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Rare Diseases of the Oral Cavity, Neck, and Pharynx

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ABSTRACT

Diseases occurring with an incidence of less than 1–10 cases per 10 000 individuals are considered as rare. Currently, between 5 000 and 8 000 rare or orphan diseases are known, every year about 250 rare diseases are newly described. Many of those pathologies concern the head and neck area. In many cases, a long time is required to diagnose an orphan disease. The lives of patients who are affected by those diseases are often determined by medical consultations and inpatient stays. Most orphan diseases are of genetic origin and cannot be cured despite medical progress. However, during the last years, the perception of and the knowledge about rare diseases has increased also due to the fact that publicly available databases have been created and self-help groups have been established which foster the autonomy of affected people. Only recently, innovative technical progress in the field of biogenetics allows individually characterizing the genetic origin of rare diseases in single patients. Based on this, it should be possible in the near future to elaborate tailored treatment concepts for patients suffering from rare diseases in the sense of translational and personalized medicine. This article deals with orphan diseases of the lip, oral cavity, pharynx, and cervical soft tissues depicting these developments. The readers will be provided with a compact overview about selected diseases of these anatomical regions. References to further information for medical staff and affected patients support deeper knowledge and lead to the current state of knowledge in this highly dynamic field.

CONTENTS

1. Introduction

For a long time, patients suffering from rare diseases were considered as "Orphans of Medicine". Despite medical progress, their lives are still often characterized by uncounted consultations and inpatient stays. Still, many orphan diseases cannot be cured. A considerable percentage of those pathologies appears in the head and neck region.

The definition of rare or orphan disease is inconsistent and varies between the different continents: in the European Union (EU) a disease is called rare when 50 or less per 100 000 of the population (< 0.05 %) are affected. In the United States of America, however, a disease is considered as rare when less than 200 000 inhabitants (< 0.06 %) are affected, in Asia and Australia the incidence of 0.01 to 0.04 % is given. According to the definition of the World Health Organization (WHO), diseases are rare when a prevalence of less than 0.065 to 0.1 % is observed. About 80 % of the so-called orphan diseases have a genetic origin, and about 50 % of the affected patients are children. More than half of them (about 60 %) do not become older than 5 years. Currently between 5,000 and 8,000 orphan diseases are known, each year 250 rare diseases are newly described (www.eurordis.org).

In order to increase the knowledge about orphan diseases and to improve the care for affected patients, specific databases and networks have been established in the past. In this context, the international database of orphan diseases called *Orphanet* (EU; http://orphanet.net) and the database of the *National Organization for Rare Disorders* (USA; https://www.rarediseases.org) should be mentioned. At the same time, self-help groups and patient networks have been established that take care for the needs of patients under the umbrella of the *European Organization of Rare Diseases* (http://www.eurordis.org), the *Versorgungsatlas für Menschen mit seltenen Erkrankungen* (http://www.se-atlas.de) the *Allianz Chronischer Seltener Erkrankungen* (ACHSE; https://www.achse-online.de) the *Bundesarbeitsgemeinschaft Selbsthilfe* (http://www.bag-selbsthilfe.de) or the *Nationale Kontakt- und Informationsstelle für Selbsthilfegruppen* (NAKOS; http://www.nakos.de).

The Annual Meeting of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery, of 2021 focuses on rare diseases. In this way, a contribution to further improvement of the care and treatment of patients with rare diseases of the head and neck will be made. The present article will provide a compact overview of selected rare pathologies of the lip, the oral cavity, the pharynx, and the cervical soft tissue. References to further information about this highly dynamic topic allow interested medical staff to deepen their knowledge about individual diseases and mention possibilities to access the current state of knowledge. Finally, affected patients will be provided with contact data – if available – of self-help groups and patient networks.

2. Lip, Oral Cavity, and Pharynx

2.1 Rare anomalies and malformations

Due to the fact of its particular anatomical situation as entrance of the body, the head and neck area is closely related to the immune system. In the first years of life, crucial maturation processes occur

in this region based on the direct contact with pathogens which results among others in a hyperplasia of the pharyngeal and palatal tonsils. It is well known that certain conditions may cause the development of middle ear pathologies or impairment of respiration (in particular during sleep) because of these anatomical pathologies that might have severe consequences for the development of affected children if they remain untreated. In adults, anatomical alterations of the oral cavity and the pharynx leading to obstructive breathing disorders during sleep are considered as significant risk factors for the development of cardiovascular diseases. In the context of assessing these probably underdiagnosed pathological alterations, this area should also be examined with regard to heterotopies of tissue of the salivary glands, thyroid glands, thymus, or parathyroid glands [84, 175, 189, 205]. Anatomical anomalies of the lingual surface as observed in geographic tongue (prevalence of 0.3–15 %), black hairy tongue (prevalence of 0.15–3 %), fissured tongue (prevalence of 2–20 %), or *glossitis rhombica mediana* are also frequently found in the population [128]. Regarding patients with diffuse swallowing disorders and/or pain in the head and neck area, the differential diagnoses should also include a long styloid process (prevalence of 4–7 %) or ossification of the stylohyoid ligament (prevalence of 4–30 %) (Eagle syndrome) which may lead to complaints in up to 10 % of the cases [152,214]. More rarely, also osteophytes of the spine (Forestier's disease, hyperostotic spondylosis) [1], a longer cornu superior of the thyroid cartilage [138] or an extended pterygoid hamulus [197] may be responsible for such symptoms. Also a very rarely occurring amyloidosis, xanthomatosis, or lipoid proteinosis (Urbach-Wiethe syndrome) in this area must be included in the differential diagnosis of swallowing disorders [20, 79, 176]. In the following, a selection of rare anatomical anomalies and malformations of the lip, the oral cavity, and the pharynx will be elaborated in more detail.

2.1.1 Zenker's diverticulum

Zenker's diverticulum describes a bag-like protrusion of mucosa and submucosa or the dorsal wall of the hypopharynx cranial to the upper esophageal sphincter, the so-called Killian's triangle. Thus, it is a so-called pulsion or pseudo-diverticulum that was first described in 1764 by the anatomist Abraham Ludlow and then named after the pathologist Friedrich Albert von Zenker from Erlangen, Germany. Zenker's diverticulum manifests mainly in male patients of higher age, has a prevalence of less than 0.1 % and so it is rare. Typical symptoms of affected patients are dysphagia, regurgitation of undigested food, and halitosis. Cachexia and aspiration pneumonia may be severe complications. By means of preoperative radiological swallowing studies, the diagnosis of Zenker's diverticulum may be confirmed [92, 100]. It must be differentiated from Kilian-Jamieson's diverticulum (in the area of the upper esophageal sphincter) or pharyngoceles. Beside surgical transcervical resection of the diverticulum by means of a stapler, it is increasingly treated by means of peroral myotomy under rigid endoscopic control with the CO_2 laser, diathermic scissors, or stapler. Also myotomies using flexible endoscopes under analgosedation are possible in case of suitable anatomical conditions. All three methods are promising regarding an improvement or even elimination of the complaints. In comparison to the endoluminal procedures, the complication rate is higher with the open surgical technique. Endoluminal procedures, however, are not possible in up to 13 % of the patients due to anatomical reasons [92, 100].

Further information
For medical staff: [92]

2.1.2 Isolated cleft palate

Craniofacial clefts are the second frequent group of congenital malformations and with a prevalence of 1 of 500 (0.2 %) of the population, they are comparably frequently observed. Clefts are mostly found in the the lip, the upper jaw, and/or the palate. Significantly more rarely, clefts occur in the the nose, the cheek, or the mandible. Combined cleft lip and palate are most frequently found (about 40–65 %), followed by cleft lip and jaw, cleft lip (about 20–25 %), or cleft palate (up to 30 %). Males are more frequently affected than females (ratio 3:2); left-sided clefts occur more frequently than right-sided ones (ratio: 2:1), or as median clefts [27, 159].

Cleft lip and jaw develop between the 5th and 7th week of pregnancy, cleft palate between the 8th and 12th week of pregnancy. Their etiology is based on a complex interaction between genetic and environmental factors. Alcohol and tobacco abuse, the intake of retinoids, or the antiepileptic drug topiramate, ionizing radiation, and environmental contaminants as well as folic acid deficiency during pregnancy are suspected to promote the development of clefts [27, 159]. Generally, the diagnosis is possible as of the 22nd week of pregnancy by means of ultrasound. Children of parents suffering from clefts have an increased risk of craniofacial cleft development as well as other children of parents who already have a child suffering from a cleft. Often those clefts are associated with other anatomical malformations or syndromes (see ▶ **Table 1**) such as the Van der Woude syndrome (**see 2.1.3**). With a prevalence of 1:2,000 (≙0.05 %), the occurrence of isolated cleft palate is rather rare [27, 159].

Therapy aims at establishing a regular function of breathing, hearing, speaking, and chewing until school age which requires an interdisciplinary approach for the patients that is called primary treatment. In this context, measures of the disciplines of orthodontics, surgery, phoniatrics and pediatric audiology as well as speech therapy are applied. The surgical closure of the lip is usually performed between the 4th and 6th month of life or with a body weight of at least 5 kg; the closure of the soft palate is performed between the 7th and 15th month of life. The closure of the hard palate is scheduled between the 2nd and 5th year of life. In the context of secondary treatment, corrective surgeries are performed after cleft closure. Clefts in the nose, however, are usually corrected when the patients reach the adult age [195].

2.1.3 Van der Woude syndrome (VWS)

The Van der Woude syndrome (VWS, synonyms: lip pits, Demarquay syndrome, cleft lip with or without cleft palate with mucosal cysts of the lower lip; lower lip fistulas with facultative combination with clefts) is characterized by fistulas in the area of the lower lip (▶ **Fig. 1**) together with clefts of the lip with or without cleft palate [204]. In addition, also hypodontia and dental hypoplasia are often observed in affected patients [142]. This disease mostly relies on an autosomal dominant mode of inheritance and represents the most frequent monogenetic type of cleft lip and palate with a

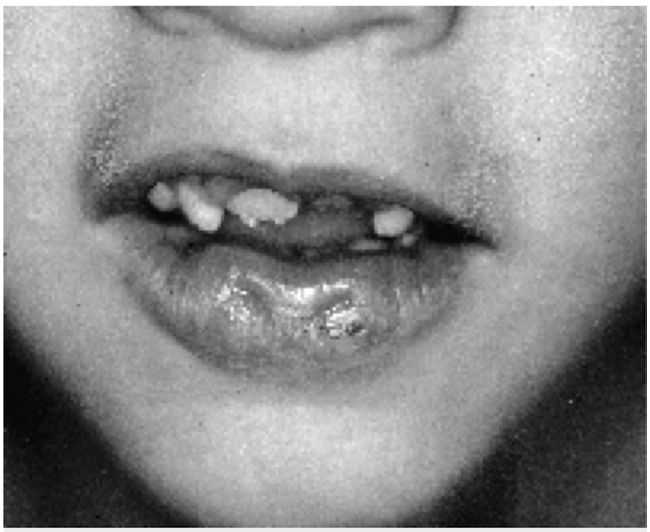
▶ **Table 1** Rare syndromic malformations.

