarding the diagnosis and treatment of facial nerve schwannomas is that many facial nerve schwannomas are considered as the more frequently occurring vestibular schwannoma until the tumor is exposed during surgery. As long as the facial nerve function is normal, many authors recommend a conservative procedure with regular MRI [270–272]. Angeli and Brackmann described facial nerve decompression as "conservative" surgical treatment. Hereby, the pressure is reduced but the nerve continuity is preserved. The tumor continues growing but very slowly and with less neuronal damage [273]. The method of tumor debulking is controversially discussed because of the high risk of facial palsy. Proponent of debulking argue that parts of the tumor that cannot be stimulated may be removed under facial nerve monitoring. Mowry et al. even reported about improved facial function of House-Brackmann III and IV to I or II after tumor debulking [274]. For patients with poor facial nerve function (House-Brackmann > IV) a complete resection with facial nerve reconstruction (interposition, rarely end-to-end anastomosis) is the best option. The expected result is not better than House-Brackmann III. If the facial palsy is does not improve or deteriorates, other reanimation procedures of the facial nerve may be taken into consideration [271]. An alternative of surgical intervention is the stereotactic radiosurgery by means of gamma knife as single fraction therapy. The tumor control rates vary in the literature between 83.3 and 100 %. The rates of posttherapeutic facial palsy amount to 0–50 %. Another alternative is fractionated radiotherapy with 50Gy in 25 fractions. Both irradiation modalities may lead to hearing loss rates of up to 15 % or higher [275–277]. For the individual therapy decision, the postoperative and post-radiation complications (especially facial palsy and hearing loss) must be discussed in consideration of the patient's age and the overall constellation of the risk of permanent facial nerve palsy and sometimes deafness if the



▶ **Fig. 4** T1 weighted MRI with contrast agent of a facial nerve schwannoma. The axial view shows a typical sandglass phenomenon (arrow). The ventral fraction is found in the area of the major petrosus nerve and the dorsal fraction is located in the area of the tympanic course of the facial nerve. Courtesy of Prof. Christoph Groden, Department of Neuroradiology, University Hospital of Mannheim.

disease is not treated. It should also be observed that the histological confirmation of the diagnosis is missing in cases of conservative wait-and-scan procedure as well as radiotherapeutic management, and a differentiation of vestibular schwannoma is nearly impossible. Lifelong regular MRI controls should be performed after resection as well as after irradiation in order to exclude tumor progress or recurrence.

3.5.2 Neurofibromas

Neurofibromas are also benign tumors of the peripheral nerve sheath. Histologically, they are plexiform mixtures of Schwann cells, perineural elements, fibroblasts, and hematopoietic cells embedded in collagen. Neurofibromas may occur sporadically or be associated with neurofibromatosis. The associated type includes the cutaneous subtype (neurofibromatosis 1 or 2), the massive subtype (neurofibromatosis 1), and the plexiform subtype (neurofibromatosis 1) [278]. Malignant transformation is rare but nonetheless is may occur in the context of neurofibromatosis type 1 (von Recklinghausen disease). Therefore, also benign lesions should be followed-up in narrow intervals [279]. In contrast to schwannoma of the peripheral facial nerve, sporadic neurofibromas – even large lesions – only rarely lead to facial nerve palsy. Regarding treatment, it has to be taken into account that the axons of the neurofibromas show another behavior than those of schwannomas. In cases of schwannomas, they have no relation to the tumor whereas in neurofibromas the axons directly penetrate the tumor. This is one reason why facial schwannoma can be separated from the nerve in contrast to neurofibromas. Complete excision is thus always associated with nerve damage. Therefore, neurofibromas should not be removed surgically if possible, except from malignant degeneration or type 1 neurofibroma [280]. If resection cannot be avoided, nerve reconstruction should be performed by means of interposition or (rarely possible) end-to-end anastomosis.