Abruzzo-Erickson syndrome
Ankyloblepharon filiforme adnatum-imperforate anus syndrome
Ankyloblepharon-ectodermal defects-cleft lip/palate syndrome
Arthrogryposis-ectodermal dysplasia cleft lip/palate retardation syndrome
Atelosteogenesis type 1
Atelosteogenesis type 2
Atelosteogenesis type 3
Auriculocondylar syndrome
Ausems-Wittebol Post-Hennekam syndrome
Bamforth syndrome
Barakat syndrome
Beckwith-Wiedemann syndrome
Bixler-Christian-Gorlin syndrome
Blepharo-cheilo-odontic syndrome
Blepharonasofacial malformation syndrome
Pharyngeal arch syndrome, x chromosomal
Branchio-oculo-facial syndrome
Branchiootic syndrome
Branchiootorenal syndrome
Carey-Fineman-Ziter syndrome
Catel-Manzke syndrome
Cerebro-oculo-facial-skelettal syndrome
Charcot-Marie-Tooth disease
CHARGE syndrome
Chitayat-Meunier-Hodgkinson syndrome
Cleft palate-short stature-vertebral anomalied syndrome
Conductive hearing loss-malformation of the auricle syndrome
Cornelia-de-Lange syndrome
Crane-Heise syndrome
Diamond-Blackfan anemia
Femoral-facial syndrome
Fetal hydantoin syndrome
Fraser syndrome
Fryns syndrome
GEnitopalatocardiac syndrome
Goldberg-Shprintzen megacolon syndrome
Goldenhar syndrome
Gordon syndrome
Hardikar syndrome
Hemifacial microsomia
Histiocytosis-lymphadenopathy syndrome
Hydrocephalus-cleft palate-joint contractures syndrome
Hypoglossia-hypodactyly syndrome
Jones syndrome
Kapur-Toriello syndrome
Kniest dysplasia
Larsen syndrome

▶ **Table 1** Continued.

Malignant hyperthermia-arthogryposis-torticollis syndrome
Mandibulofacial dysostosis-microcephaly syndrome
Maternal hyperphenylaninemia
Marden-Walker-like syndrome
Marden-Walker syndrome
Maxillonasal dysplasia, Binder syndrome
Meckel syndrome
Medeira-Dennis-Donnai syndrome
Median cleft of the upper lip with facial and nasal polyps syndrome
Microbrachycephaly-ptosis-cleft lip syndrome
Microcephaly-deafness syndrome
Miller syndrome
Nager syndrome
Omphalocele-cleft palate syndrome, lethal
Orofaciodigital syndrome, type 1–11
Otopalatodigital syndrome type 1
Otopalatodigital syndrome type 2
PAI syndrome
Pallister-W syndrome
PARC syndrome
Pierre-Robin sequence
Popliteal pterygium syndrome
Popliteal pterygium syndrome Bartsocas-Papas type
Rapadilino syndrome
Richieri-Costa-Pereira syndrome
Roberts syndrome
Say syndrome
STAC3 disease
Syngnathia-cleft palate syndrome
TARP syndrome
Toriello-Carey syndrome
Treacher-Collins syndrome
Ventricular extrasystoles with syncopal episodes-perodactyly-Robin sequence syndrome
Verloove-Vanhorick-Brubakk syndrome
Vohwinkel syndrome
Waardenburg syndrome, type 1–4
Warfarin syndrome
Zlotogora syndrome

A selection of rare syndromes is listed that manifest in the context of malformation of the lip, the oral cavity, the pharynx, and the cervical soft parts (own list taken from www.orpha.net).



▶ **Fig. 1** Fistulas of the lower lip. Clinical manifestation of fistulas in the area of the lower lip (bilateral) of a 7-year-old male patient (figure taken from [40]).

prevalence of 1–9 of 100 000 (corresponding to 0.001 to 0.009 %) in the European and Asian population with high penetrance and variable expression. Hence, it is responsible for about 2 % of all cleft lip and palate occurrences. Both genders are equally affected by VWS. In type 1 (which is found in about 70 % of the patients with VWS), mutations of the interferon-regulating factor 6 gene are observed (IRF-6; locus: 1q32.2); the gene product regulates the proliferation and differentiation of keratinocytes. The majority of those mutations are found in exon 3 and 4 (DNA binding domain) as well as exon 7 to 9 (protein binding domain) [47]. In cases of type 2 (which affects about 5 % of patients with VWS), mutations are found in the gene of the nuclear transcription factor called grainyhead-like transcription factor 3 (GRHL3; locus: 1p36.11). The origin of the remaining 25 % of the cases is still unknown [121]. The diagnosis of these diseases is made based on the typical clinical findings, the family history, and genetic examination results. Typically, the treatment comprises surgery and orthodontic therapy (**see 2.1.2**).

Congenital fistulas in the lower lip also occur in other syndromes:

- Orofaciodigital syndrome 1 (OFD1; congenital fistulas of the lower lip together with anomalies in the area of the oral cavity, face, hands, feet, brain, and kidneys) that is inherited with a prevalence of 1:50 000 of the population (corresponding to 0.002 %) by X chromosomal dominant mutations of the CXORF5 gene [63]. It is associated with dysfunction of the primary cilia and lethal in male fetuses [52, 70].
- Kabuki syndrome (synonyms: Kabuki-makeup syndrome, Niikawa–Kuroki syndrome; prevalence of 1:36 000 [0.003 %]; congenital fistulas are found in the area of the lower lip together with a facial dysmorphia, postnatal growth retardation, skeletal anomalies, mental retardation, unusual dermal papillae) is caused by mutations of the KMT2D (56–75 %) or KDM6A gene (3–8 %) and reminds of the traditional Japanese theater ("Kabuki") [23, 144].
- Popliteal pterygium syndrome (PPS; congenital fistulas in the area of the lower lip together with popliteal pterygia, oral clefts, syngnathia, dysplasia of the toenails, syndactyly of the toes, congenital heart defects, and genital malformations) occurs with a prevalence of 1:300 000 neonates (0.0003 %) and is also inherited by autosomal dominant mutations of the IRF-6 gene [115].

2.1.4 22q11.2 deletion syndrome

The 22q11.2 deletion syndrome (synonyms: velocardio-facial syndrome, Shprintzen syndrome or – with immune defects – DiGeorge syndrome) is a spontaneously developing (in about 85 % of the cases) or autosomal-dominantly inherited disease which is highly variable in its manifestation. With a prevalence of 0.025–0.05 % of the population it is the most frequently observed chromosomal microdeletion in humans. The majority of the affected patients show a 3 Mb DNA deletion on chromosome 22 leading to a haploinsufficiency of around 106 genes. They comprise coding and non-coding RNA as well as pseudogenes. In this context, T-box transcription factor 1 (TBS1) and DiGeorge critical region 8 (DGCR8) play a crucial role for the clinical presentation of the affected patients. The significant differences in the characteristics of the disease can be explained by mutations of further genetic and epigenetic factors [53]. The diagnosis of this disease is made by genetic analysis, in cases of planning to become pregnant, genetic analyses are recommended.

Beside congenital middle ear malformations, heart defects (*e. g.*, ventricular septal defect, tetralogy of Fallot, truncus arteriosus, interrupted aortic arch), immune deficiencies (due to thymus hypoplasia), hypoparathyroidism, developmental disorders, behavioral disorders, and facial dysmorphia, the 22q11.2 deletion syndrome is often associated with anomalies in the area of the palate. Hereby, weakness of the palatal muscles, (submucous) cleft palate, or uvula bifida are found. Furthermore, also laryngo-tracheo-esophageal, gastrointestinal, genital, skeletal, ophthalmological, and central nervous anomalies as well as psychiatric, autoimmune, and malignant diseases may be associated with the 22q11.2 deletion syndrome. Female and male individuals are equally affected, further there is no ethnical predilection. However, the mean life expectancy of patients suffering from 22q11.2 deletion syndrome is limited [15, 162].

The therapy of heart defects, cleft palate, and middle ear malformations of patients with 22q11.2 deletion syndrome is usually based on a multidisciplinary approach. Besides, an early, comprehensive, and long-lasting socio-medical support of the affected patients is necessary. For children that are prone to infections, infection prophylaxis is required [16].

Further information

For medical staff: Guideline of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF; http://www.awmf.org).

For affected patients: self-help association (Selbsthilfevereinigung für Lippen-Kiefer-Gaumen-Fehlbildungen e.V.; http://www.lkg-selbsthilfe.de), Lippen-Kiefer-Gaumenspalten Forum (http://

www.lkgs.net), Deutscher interdisziplinärer Arbeitskreis Lippen-Kiefer-Gaumenspalte/Kraniofaziale Anomalien (http://www.ak-lkg.de).

2.1.5 Double lip

A double lip is characterized by a soft tissue excess in the area of the inner aspect of the lip which originates from hyperplasia of the labial gland tissue. It mostly occurs on both sides of the upper lip, but it may also develop only on one side and/or affect the lower lip. Ethnical or gender-specific predilection is not known. However, are differentiated congenital and an acquired type. It is assumed that the congenital type of double lip develops due to a persisting sulcus between the pars glabrosa and pars villosa of the lip during the first three months of gestation. The acquired type of double lip, however, is assumed to develop because of (recurring) local trauma [8]. Furthermore, a double lip occurs in the context of Ascher's syndrome associated with the triad of blepharochalasis, non-toxic euthyroid goiter, and double lip, which has been described in about 100 cases up to now [3]. The double lip is mostly free of symptoms, however, it may also cause problems with speaking and chewing. The surgical removal of the hypertrophic tissue with preservation of the underlying muscles provides good functional and esthetic results.

Further information
For medical staff: [3].

Teleangiectasias in the context of Rendu-Osler disease (prevalence of less than 0.0005 %) often occur also in the lip, the oral cavity, and the pharynx, but they mostly become symptomatic in the area of the nasal mucosa. Here, the contribution of Fabian Sommer in this volume and the review article of Haubner and Kühnel [81] are recommended. An overview about further rare syndromic malformations of the lip, the oral cavity, and the pharynx is given in ▶ **Table 1**.

2.2 Rare non-neoplastic diseases

The particular anatomical characteristics of the head and neck area do not only explain the exceptional significance of this body region for immunological processes, but are also the basis for the extraordinary importance of infectious diseases in Oto-rhino-laryngology. Viral (mostly caused by adenoviruses, influenza/parainfluenza viruses, rhinoviruses, enteroviruses, corona viruses, respiratory syncytial virus, Epstein-Barr virus, and other viruses) and bacterial (mostly caused by *Streptococcus pyogenes*, *Streptococci* of the groups C and G, *Haemophilus influenzae*, *Nocardia*, corynebacteria, *Neisseria gonorrhoeae*, and other bacteria) tonsillopharyngitis is the most frequently observed disease of the head and neck giving reason for more than 5 % of all medical consultations in Germany. Therefore, the identification and treatment of rarely occurring complications of these pathologies such as abscess formation (30 cases per 100 000 people per year) belongs to the daily routine of oto-rhino-laryngologists [85]. Furthermore, also inflammatory alterations frequently occur in the lip (cheilitis) as they are observed in the context of *herpes simplex labialis* (prevalence of more than 90 % of the population) and the angular cheilitis (synonyms: rhagades, *perlèche*; prevalence of 0.7 %) or of the oral mucosa as observed in *gingivostomatitis herpetica* (synonyms: aphthous stomatitis, oral thrush), of *herpes zoster* (incidence of about 1 % per year), or habitual aphthae (prevalence of about 5–60 %). Furthermore, also in the context of autoimmune processes such as lichen ruber mucosae (prevalence of about 0.5 %) or chronic-inflammatory gut diseases (prevalence of 0.2 %) efflorescences of the oral and pharyngeal mucosa are frequently found. Also iatrogenic alterations of the mucosa and mycoses (*e. g.*, caused by *Candida spp., Aspergillus spp., Cryptococcus spp., Rhizopus spp., Mucor spp., Histoplasma spp., Blastomyces spp., Sporothrix spp., Trichophyton spp.*, or *Rhinosporidium seeberi*) in the oral cavity and pharynx after irradiation and/or chemotherapy, after bone marrow or stem cell transplantation as well as in the context of graft vs. host reactions are often found by oto-rhino-laryngologists in their daily routine [139]. The same is true for damage in this area by foreign bodies, acids, or alkaline solutions. For oral manifestations of diseases that very rarely occur in middle Europe and that are caused by protozoa, arthropods, and other parasites (*e. g., Leishmaniosis, larva migrans*) or bacteria (*e. g., bacillus anthracis*), the author refers to the specific literature regarding infectiology and tropical medicine. Referring to angioedema which is well known to oto-rhino-laryngologists (prevalence of about 1:100 000) a recent review article of Bas [14] and the guideline of the AWMF are recommended. Regarding disorders of tasting, for which the incidence together with the incidence of olfactory disorders is supposed to amount to 50,000 newly occurring cases per year, the guideline of the AWMF is recommended. The following paragraph will focus on rare non-neoplastic diseases of the lip, the oral cavity, and the pharynx.

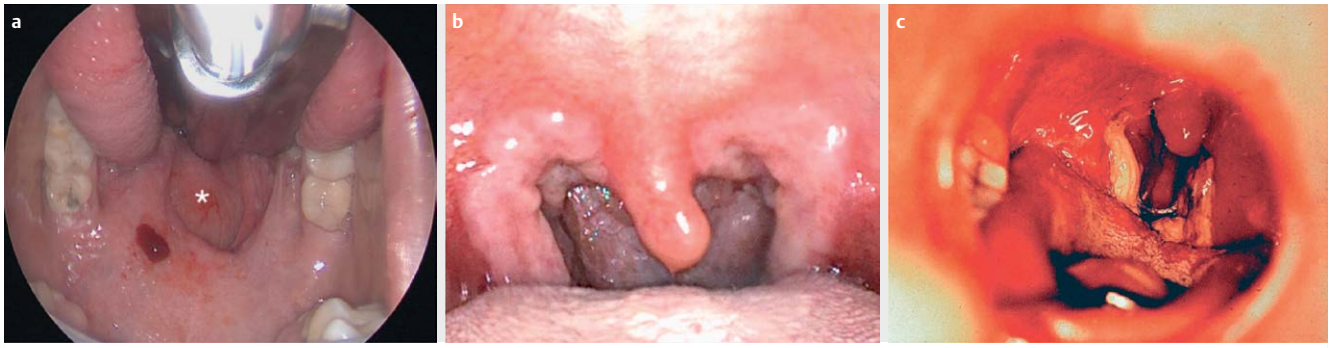
2.2.1 Specific tonsillo-pharyngitis

In cases of persistent courses of sore throat, immune deficiency must also be included as differential diagnosis [93] as well as specific infections (▶ **Fig. 2**).

The mycobacterium tuberculosis complex (*M. tuberculosis, M. bovix [ssp. bovis* and *caprae], M. africanum, M. microti, M. canetti* and *M. pinnipedii*) causes extrapulmonary manifestations of tuberculosis in 10 % of the cases, even rarer in the head and neck area. Beside the cervical lymph nodes (about 35 %) and the larynx (about 27–30 %), also the oropharynx (about 13–15 %) is a predilection site. Clinically, often a painful ulcer is found in the affected mucosa [26]. The treatment employs an antibiotic combination therapy. For this purpose, substances including isoniazide, rifampicin, ethambutol, pyrazinamide, streptomycin are currently available.

Also syphilis in the oral cavity and the pharynx occur rarely. Clinically, they present at the location of a primary affection caused by an infection with *Treponema pallidum* as an indurated painless ulcer (chancre) which spontaneously heals after 4–6 weeks. In the secondary stage, multiple plaques may develop in the mucosa of the mouth, tongue, and pharynx. Due to the missing resistance to antibiotics of *Treponema pallidum*, syphilis is still treated with penicillin V [99, 119].

Actinomycetes are bacteria of the physiological oral flora that usually develop their pathogenic potential only in submucous tissue layers and in the context of (often posttraumatic) mixed infections in combination with other pathogens. In cases of cervico-facial actinomycosis, nodes develop in the different regions of the head and neck that may mimic nearly every disease. Their incidence



▶ **Fig. 2** Specific inflammation of the oral cavity and the pharynx. Representative pictures taken from manifestations of tuberculosis (a; * shows the retropharyngeal swelling caused by tuberculosis [86]), of syphilis (b [166]), and diphtheria (c [126]) in the area of the oral cavity and the oropharynx.

is estimated to 2–5 cases per 100 000 people per year. Typically, the lesions may break open and leak large amounts of pus, which often contains characteristic granules. Therapeutically, a long-term treatment with penicillin is applied. Alternatively, also tetracyclines, erythromycin, clindamycin, or ciprofloxacin turned out to be effective [174].

Francisella tularensis spp. are a group of gram-negative, aerobe bacteria that are mainly transmitted by rabbits or hares and cause tularemia (rabbit fever). Furthermore, the transmission may also occur via horseflies, flies, and tics or via contaminated water, dust, or food. In Germany, 10–30 cases of this kind of zoonosis are reported per year, can be differentiated glandular, ulceroglandular, occuloglandular, typhoid, pulmonary, and pharyngeal tularemia; the pharyngeal type is most rarely observed. Clinically, multiple painful ulcerations in the mouth and oral cavity become apparent. Therapeutically effective are aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, and rifampicin. Without treatment, the diseases may become lethal in up to 60 % [50, 82, 183].

Diphtheria (formerly referred to as "true croup") is caused by toxin-developing strains of the bacterium *Corynebacterium diphtheriae* (host: humans) as well as the strains of *C. ulcerans* (broad spectrum) and *C. pseudotuberculosis* (host: sheep, goat) via airborne and contact infection. The incubation time amounts to 2–5 days. Clinically, severe inflammation of the pharynx and larynx is found, sometimes also of the skin with grey-whitish, easily blooding surface and sweetish smell from the mouth. The inflammatory swelling may even lead to suffocation. In addition, a toxic damage of heart, kidneys, and nerves may occur. The contagiousness amounts to 2–4 weeks and longer, with antibiotic therapy it is reduced to 48–96 hours. A high number of infections acquired in Germany is associated with the contact to dogs, cats, and farm animals (*C. ulcerans*). If clinically suspected, a swab should be taken immediately in order to identify the pathogen and the toxin. Afterwards, the antitoxin must directly be applied to block the toxin-mediated protein synthesis inhibition and antibiotic therapy with penicillin or macrolides should be started to eradicate the pathogen [179]. The antitoxin application already at the time of clinical suspicion is crucial for the further course of the disease because cellularly bound diphtheria toxin can no longer be neutralized by the antitoxin. The STIKO (Ständige Impfkommission, Standing Committee on Immunization) recommends prophylactic vaccination.

Further information

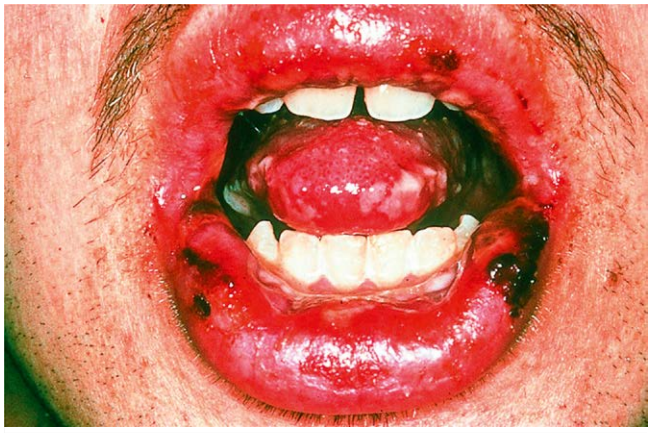
For medical staff: Robert Koch Institut (http://www.rki.de), Paul Ehrlich Institut (http://www.pei.de).

2.2.2 Drug-related exanthema and enanthema

Erythema exsudativum multiforme (incidence of 0.01–0.1 % per year) describes an acute inflammatory reaction that causes convex, cockade-like skin or mucosal lesions (▶ **Fig. 3**). A minor form affecting mainly distally the upper extremities and a major form with skin affection of the whole body including lip and oral mucosa are distinguished. Lesions generally recede spontaneously, however, they often recur. Infections especially with herpes simplex viruses or mycoplasms as well as more rarely also drugs are suspected to be triggering factors of erythema exsudativum multiforme. The diagnosis is made clinically. Therapeutically, immunosuppressants and, if needed, antiviral medication is applied [17, 73].

The Stevens Johnson syndrome and the toxic epidermal necrolysis (TEN; incidence of about 0.001 % per year) are mostly triggered by sulfonamides, allopurinol, aromatic anticonvulsants, lamotrigine etc. and are severe blistering skin reactions. The symptoms typically develop 4–28 days after medication. While only small skin areas are affected in Stevens Johnson syndrome (< 10 % of the body surface), more than 30 % of the body surface are involved in cases of TEN. Beside fever and general symptoms, also regularly erosive, crusting mucosal alterations in the lip, oral cavity, and pharynx are found as well as in the eyelids and genitals. For treatment, immunosuppressants and antibiotics are used, an intensive medical care with reverse isolation may be necessary. The mortality of this disease amounts to 5 % (Stevens Johnson syndrome) or up to 25 % (TEN), respectively [17, 73].