3.5.3 Hemangiomas

Hemangiomas of the facial nerve originate from the geniculate ganglion. They are very rare and make up 0.7 % of the tumors in the temporal area [281]. These tumors are actually no neural tumors but extraneural neoplasms that develop from the vascular plexus surrounding the nerve. At the geniculate ganglion, this vascular plexus is particularly dense [282]. Hemangiomas grow very slowly but already in an early stage they may lead to progressive facial palsy. A significant number of patients suffer additionally from facial spasms. 25 % of the patients observe hearing loss. With increasing size, either cochlear fistulas with sensorineural hearing loss or destruction of the ossicular chain with conductive hearing loss or both develop [283]. Electroneurography reveals a significant reduction of the amplitudes. Electromyography shows a characteristic alternating pattern of regeneration and degeneration with at the same time present fibrillation potentials and multiphase action potentials. This continuous degeneration and regeneration seems to be characteristic for facial hemangiomas [284]. Computed tomography reveals a moth bite like image due to erosion of the floor of the middle cranial fossa with punctured calcifications. In the T2 weighted imaging, MRI shows a heterogeneous hyperintense mass in contrast to isointense schwannomas. It must be taken into account that 80 % of the hemangiomas are smaller than 1 cm and can be easily overlooked [284]. The optimal treatment method for facial nerve hemangiomas is difficult to find since there are only very few reports in the literature. Based on the little data that are available, they should initially be observed as long as no paresis or hearing loss become apparent. In cases of good hearing function and facial palsy of House-Brackmann grade III or higher a preserving resection via a transcranial (subtemporal) access to the middle cranial fossa should be performed. Hereby a good exposition of the geniculate ganglion is possible with a high chance of hearing preservation. The resection is made microsurgically under facial nerve monitoring. In cases of already existing deafness or high-grade hearing loss, a translabyrinthine access may be chosen [284].

3.5.4 Paragangliomas

Paragangliomas of the facial nerve are very rare. Most paragangliomas (glomus tumors) of this region manifest as glomus tympanicum or glomus jugulare. When these lesions grow, the facial nerve may be secondarily involved. Primary facial paragangliomas are extremely rare. In the literature, only 21 further primary cases could be found since the first description in 1986 [285–300]. Most of these tumors are identified in the vertical part of the facial nerve near the bulb of the jugular vein and the stylomastoid foramen. In the few described cases, facial palsy seems to be the most frequent symptom followed by pulsatile tinnitus. The characteristics of CT and MRI are similar to those of other paragangliomas: bone destruction, high T2 signal, “salt and pepper” pattern with clear enhancement in the T1 weighted imaging. The ^{18}F-dihydroxyphenilalanin (DOPA) positron emission tomography (PET) seems to be superior in very small tumor (< 1 cm) compared to MRI [301]. The majority of the described tumors was resected. Such as for other paragangliomas, the therapy depends on the location of the tumor and its size. The treatment of paragangliomas in general has developed from radical resection to surgical tumor reduction with preservation of the function as well as local control of residual tissue during the last decade. In individual cases, the local control may include primary or postoperative radiotherapy or wait-and-scan strategy.

Conclusion

The present article gives an overview of the current literature of rare salivary gland diseases and rare diseases of the facial nerve. Diagnostics and therapy of rare chronic non-infectious sialadentitis and sialadenosis represent a particular challenge. An interdisciplinary approach is crucial. The rapid development in molecular genetics makes the treatment of rare salivary gland tumors even more complex, but with regard to target therapy it provides probably new options in the near future. In the context of treating rare tumors of the facial nerve the therapy has changed from radical procedures to rather reluctant treatment. The overview of all the diseases described in this article makes clear that especially the treatment of rare pathologies should be reserved to specialized centers. In these centers, sufficient experience can be provided. Aiming at the collection of large numbers of cases, the initiation of multicenter trials and establishment of national and international registries is desirable.

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Conflict of interest

The author states that there is no conflict of interest.

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