Sweet syndrome (Synonym: acute febrile neutrophil dermatosis) is a very rare, often recurrent disease (up to now about 100 cases have been described) which is characterized by the sudden development of fever, neutrophilia in the peripheral blood, and skin changes (papules and plaques with dermal infiltration by neutrophilic granulocytes). Rarely, also the oral and pharyngeal mucosa are involved [192]. The idiopathic/classic type (about 60–80 % of the cases; mostly women, most frequently in the context of infections of the upper respiratory pathways or the gut and during pregnancy), the malignoma-related type (about 20 % of the cases, most frequently in the context of acute myeloic leukemia), and the drug-



▶ **Fig. 3** Drug-induced exanthema and enanthema. Manifestation of the erythema exsudativum multiforme in the head and neck as exfoliative cheilitis with hemorrhagic crusting of the lip vermilion (figures taken from [188]).

induced type (about 5 % of the cases, most frequently after treatment with granulocyte colony stimulation factor [G-CSF]). The treatment of Sweet syndrome includes applying immunosuppressants [169].

2.2.3 Pemphigoid

The so-called pemphigoids are rare diseases of the skin and the mucosa characterized by intra- or subepidermal blistering. The origin are autoantibodies directed against certain structural proteins of the dermis and epidermis. The diagnosis is made clinically, serologically, and histopathologically are differentiated. A two groups of this disease: pemphigus (incidence of 1–2 cases per 1 000 000 people per year corresponding to 0.0001–0.0002 %) and pemphigoid (incidence of 13 cases per 1 000 000 people per year, corresponding to 0.0013 %). Therapeutically, immunosuppressive drugs are applied [171, 172].

In cases of pemphigus, antibodies directed against the desmosomal structural proteins 1 and 3 are found resulting in an intraepithelial, suprabasal acantholytic blistering. While the more frequently occurring subtype of pemphigus vulgaris often leads to alterations of the oral mucosa (▶ **Fig. 4**), the less frequently occurring subtype of pemphigus foliaceus only rarely leads to lesions in the area of the oral cavity. In cases of the subtype of paraneoplastic pemphigus which may develop in the context of neoplastic processes (*e. g.*, B-cell Non-Hodgkin lymphoma, chronic lymphatic leukemia), also intraepidermal blistering with acantholysis occurs, however, hereby the autoantibodies are directed against plakin proteins [171].

In cases of pemphigoid, however, a subepidermal blistering develops which is caused by autoantibodies directed against the components of the hemidesmosomal complex in the area of the basal membrane. Among others, bullous pemphigoid (only in 10–20 % the mucosa of the oral cavity is affected), mucosa pemphigoid, and scarring pemphigoid (no predominant mucosa affection) subtype are differentiated. The involvement of the eyes is a complication of the pemphigoid which may even lead to blindness [172].

Further information

For medical staff: Dermatologic literature as well as guidelines of the AWMF (http://www.awmf.org).

For patients: Pemphigus + Pemphigoid Self-Help Group e.V. (http://pemphigus-pemphigoid-selbsthilfe.de).

2.2.4 PFAPA syndrome

The non-hereditary PFAPA syndrome (synonym: Marshall syndrome with periodic fever) is characterized by periodic fevers lasting for 3–6 days, aphthous stomatitis, pharyngotonsillitis, and cervical lymphadenitis as well as the absence of diarrhea, breast pain, skin rashes, and arthritis. The diagnosis is made based on the Eurofever/PRINTO classification by the presence of 7 out of these 8 criteria [66]. PFAPA syndrome is observed more frequently in boys than in girls and manifests mainly at the age of 2–5 years. The prevalence of this disease is unclear – up to now at least 500 cases have been documented in the literature. It seems to be pathogenetically significant that the pro-inflammatory cytokine interleukin-1β is released in an uncontrolled way, the origin depends on several factors. Therapy comprises the administration of corticosteroids as well as tonsillectomy, in cases of mild courses or for palliation of the symptoms NSAR is applied. Refractory cases (after tonsillectomy) are rare [184].

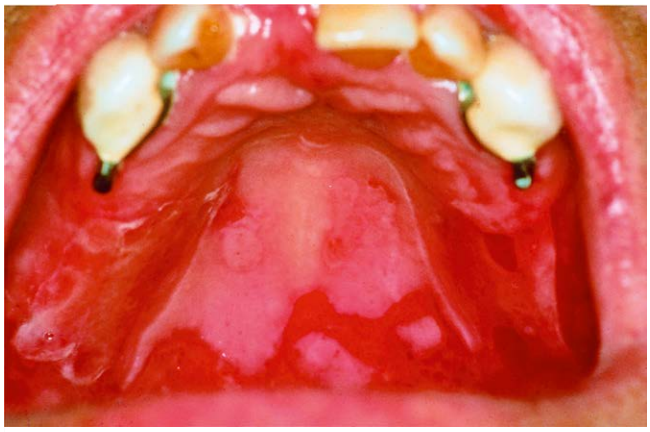
For differential diagnosis, especially monogenic autoinflammatory syndromes must be excluded. Those are for example the familial Medierranean fever (FMF; mutations in the MEFV gene), the TNF receptor-associated periodic fever syndrome (TRAPS, mutations in the TNFS-RF1A gene), the hyperimmunoglobulin D syndrome/mevalonate acid kinase syndrome (HIDS/MKD, mutations in MVK gene), and the cryopyrin-associated periodic syndrome (CAPS, mutations in NLRP3 gene). In the context of CAPS, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological, cutaneous, and articular syndrome (CINCA), and neonatal-onset multisystem inflammatory disorder (NOMID) have to be distinguished [184].

Further information

For medical staff: Pediatric literature as well as guidelines of the AWMF (http://www.awmf.org). Pediatric Rheumatology International Trials Organisation (PRINTO, http://www.printo.it).

2.2.5 Melkersson-Rosenthal syndrome

The idiopathic orofacial granulomatosis (OFG) describes a rare chronic inflammatory disease which summarizes Miescher cheilitis (isolated cheilitis granulomatosis) and the Melkersson-Rosenthal syndrome. Melkersson-Rosenthal syndrome is characterized by the symptom triad of orofacial swelling, lingua plicata (about 30–80 %) and attacks of peripheral facial paresis (about 30–90 %); with a prevalence of 4–8 per 10 000 people (corresponding to 0.04–0.08 %) it belongs to the group of rare diseases. The three symptoms do not always occur simultaneously (in about 20–75 % of the cases). The origin of this syndrome is still unknown, however, an autosomal dominant inheritance is assumed. Females are more frequently affected than males, the symptom onset usually occurs in the early adulthood. With regard to children, only 30 cases of Melkersson-Rosenthal syndrome have been described. The diagnosis is considered as confirmed with the clinical manifestation together



▶ **Fig. 4** Blistering autoimmune dermatoses. Manifestation of pemphigus vulgaris in the area of the hard palate (figures taken from [188]).

with the histological evidence of cheilitis granulomatosa. In cases of developing symptoms, therapy includes oral and topical/intralesional application of corticosteroids. In cases of refractory/recurrent course, other immunosuppressants are applied, if needed, also surgical decompression of the facial nerve should be discussed [44, 164].

Regarding granulomatous diseases that manifest mostly in the nose such as rhinoscleroma or granulomatosis with polyangiitis (former: Wegener's disease) of the head and neck, the contributions of Fabian Sommer and Stephan Hackenberg are recommended.

2.2.6 Behcet-Adamantiades syndrome

Behcet-Adamantiades syndrome is a systemic autoimmune disease of the small vessels, which is frequently observed in the Eastern Mediterranean regions, central and Eastern Asia. In Turkey, a prevalence of up to 420 per 100 000 people (0.42 %) is reported, while only 5.2 per 100 000 people (0.0052 %) are affected in the USA [9, 28]. The occurrence of this disease is associated with a genetic disposition (HLA-B51/B5) and is triggered by acute infections and environmental factors. The disease mainly manifests in the 3rd decade of life. Clinically, typical aphthous lesions are found in the whole oral and pharyngeal mucosa (98.5 % of the patients), genital ulcerations (63.7 % of the patients) as well as skin alterations (papulopostular lesions, erythema nodosum; 62.5 % of the patients), arthropathies (53 % of the patients), and ocular manifestations (58.1 % of the patients). Hereby nearly all structures of the eye may be affected which may lead to blindness within very few years. In rare cases, venous thrombosis (22.7 % of the patients), neurological or psychiatric manifestations (10.9 % of the cases), or gastrointestinal involvement (11.6 % of the patients) are observed. Also pulmonary, cardiac, and renal manifestations have been described, severe courses occur in 12 % of the patients. Oral aphthae are mainly treated with chlorhexidine solution, also local anesthetics, NSAR, or 5-amino-salicylic acid are applied. Isolated lesions may be etched for example with silver nitrate. Furthermore, systemic immune suppressive/modulatory drugs are applied [80].

Further information

For medical staff: Guideline of the AWMF (http://www.awmf.org).

For patients: Deutsche Rheumaliga (http://www.rheuma-liga.de), Deutsches Register M. Adamantiades-Behcet (http://www.behcet.de), Behcet self-help (http://www.behcet-selbsthilfe.de).

2.2.7 Vago-glossopharyngeal neuralgia

If the primary clinical and radiological findings are inconspicuous, also a rarely occurring vago-glossopharyngeal neuralgia must be taken into consideration in cases of the leading symptom of "sore throat". The incidence of this disease is estimated to 0.7 cases per 100 000 people per year [112]. Typically, sudden sharp pains occur, sometimes even longer lasting, in the area of the ear, the tonsils, the larynx and/or the base of tongue that may be triggered by swallowing, speaking, chewing, or coughing. Accompanying symptoms may be bradycardia, hypotonia, syncopes, or even asystoles. Interestingly, spontaneous remission is described in up to 80 % of the cases. It is assumed that the vago-glossopharyngeal neuralgia is based on a neurovascular compression by the posterior cerebellar artery or vertebral artery. Therapeutically, carbamazepine and gabapentin are applied. Alternatively, microsurgical decompression of the nerves may lead to good symptom control [106].

Regarding further neurological diseases that may manifest as dystonia or myoclonus in the area of the lingual, palatal, and pharyngeal muscles, specific neurological literature is recommended.

Further information

For medical staff: Guideline of the AWMF (http://www.awmf.org).

For patients: Deutsche Schmerzgesellschaft (https://www.schmerzgesellschaft.de).

2.3 Rare neoplastic diseases

In many cases, neoplasms of the oral cavity and the pharynx are benign. Tornwaldt cysts (bursa pharyngealis) are considered as the most frequently observed congenital masses of the nasopharynx with a prevalence of up to 4 % in the population [135]. Further examples of benign neoplasms in this area are papillomas, fibromas, hemangiomas, lipomas, rhabdomyomas, leiomyomas, chondromas, and osteomas. Much more rarely (less than 1 % of all head and neck tumors), juvenile angiofibromas are found in the nasopharynx that are nonetheless well known to experienced oto-rhino-laryngologists [129]. However, also the prevalence of precancerous conditions such as leukoplakia or erythroplakia is rather high and is estimated to 1–5 % worldwide, while leukoplakia are most frequently found with a prevalence of about 2 %. More than 90 % of all malignant neoplasms of the head and neck are squamous cell carcinomas. Cancer of the larynx (in Germany currently 4.3 newly diagnosed patients per 100 000 people per year, corresponding to 0.0043 %), of the oropharynx and the oral cavity (in Germany currently 4.3 newly diagnosed cases per 100 000 people per year, corresponding to 0.0043 %), of the lip (in Germany currently 1.8 newly diagnosed patients per 100 000 people per year corresponding to 0.0018 %), of the hypopharynx (in Germany currently 1.7 cases per 100 000 people per year corresponding to 0.0017 %), and the nasopharynx (in Germany currently 0.5 newly diagnosed patients per year corresponding to 0.0005 %) are nominally rare, but taken together squamous cell carcinomas of the head and neck rank sixth

on the list of malignant tumor diseases worldwide. Regarding the treatment of these malignomas, still mainly multimodal concepts are applied that comprise surgery, radiotherapy, and pharmacological therapies. Hereby, increasingly immune therapy and proton irradiation gain importance [198]. Furthermore, lymphomas are diagnosed as second most frequent primary malignant tumor disease of the head and neck [193]. Overall, 25 % of all extranodal lymphomas have their origin in the head and neck region. The treatment of these malignant tumors is generally performed by the colleagues of medical oncology. In this context, the specific literature and the current guidelines of the AWMF are recommended. Further rare benign and malignant neoplastic diseases that may not only affect the lip, oral cavity, and pharynx, but also cervical soft tissues, will be discussed in Chapter 3.3.

3. Cervical Soft Tissues

3.1 Rare anatomical anomalies and malformations

In the context of anatomical anomalies and malformations of the cervical soft tissues, first median and lateral cervical cysts and fistulas must be taken into account. Their prevalence amounts to about 5 or 2 %, respectively [2]. An extreme form of a remnant from the embryonic stage is the extremely rare occurrence of an immature twin within the more mature twin (*fetus in fetu*) in the neck area for which only few case reports have been published [207, 213]. More frequently, the congenital or acquired misalignment of the neck called torticollis is observed that affects about 0.5 % of the population and thus it is not an orphan disease according to the definition [51]. One possibly underdiagnosed cause for torticollis may be the pain-related relieving posture of the neck due to an inflammatory atlanto-axial subluxation that may occur in the context of infections of the upper airways or after surgical interventions of the head and neck. As well-known, this disease is named after the French surgeon Pierre Grisel as Grisel syndrome (synonym: torticollis atlantoepistrophealis, Watson-Jones disease) [54]. The following chapter will deal with nominally rare anatomical anomalies and malformations of the cervical soft tissues.

3.1.1 Lymphatic and arteriovenous malformations

Irregular anatomical courses and aneurysms of cervical vessels are not rare but they may be crucial to head and neck surgeons for preoperative planning. Furthermore, the prevalence of congenital vascular malformations is estimated to 4–5 % in the population, 60 % of which involve the head and neck [71]. According to the classification of the International Society for the Study of Vascular Anomalies (ISSVA), vascular malformations are categorized with regard to their hemodynamic properties. Capillary, venous, and lymphatic low-flow lesions may occur in an isolated way, but also in combination with other anatomical anomalies as in the context of Klippel-Trénaunay, Sturge-Weber, or Proteus syndrome. Similarly, it is the case with arteriovenous high-flow lesions as they occur in cases of Parkes-Weber or CLOVES syndrome. While capillary (prevalence of 0.3 %), venous (prevalence of about 1 %; formerly called cavernous hemangioma), and combined vascular malformations are observed relatively frequently in the population, lymphatic (prevalence of about 0.01 %; formerly called lymphangioma) and arteriovenous (prevalence of about 0.01 %; formerly called arteriovenous hemangioma) malformations and fistulas belong to the field of orphan diseases.

Lymphatic malformations are congenital malformations of the lymphatic system [72]. They develop based on defects during embryonic lymphangiogenesis. The exact pathological mechanisms are still unknown. In the neck, where they are found most frequently (in about 75 % of the cases) [38], lymphatic malformations are also called cystic hygroma or *hygroma cysticum* or *lymphangioma colli*. Mostly, these malformations occur sporadically and unifocally. On palpation, lymphangiomas appear soft, pulseless, and without pain on pressure. Often they shimmer bluish through the skin. Beside esthetic impairment, they may cause significant functional problems (*e. g.,* turning the head, opening the mouth) up to obstruction of the airways. Complications occur in particular when these malformations are infected which often leads to an acute growth of the lesions. The diagnosis is made by ultrasound and MRI based on their morphological and hemodynamic properties. Depending on their structure, solid, micro- (cyst diameter of less than 2 cm) and macro-cystic (cyst diameter of more than 2 cm) are differentiated. Beside surgery (especially in cases of solid lesions), sclerotherapy may be performed in particular for micro- and macrocystic lesions (*e. g.,* with Picibanil [OK-432, Chungai Pharmaceutical Co., Tokyo, Japan], ethanol, bleomycin, or doxycycline) [10]. In particularly complex cases, the application of mTOR inhibitors such as sirolimus may be appropriate which is currently investigated in the context of clinical trials [210].

Arteriovenous malformations and fistulas are congenital vascular malformations where blood from the arterial vessels directly flows into the venous vascular system without passing through the capillary system. Due to their typical infiltrative growth behavior, they may destroy surrounding tissue including bone while massive life-threatening bleeding may occur. Extracranial arteriovenous malformations are mostly observed in the head and neck region. For diagnosis, MR and CT angiography are applied that allows assessing the hemodynamism and invasiveness of the lesions. The treatment of those lesions is performed by means of transarterial, -venous or -cutaneous embolization or surgical removal as well as a combination of both treatment modalities [109].

Further information

For medical staff: International Society for the Study of Vascular Anomalies (https://www.issva.org), Deutsche interdisziplinäre Gesellschaft für Gefäßanomalien e.V. (https://diggefa.de).

For patients: Bundesverband Angeborene Gefäßfehlbildungen e.V. (www.angiodysplasie.de).

3.1.2 Congenital midline cervical cleft

The congenital midline cervical cleft (CMCC) is a very rare anatomical anomaly of the anterior neck. This malformation was first described in the middle of the 19th century by the anatomist Hubert von Luschka from Heidelberg, Germany [77], before it was presented also to the English speaking readership by Bailey in 1925 [76]. Regarding its pathogenesis, a multitude of different hypotheses is discussed – according to the general opinion, a missing intrauterine fusion of the facial processes of the first and second pharyngeal arch due to mechanical or vascular factors is responsible for this

developmental disorder [11]. More recent investigations indicate that polymorphisms of single nucleotides might be the cause of the development of the congenital midline cervical cleft [132].

Up to now, around 200 cases of congenital midline cervical clefts have been described, only few of them are associated with other cleft formations in the body midline [30]. In order to avoid contractures in the neck and from an esthetic point of view, early surgical excision of the malformation with defect closure by means of W or Z plastic is recommended [12].

Further information
For medical staff: [153]

3.1.3 Hypertrichosis of the anterior neck

An abnormal amount of hair growth at the anterior neck is a localized type of hypertrichosis which is limited to the area of the cervical skin at the level of the laryngeal prominence. This disease may be inherited or acquired and manifest already at birth or later in childhood. Up to now, at least 40 cases of isolated hypertrichosis of the anterior neck have been observed [21, 42, 61, 133, 148, 157 , 196, 201]. In 30 % of these cases, additionally an association with peripheral sensomotor neuropathy and mental retardation was found. The origin of this disease is not known. For therapy, epilation is applied in order to reduce the abnormal hair growth.

Further information
For medical staff: [133]

3.1.4 Hereditary thyroglossal durct cyst

As mentioned above, cyst of the thyroglossal duct is one of the most frequently observed malformations of the neck with a prevalence of about 5 % in the population [2]. This cystic lesion is based on a persistence of the thyroglossal duct and becomes apparent in childhood as painless, elastic swelling in front of the lingual bone, often accompanied by swallowing disorders or in the context of superinfection. Sonographic criteria for the presence of a median cervical cyst are an irregular, poorly defined cystic wall as well as intralesional septa with liquid and solid parts [94]. In rare cases, a papillary thyroid carcinoma is found in the cyst epithelium [18, 141, 199].

While most cases occur sporadically, there are interestingly also very rare hereditary forms that have been observed in at least 9 families with a total of 30 affected persons [154, 170]. Beside autosomal-recessive inheritance, the majority consisted in autosomal-dominant types. The exact genetic origin of this hereditary type of median cervical cyst is still unknown.

The current treatment standard consists of complete surgical excision of the median cervical cyst including the removal of the median part of the lingual bone and if needed of parts of the tongue (surgery according to Sistrunk with different modifications [181]). In this way, the recurrence rate after surgery may be reduced to less than 5 % [48]. Besides, recent clinical trials give hints that also sclerotherapeutic approaches (e. g. with ethanol or OK-432) may be successful in this context [32, 194].

3.2 Rare non-neoplastic diseases

The treatment of phlegmonous or abscessing inflammations of the cervical soft tissues as well as hemangiomas or seromas in this region which may occur in the context of postoperative complications belongs to the routine of experienced ENT specialists. Regarding neoplastic pathologies which manifest mainly in the salivary glands in cases of IgG4-associated diseases of the head and neck, the article written by Claudia Scherl in this booklet is referred to. Thromboses of the internal jugular vein, the feared necrotizing fasciitis, or rare non-neoplastic pathologies that are primarily found in the lymph nodes or as pseudotumors, however, are more “exotic” findings of the head and neck and will be discussed in the following chapters.

3.2.1 Thrombosis of the internal jugular vein

Deep vein thromboses occur with an incidence of 1:1,000 people per year, but only 4–10 % of these events involve the upper extremities. While the subclavian vein is affected relatively frequently (about 62 %), thromboses of the internal jugular vein (comparable to the axillary vein) are found in only 45 % of the cases [43]. Thrombosis of the internal jugular vein has to be considered as rare disease with an incidence of 0.018–0.0045 % per year.

As risk factors for the development of internal jugular vein thrombosis, the insertion of a central venous catheter or pacemaker must be mentioned, but also a tumor-related hypercoagulation of the blood and inhaled tobacco smoke. Besides, also genetic reasons such as a factor-V-Leiden mutation or medication (*e. g.*, high-dose corticosteroids) may promote the development of thrombi [187]. In most cases, the disease remains asymptomatic or is associated with unspecific symptoms such as swelling or pain in the neck [118, 167]. Typical complications are the post-thrombotic syndrome, chronic venous insufficiency, and thrombophlebitis. Pulmonary embolism or the superior vena cava syndrome only rarely occur. Compression ultrasound together with Doppler-/color-coded duplex sonography is the diagnostic measure of choice due to a sensitivity of 97 % and a specificity of 96 % [49]. Regarding the initial treatment of jugular vein thrombosis, unfractionated or low-molecular heparin is applied, but also new oral anticoagulants (NOAC) such as rivaroxaban or apixaban are applied. The preservation therapy is continued with vitamin K antagonists or NOAC at least until the origin is eliminated (see current AWMF guideline on venous thrombosis and pulmonary embolism) [83, 97].

A very rare origin for thrombosis of the internal jugular vein may be septicemia developing from an inflammation of the pharyngeal space which was named after the first description of André-Alfred Lemierre as Lemierre syndrome. The most frequent pathogens detected are fusobacterium necrophorum and other fusobacteria, less frequently streptococci, staphylococci, enterococci, and Klebsiella pneumoniae [113]. Clinically distinct symptoms of Lemierre syndrome do not exist. Metastatic abscesses in the joints, the lung, and the brain are feared complications. The mortality of Lemierre syndrome amounts to 2–10 % [33]. The treatment comprises targeted antibiotic and antithrombotic therapy as well as surgery of infection foci [113].

Further information
For medical staff: guideline of the AWMF (http://www.awmf.org)
For patients: Deutsche Gefäßliga (http://deutsche-gefaessliga.de)

3.2.2 Necrotizing fasciitis

Necrotizing fasciitis is a life-threatening bacterial infection that may affect all fascia of the body and that is characterized by a fulminant distribution of colliquative necrosis in the area of those structures [64]. In most cases, it is caused by mixed infection due to minor trauma of different anaerobic and aerobic pathogens (type 1), however, also an infection with group A β-hemolytic streptococci alone, sometimes in combination with *staphylococcus aureus* or *staphylococcus epidermidis*, is possible as origin of the disease (type II; [69]). With an incidence of 0.2–400 per 100 000 people per year, it is a rare disease, while only 1–10 % occur primarily in the head and neck and have an odontogenic focus [74].

An indicator for the presence of necrotizing fasciitis may be extreme local pain which is caused by ischemia in the area of the fascia. Only with advanced stages of the disease, skin alterations become apparent that range from edematous and erythematous changes up to livid, map-like skin necrosis. Crepitus indicates the presence of mixed infection. CT scans show abscesses and air accumulation. Diagnostically, necrotizing fasciitis has to be differentiated from gas gangrene (caused by *clostridium perfringens* and subtypes) and the *streptococcus*-associated toxic shock syndrome. In this context, the so-called "laboratory risk indicator for necrotizing fasciitis" (LRINEC) score (▶ **Table 2**; [211]) was developed. Its significance, however, is controversially discussed [89]. Risk factors are an age of more than 65 years as well as preexisting conditions such as diabetes mellitus, immune suppression, peripheral arterial closure, and vasculitis. Regarding the clinical course, an early diagnosis as well as immediate therapeutic intervention are crucial.

For the treatment of necrotizing fasciitis, a calculated multi-antibiotic therapy, radical surgical debridement of the affected tissue (which often has to be performed several times in the course of the disease) as well as intensive care of the patient are required. In this way, the lethality rate may be reduced to less than 20 % [191], delayed therapy, however, may increase this rate to more than 75 % [104]. The benefit of hyperbaric oxygen therapy or intravenous immunoglobulin application is disputed because of missing randomized prospective trials [91].

▶ **Table 2** LRINEC Score.

Lab parameter	Value	Unit	Score
CRP	< 15	mg/dl	0
	> 15	mg/dl	4
Leukocytes	< 15 000	cells/mm³	0
	15 000–25 000	cells/mm³	1
	> 25 000	cells/mm³	2
Hemoglobin	> 13.5	g/dl	0
	11.0–13.5	g/dl	1
	< 11.0	g/dl	2
Natrium	> 135	mmol/l	0
	< 135	mmol/l	2
Creatinine	< 1.6	mg/dl	0
	> 1.6	mg/dl	2
Glucose	< 180	mg/dl	0
	> 180	mg/dl	1

The "Laboratory Risk Indicator For Necrotizing Fasciitis" (LRINEC) is depicted. An overall score of 6 or more indicates the clinical assumption of the presence of necrotizing fasciitis [211].

Further information

For medical staff: [91]

3.2.3 Benign lymph node diseases and pseudotumors

In Rosai-Dorfman disease, children and young adults develop mostly bilateral abundant histiocytosis in the cervical lymph nodes leading to massive painless lymphadenopathy. In addition, affected patients suffer from fever, and in about 40 % of the cases also extranodal manifestation is observed which may affect all parts of the body, in particular the central nervous system. The diagnosis is made based on histopathology, its etiology and pathogenesis are still unknown. Generally, Rosai-Dorfman disease heals spontaneously, for palliation of the symptoms, surgical measures and immunosuppressants are applied [25].

Especially in young Asiatic adults, Kimura disease leads to unilateral painless cervical lymphadenopathy which is characterized by lymph node infiltration with eosinophilic granulocytes. In addition, eosinophilia is found in the peripheral blood as well as increased IgE levels. Furthermore, half of the patients develop renal and cutaneous manifestations. The major salivary glands of the head may be affected. Also this disease is diagnosed by means of histopathology. Its origin is unknown. For therapy, surgical excision of the affected lymph nodes, radiotherapy, immunosuppressants, and antihistamines are applied. Most cases heal spontaneously, in 25 % of the cases, however, recurrences are observed [161].

Castleman disease describes a very rare benign lympho-proliferative disease which occurs with a prevalence of about 2.4 per 100 000 people in the population and is associated with viral infections, *e. g.*, by human herpes virus 8 (HHV-8). A localized type that affects only a group of lymph nodes and the multicenter type where several lymph node groups are affected and that often concerns HIV patients are distinguished. Beside lymphadenopathy, the patients suffer from unspecific symptoms such as fatigue, fever, and weight loss, the multicenter type may also lead to hepato-splenomegaly and POEMS syndrome. From a pathogenetic point of view, it seems to be relevant that cytokines are abundantly released, especially interleukin 6. The diagnosis is made based on histology. The localized type of Castleman disease is treated by complete surgical removal of the affected lymph nodes which leads to healing in most cases. The multicenter type is treated with medication (*e. g.*, using chemotherapeutics, immune modulators, and antiviral therapeutics). The prognosis is poor, malignant transformation is possible [88, 124].

Inflammatory pseudotumors are benign processes with infiltrative character that consist of lymphocytes, plasma cells, macrophages, fibroblasts as well as eosinophilic and neutrophilic granulocytes. From their macroscopic aspect they are similar to malignant neoplasms. Their etiology is still not clear, autoimmune processes

(with IgG4 association), infections (*e. g.,* with mycobacteria, Rhodococcus equi, Klebsiella rhinoscleromatis), foreign bodies, and trauma are discussed as possible causes for this disease. Mostly, those pseudotumors are found in the lung, however, they may develop everywhere in the body and thus also in the head and neck. The treatment of this disease mainly consists of corticosteroids and surgical measures. If corticosteroids and surgery do not lead to improvement, radiotherapy is performed [108].

3.3 Rare neoplastic diseases

Swellings localized in the cervical soft tissues are often due to growth of the cervical lymph nodes. Often bacterial or viral infections are responsible for their etiopathogenesis. Frequently, however, also malignant diseases manifest in this way such as lymph node metastases or lymphomas. Furthermore, the occurrence of atheroma in the neck area (overall prevalence of 20 %, 80 % of them present in the head and neck), hemangiomas (overall prevalence of 3–5 %, 60 % of them in the head and neck), and lipomas (overall prevalence of 2 %, 15–20 % of them in the head and neck) is frequently observed. A rare extreme type of fat accumulation in the head and neck is the familial symmetric lipomatosis (Madelung disease). Its exact prevalence is still unknown [41]. Very rarely, benign tumors may also develop from residues of fetal brown fatty tissue that are called hibernomas and do not recur if they are completely removed [202]. In the last chapter of this article, further rare neoplastic diseases of the neck will be discussed. Neoplasms of the salivary glands will be presented in the article by Claudia Scherl. Regarding neoplasms of the skin, the dermatological literature as well as the current guidelines of the AWMF are referred to (http://www.awmf.org).

3.3.1 Hamartoma

Hamartomas are benign, mainly congenital neoplasms that consist of an imbalanced composition of local mature tissue and thus they may occur in every part of the body. These pseudotumors are rarely found in the neck with an incidence of 1:10 000 people per year [114]. Regarding the tongue, however, they rank third after hemangiomas and lymphangioms as neoplasms in the childhood [117]. Mesenchymal and epithelial hamartomas can be differentiated. If they are completely resected, generally no recurrences appear [163].

The PTEN hamartoma tumor syndrome summarized several diseases that are characterized by the occurrence of multiple hamartomas caused by an autosomal dominantly inherited mutation in the tumor suppressor gene PTEN via the activation of the PI3K/AKT signaling pathway [78]. The Cowden syndrome (prevalence of 1:200 000 people) is associated with the development of benign and malignant tumor of the thyroid gland, breast and endometrium as well as renal cell carcinomas, colon carcinomas, and melanomas. Affected patients often also have macrocephaly (head size of more than 97th percentile) and skin anomalies [151]. In cases of Bannayan-Riley, Ruvalcaba syndrome, intestinal hamartoma-like polyps, macrocephaly, and hyperpigmentation in the area of the male genital are characteristic [95].

The Proteus/Proteus-like syndrome is characterized by a point mutation of the AKT-1 gene (downstream of PTEN) and an excessive growth of bone, skin, and other tissue [36]. Also autism spectrum diseases with macrocephaly show PTEN mutations in 10–20 % of the cases. Lhermitte-Duclos syndrome is a variant of Cowden syndrome; in this context, hamartoma-like neoplasms develop in the area of the cerebellum in adulthood. Clinically, the affected patients have ataxia, seizures, and increased brain pressure. The pediatric juvenile polyposis (of the gut) is very rare and also points to mutations in the PTEN gene [150].

Further information

For medical staff: Guideline of the AWMF (http://www.awmf.org).
For patients: Self-help CoBaLd (http://www.shg-cobald.de).

3.3.2 Teratoma

Teratomas are congenital germ cell tumors containing tissue components from ectoderm, mesoderm, and endoderm [103]. They occur with an incidence of 1:40 000 people per year, about 5 % of them are found in the head and neck area [13]. The vast majority of those neoplasms is diagnosed and treated in newborns and children (about 90 %). In adults, they occur only rarely (about 10 %; [101]). Teratomas appear mostly as so-called mature cystic (dermoid/dermoid cyst) or solid benign tumors that already have the potential of malignant transformation. In about 5 % of the cases, so-called immature malignant teratomas are found.

Teratomas of the neck are often located anterolaterally and may impair already the intrauterine development of the fetus by compressing the digestive tract or by obstructing the airway during birth. So the diagnosis should already be confirmed *in utero* by means of ultrasound and MRI. Immediately after birth, a complete surgical excision of the tumor should be performed, in cases of highly vascularized neoplasms after preoperative vascular embolization [180]. Malignant immature tumors are further treated by chemotherapy. Alpha-fetoprotein (AFP) serves as posttherapeutic follow-up parameter [56, 203]. The influence of immune checkpoint inhibitors on immature teratomas that are considered as "cold, deserted tumors" abandoned by the immune system [24] is currently unknown.

Further information

For medical staff: guideline of the AWMF (http://awmf.org)

3.3.3 Schwannoma

Schwannomas (also known as neurilemoma, benign nerve sheath tumor; malignant peripheral nerve sheath tumors are discussed in chapter 3.3.8) are slowly growing, benign tumors of Schwann cells surrounding peripheral nerves. These neoplasms have an incidence of 1–9:100 000 people per year, about 25–45 % are found in the head and neck region [31, 39]. The peak prevalence is between the 4th and 6th decade of life. Most schwannomas have their origin in the vestibular part of the vestibulocochlear nerve, more rarely, they develop from the vagus nerve, the trigeminus nerve, the facial nerve, the glossopharyngeal nerve, the accessory nerve, the hypoglossal nerve, or the sympathetic nervous system [107]. While they are mostly observed as solitary and sporadic lesions (90 % of the cases), they occur as multiple lesions in cases of neurofibromatosis type 2 (3 % of the cases). Multiple occurrence of schwannomas independently from neurofibromatosis and vestibular schwannoma, is found in about 2 % of the cases (prevalence of 1:40 000) and

is called schwannomatosis [98, 177, 208]. In the neck, most frequently vagus schwannomas are found that are generally asymptomatic and may cause sometimes hoarseness and cough. The recurrence rate and malignant transformation potential of schwannomas is still unknown. In the neck, surgical removal of these tumors is the therapy of choice. Hereby, the continuity of the affected nerves should be preserved.

Neurofibromas are also benign neoplasms of peripheral nerves that are characterized by a different histopathological appearance and a lower S100 expression as compared to schwannomas. Spinal nerves are rarely affected, cerebral nerves nearly never. Malignant transformation of these tumors is unusual [62]. Furthermore, also rarely occurring benign granular cell tumors of Schwann cells seem to develop from peripheral nerves that are characterized by an accumulation of secondary lysosomas in the cytoplasm of the tumor cells. In more than 50 % of the cases, they affect the upper digestive tract, in particular the larynx. Malignant transformation of these neoplasms is possible [160].

Further information

For medical staff: guideline of the AWMF (http://www.awmf.org)

For patients: Bundesverband Neurofibromatose e.V. (https://bv-nf.de); Bundesweite Selbsthilfegruppe für NF2-Betroffene (https://www.nf2.de)

3.3.4 Extracranial meningioma

Meningiomas are tumors that have their origin in the pia-arachnoidal cells of the central nervous system. They have an incidence of about 8–10:100 000 people per year. With a percentage of 30 %, meningiomas are the most frequently occurring brain tumors in adults. According to the WHO classification, they are subdivided into benign (grade I, 85 %), atypical, rapidly growing as well as recurrent (grade II, 8–10 %), and infiltratively growing anaplastic (grade III, 2–5 %) lesions. The peak of occurrence is observed between the 5th and 6th decade of life. In up to 20 % of the affected patients, multiple lesions are observed. Ionizing radiation is considered as risk factor. In single cases, meningiomas are inherited, *e. g.*, in the context of neurofibromatosis type 2 [165].

Interestingly, also (primary or secondary) extracranial meningiomas are found in the head and neck in about 2 % of the cases, mainly as benign lesions (WHO grade I) [65]. While intracranial meningiomas are more frequently diagnosed in females, extracranial meningiomas are more often found in males [34]. Most of them are located in the skull base. In the parapharyngeal space, they occur only rarely, in the literature only one case of a primary meningioma was reported in the palatal tonsil [140]. The cellular origin of these neoplasms is assumed to be ectopic arachnoidal cells. The diagnosis of meningioma can often be made by means of CT and MR imaging. If possible, intra- and extracranial meningiomas are preferably treated by surgery. In particular meningiomas of higher grades well respond to radiotherapy which is applied in cases of inoperability or as adjuvant therapy. In the future, also immune checkpoint inhibitors might play an important role in the treatment of aggressive meningiomas [67, 123, 156].

Further information

For medical staff: guideline of the AWMF (http://www.awmf.org); NIH National Cancer Institute (https://www.cancer.gov/publications/pdq/information-summaries)

For patients: Deutsche Krebsgesellschaft (http://www.krebsgesellschaft.de); Deutsche Kinderkrebsstiftung (http://www.kinderkrebsstiftung.de); Deutsche Hirntumorhilfe e.V. (http://www.hirntumorhilfe.de); Bundesverband Neurofibromatose e.V. (https://bv-nf.de); Bundesweite Selbsthilfegruppe für NF2-Betroffene (https://www.nf2.de)

3.3.5 Ectopic chordoma

Chordomas are rare (prevalence of less than 1:1 000 000 people), infiltratively growing tumors that develop from residues of the chorda dorsalis (notochord) in the area of the spine and form metastases in about 10–20 % of the cases. Most frequently, they are found in the coccyx and the clivus [186], single cases of ectopic chordomas (*e. g.*, in the pharynx) have been described in the literature [122]. The therapy of choice comprises the complete surgical removal of the tumors, followed by adjuvant radiotherapy. The 5-year survival rate currently amounts to 50 %. In the future, immunotherapeutic [60] and other targeted treatment approaches [185] might significantly improve the prognosis of these tumors.

3.3.6 Neuroblastoma

Neuroblastomas are malignant neuroectodermal neoplasms of the sympathetic nervous system being the most frequently occurring solid neoplasm in children. Overall, neurobalstomas have an incidence of 1:100 000 people per year, the neck area is affected only in about 5 % of the cases. 90 % are diagnosed within the first 5 years of life, boys are more frequently affected than girls [125]. When diagnosed, 50 % of the diseased patients already bear hematogenic metastases in the bone marrow, bones, liver, brain, or skin. Most neuroblastomas develop spontaneously, in 1–2 % of the cases they are inherited. Hereby, an association with Hirschsprung's disease, Undine syndrome, Costello syndrome (CDKN1C mutations), Noonan syndrome, neurofibromatosis type 1, Li-Fraumeni syndrome (TP53-R337H mutations), ROHHAD syndrome, Beckwith-Wiedemann syndrome (CDKN1C mutations), Sotos and Weaver syndrome is observed. The "International Neuroblastoma Risk Group (INRG)" staging system includes radiologic extent and metastatic status. The INRG classification further takes into account the patients' age, histopathological properties, MYCN status, chromosome 11q aberration status, degree of ploidy, and the risk profile before therapy [37]. The clinical appearance of the patients depends on the location of the primary tumor, often the patients are asymptomatic or suffer from uncharacteristic symptoms. Most neuroblastomas produce catecholamine which may lead to maternal tachycardia, hypertonia, and emesis already before birth. The concentration of vanillylmandelic acid or homovanillic acid in the urine is increased in more than 90 % of the patients. For treatment of neuroblastomas, generally multimodal therapy concepts are applied including surgery, radiotherapy, and polychemotherapy. First positive case reports about immunotherapeutic approaches have been published recently [55]. If the disease is diagnosed within the

first year of life the 5-year survival rate amounts to 86–95 %, in older children it decreases to 24–68 % [182].

Further information

For medical staff: guideline of the AWMF (http://www.awmf.org); International Neuroblastoma Risk Group (http://www.inrgdb.org); NIH National Cancer Institute (https://www.cancer.gov/publications/pdq/information-summaries).

For patients: Deutsche Krebsgesellschaft (http://www.krebsgesellschaft.de); Deutsche Kinderkrebsgesellschaft (http://www.kinderkrebsstiftung.de); Fördergesellschaft Kinderkrebs-Neuroblastom-Forschung e.V. (http://www.neuroblastoma.de); Deutsche Hirntumorhilfe e.V. (http://www.hirntumorhilfe.de).

3.3.7 Extra-adrenal paragangliomas

Extra-adrenal paragangliomas (also formerly known as glomus tumors) are highly vascularized neoplasms that originate from chromaffine cells of the sympathetic and parasympathetic nervous system. They have an incidence of less than 1:100 000 people per year [19]. Extra-adrenal paragangliomas mostly show a benign biological behavior, however, the probability of malignant transformation is estimated to 2–13 % (malignant paragangliomas). In this context, lymphogenic metastasis occurs [22], the 5-year survival rate amounts to 40–77 % [143]. Most paragangliomas develop sporadically. In 30–40 % of the cases, however, familial occurrence is observed, often in the context of autosomal-dominantly inherited familial pheochromocytoma paraganglioma syndrome which is based on different mutations of the mitochondrial succinate dehydrogenase (SDH). Here, three subtypes (PGL1, PGL3, and PGL4) are distinguished that cannot be clearly differentiated clinically and have to be diagnosed genetically. In addition, they often occur in patients with von-Hippel-Lindau syndrome (VHL syndrome), neurofibromatosis type 1 (NF1), or multiple endocrine neoplasm type II (MEN-II). Females seem to be preferably affected by paragangliomas, the mean age of disease onset is in the middle age of life. Typical anatomical locations are the carotid bifurcation (60 % of the cases), the jugular foramen, the middle ear (originating from the glossopharyngeal nerve), or the vagus nerve in its course (5 % of the cases). Glomus caroticum tumors are mostly symptom-free and can be moved in lateral (not vertical!) direction, which is called Fontaine sign [136]. If a glomus caroticum tumor compresses the vagus nerve, symptoms similar to glomus vagale tumors may occur such as swallowing disorder, hoarseness, or Horner's syndrome. While glomus jugulare tumors show a relatively aggressive growth behavior in the petrous bone, glomus tympanicum tumors are rather slowly growing. Clinically, these two paragangliomas may be accompanied by pulsatile tinnitus or unilateral hearing loss. For diagnosis, primarily ultrasound, MRI- and 18F-Dopa-PET are applied. For differentiation of glomus jugulare and glomus tympanicum tumors, CT scans are used. The complete surgical removal after vascular embolization is the current gold standard for the treatment of paragangliomas [173]. Non-resectable tumors undergo radiotherapy [120, 190]; in the metastatic situation, chemotherapy [90, 137] or targeted therapeutics such as the tyrosine kinase inhibitor of Sunitinib are employed [102].

Further information

For medical staff: NIH National Cancer Institute (https://www.cancer.gov/publications/pdq/information-summaries)

3.3.8 Soft tissue sarcoma

Sarcomas are rare malignant tumors of the mesenchymal tissue that occur with an incidence of 1.8–5:100 000 people per year and make up about 1 % of all head and neck malignancies [146, 209]. 80–90 % of the soft tissue sarcomas affect adults, 10–20 % involve children and adolescents [116]. Risk factors of the development of soft tissue sarcomas include radiotherapy, chronic lymphedema (lymphangiosarcoma), exposition to chemical substances such as thorium dioxide, vinyl chloride, and arsenic (hepatic angiosarcoma) as well as infections with HIV and HH8 viruses (Kaposi sarcoma). Higher prevalence of soft tissue sarcomas is observed among others in patients with Gardner syndrome (APC mutation), Li-Fraumeni syndrome (TP53 mutation), Gorlin syndrome (PTC mutation), tuberous sclerosis/Bournville disease (TSC1 or TSC2 mutation), neurofibromatosis type 1/von Recklinghausen disease (NF1 mutation), and Werner syndrome/adult progeria (WRN mutation). The WHO classification of 2020 differentiates more than 100 sarcoma entities (www.who.int or www.iarc.fr).

The most frequently occurring soft tissue sarcomas of the head and neck are fibrosarcomas, leiomyosarcomas, neurofibromatous sarcomas such as malignant peripheral nerve sheath tumors, synovial cell sarcomas, liposarcomas, angiosarcomas, and rhabdomyosarcomas [5]. Typically, soft tissue sarcomas of the head and neck present as painless swelling, they develop predominantly hematogenic metastases. After biopsy, the histopathological assessment is typically performed including national reference centers. For staging, MRI and CT scan are performed, probably also PET/CT. Therapeutically, sarcomas primarily undergo complete surgical resection of the lesion with sufficient safety margins. However, in most cases multimodal individual therapy concepts are employed that are adjusted to the respective sarcoma entity. They comprise chemo- and radiotherapeutic treatment concepts, if needed in combination with regional hyperthermia [96, 105]. In order to further improve the treatment quality, courses of the sarcoma patients are documented in registries such as the Interdisziplinäres Deutsches Sarkomregister (GISAR). Since up to now only single sarcoma entities revealed a response to treatment with immune checkpoint inhibitors, for example combinations with oncolytic viruses or vaccines or innovative immunotherapeutic approaches may represent more effective treatment strategies for sarcomas with less adverse effects. The mean 5-year survival rate amounts to 75 %, however, it is very different for the single sarcoma entities [5]. Furthermore, well differentiated sarcomas have a better prognosis than poorly differentiated neoplasms [57, 58].

Fibrosarcomas develop from (myo)fibroblasts and represent 1–3 % of all sarcomas. Fibrosarcomas developing in childhood have a more favorable prognosis than those occurring later in life [131, 200]. With about 100 published cases of infantile fibrosarcomas up to now, of which 40 % have been diagnosed at birth, these tumors may be considered as very rare [75].

Leiomyosarcomas develop from smooth muscle cells. Cutaneous tumors originating from the arrector pili muscles of the hair

follicles and subcutaneous neoplasms that develop from the smooth vascular muscles are differentiated. Cutaneous leimyosarcomas more rarely occur as subcutaneous leiomyosarcomas and seem to be less aggressive (5-year survival rate of 66.9 vs. 52.1 %; [168]).

Malignant peripheral nerve sheath tumors (MPNST; terms that are today no longer used are malignant schwannoma, neurogenic sarcoma, neurofibrosarcoma) are malignant neoplasms of peripheral nerves appearing with an incidence of 1:100 000 people and representing 5 % of all soft tissue sarcomas. Head and neck are affected in 10–20 % of the cases. Malignant peripheral nerve sheath tumors may develop sporadically or from neurofibromas, *e. g.,* in the context of neurofibromatosis type 1 (von Recklinghausen disease; > 50 % of the cases [6]). The prognosis of these head and neck tumors is very unfavorable with a 5-year survival rate of about 15–20 % [134].

Synovial cell sarcomas may appear in most different locations of the head and neck, most frequently they are located in the hypopharynx [87, 155]. It is assumed that these malignant neoplasms develop from undifferentiated or pluripotent mesenchymal stem cells, however, their exact origin is still unknown. 90–95 % of these malignant tumors have a t(x;18) (p11.2-q11.2) chromosome translocation [45]. The incidence is estimated to 0.65 per 100 000 people per year. About 5–10 % of all sarcomas are synovial cell carcinomas. Most cases are observed between the 3rd and 5th decade of life, one third of the cases are seen before the 20th year of life.

Liposarcomas are rare malignant tumors of the fatty tissue occurring with an incidence of 1:100 000 people per year. They are subdivided into 4 subtypes: well differentiated liposarcomas (40–45 %), myxoid/round cell liposarcomas (30–35 %), pleomorphic liposarcomas, and poorly differentiated liposarcomas (10 %; [146]). They mainly develop in males of higher age (mean: 7th decade), the 5-year survival rate amounts to about 67 % [206]. For histopathological differentiation between lipomas and liposarcomas, the MDM2 or CDK4 amplification is determined [4]. Between 3 and 8 % of the liposarcomas occur in the head and neck area. Well differentiated liposarcomas generally do not form metastases. Poorly differentiated liposarcomas, however, have a higher recurrence and metastatic rate than other subtypes of liposarcomas and are extremely rarely found in the head and neck region [68, 130]. Up to now, less than 50 cases of head and neck liposarcomas have been reported in the literature, 10 of them were found in the oral cavity, 3 in the neck area, and 3 in the pharyngeal space [145].

Angiosarcomas have a very aggressive biological behavior and are located mostly in UV light exposed area of the skin (about two third of the cases) and thus often in the head and neck. These tumors are more frequently seen in older males. The 5-year survival rate amounts to 30–40 %. Furthermore, radiotherapy, chronic lymphedema, and carcinogens such as vinyl chlorid, thorium dioxide, or arsenic are considered as risk factors for the development of angiosarcomas. These sarcomas also occur in the context of genetic disease such as neurofibromatosis, retinoblastoma, Ollier disease, Maffuci disease, *pigmentosum*, and Klippel-Trénaunay syndrome [29].

Rhabdomyosarcomas are malignant neoplasms of the striated muscles showing an incidence of 1:170,000 people per year. On the average, the diagnosis is made at the age of 5 years. These malignant tumors most frequently appear in the head and neck (35–40 %) [46]. A chromosome translocation is considered as pathogenetically relevant leading to the fusion of two genes coding for transcription factors. Patients with neurofibromatosis type 1, retinoblastoma, or Li-Fraumeni syndrome have an increased risk for developing such tumors [149]. Histopathologically, an embryonic, alveolar, pleomorphic, and spindle cell like/sclerosing type are differentiated. While the embryonic rhabdomyosarcoma mainly affects children and has a favorable prognosis, the aggressive alveolar rhabdomyosarcoma is predominantly found in adolescents [127]. The mean 5-year survival rate amounts to 40–54 % [147]. In contrast, rhabdoymomas are benign tumors of the striated muscles that primarily manifest in the cardiac area. Rarely, they also occur extracardially. Up to now, less than 200 cases of extracardiac rhabdomyomas have been described in the literature. They are divided into fetal (mainly located in the head and neck), adult (predominantly found in the head and neck of males, peak in the 5th decade of life), and genital (mainly found in the female vagina) neoplasms [110, 111, 158]. If they are completely removed, no recurrences are observed [59].

Kaposi sarcoma is a malignant vascular neoplasm caused by the human herpes virus type 8 in skin, mucosa, and inner organs and occurs especially in immunocompromised individuals [7]. Classic (predominantly involving the legs of older males from the Mediterranean area and Eastern Europe), endemic (children and young adults from the sub-Sahara region), HIV-associated, and iatrogenic subtypes (by drug-related immunosuppression, *e. g.,* after organ transplantation) are differentiated, while only the classic Kaposi sarcoma shows a poorly aggressive biological behavior. Clinically, red-brownish/purple, slightly convex plaques and nodules are found that may ulcer in the inner organs and cause severe bleeding. Therapy consists of surgical measures as well as radio-chemotherapy. In cases of HIV-associated and iatrogenic types, additionally (if possible) reconstitution of the immune competence should be achieved [212].

Further information

For medical staff: guideline of the AWMF (http://awmf.org); NIH National Cancer Institute (https://www.cancer.gov/publications/pdq/information-summaries)

For patients: Deutsche Sarkom-Stiftung (http://www.sarkome.de); Deutsches Krebsforschungszentrum (http://www.krebsinformationsdienst.de)

4. Conclusion and Outlook

Even today, rare diseases are associated with many tortuous paths until a diagnosis can be made. Further, there is still no curative treatment approach for many of these diseases. The establishment of national and international databases (registries) on orphan diseases as well as their increasing intertwining and public accessibility have enlarged the awareness and knowledge about these rare pathologies for medical staff and in the society. Moreover, measures such as the centralization of pathological assessments by reference centers, case discussions in interdisciplinary meetings (*e. g.,* sarcoma board) as well as the treatment of patients in the context of national and international (registry) trials led to an improved

quality of the diagnostics and therapy of rare diseases (*e. g.*, Deutsches Register Morbus Adamantiades-Behcet, Internationales Register für Phäochromozytome und Paragangliome). In addition, the active inclusion of patients in information, contribution, and decisional processes in the context of their diseases (patient empowerment) was fostered by establishing self-help groups and patient networks. The focus on "orphan/rare diseases" of the Annual Meeting of the German Society of Oto-Rhino-Laryngology, Head & Neck Surgery in 2021 will further support this important development. In this sense, the present article will contribute to one aspect of rare anatomical anomalies and malformations as well as non-neoplastic and neoplastic disease of the lip, oral cavity, pharynx, and cervical soft tissues.

Only recently, the technical progress in the field of biomedicine allows targeted decoding of genetic origins of diseases: by means of sequencing technologies such as whole genome sequencing and whole exome sequencing (= next generation sequencing) as well as high throughput DNA microarrays, already numerous gene mutations could be discovered that might lead to the development of rare diseases [35]. Hereby, the application of artificial intelligence allows processing the large volume of the collected data in a more and more efficient way [178]. In this context, it must be mentioned that genetic testing – especially if performed in the context of preimplantation or prenatal diagnostics – rises ethical questions. Thus, the results of such analyses might lead to biological selection that may lead to social discrimination of people with chronic diseases/impairment.

However, innovative gene editing tools (such as CRISPR-Cas9 or even more precise developments of this method) and proteome analysis (*e. g.*, mass spectrometry, protein microarrays) already allow validating potential target genes that have been identified in the context of gene sequencing in preclinical investigations with regard to their pathogenetic relevance. To this end, innovative treatment approaches with already available drugs have been established for some diseases [35]. In oncology, such procedures are already part of the treatment of cancer patients ("molecular tumor boards"). Furthermore, it is now possible for the first time to heal pathogentically relevant gene defects by means of these new gene editing techniques in diseased people: In clinical trials, pathological cells are taken from patients that are treated accordingly and then are re-transferred into the body of the patients as "cured" cells. In addition, the therapeutic potential of gene editing tools bound to vehicles (such as nanoparticles or viral vectors) after local or systemic application to the patient is currently under investigation [35]. Hence, it should be possible in the near future to develop individual treatment strategies also for rare, hitherto incurable diseases of the head and neck.

Conflict of Interest

The authors declare that they have no conflict of interest.

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