Salivary gland diseases in children

Abstract

Salivary gland diseases in children are rare, apart from viral-induced diseases. Nevertheless, it is essential for the otolaryngologist to recognize these uncommon findings in children and adolescents and to diagnose and initiate the proper treatment.

The present work provides an overview of the entire spectrum of congenital and acquired diseases of the salivary glands in childhood and adolescence. The current literature was reviewed and the results discussed and summarized.

Besides congenital diseases of the salivary glands in children, the main etiologies of viral and bacterial infections, autoimmune diseases and tumors of the salivary glands were considered. In addition to the known facts, new developments in diagnostics, imaging and therapy, including sialendoscopy in obstructive diseases and chronic recurrent juvenile sialadenitis were taken into account. In addition, systemic causes of salivary gland swelling and the treatment of sialorrhoea were discussed.

Although salivary gland diseases in children are usually included in the pathology of the adult, they differ in their incidence and sometimes in their symptoms. Clinical diagnostics and especially the surgical treatment are influenced by a stringent indications and a less invasive strategy. Due to the rarity of tumors of the salivary glands in children, it is recommended to treat them in a specialized center with greater surgical experience.

Altogether the knowledge of the differential diagnosis in salivary gland diseases in children is important for otolaryngologists, to indicate the proper therapeutic approach.

Keywords: salivary glands, children, inflammation, tumors, therapy

1 Embryology and anatomy of the salivary glands

The three major paired salivary glands (parotid gland, submandibular gland and sublingual gland) and the 700–1,000 minor salivary glands of the oral cavity and pharynx all come from the ectodermal germ layer. They start to appear between the sixth and tenth week of embryogenesis from cell accumulations in the embryonic foregut, with the common structural development of acini and excretory ducts. The ducts develop in parallel and have a patent lumen from the 22nd week onwards. During their growth in the surrounding mesenchymal tissue, lymphatic tissue remains within the glandular structures, especially in the case of the parotid glands. And precisely this is the reason for salivary gland involvement in certain diseases of the lymphatic system (e.g. viral infections, inflammation, and lymphomas). After birth, the glands gradually increase in size until adulthood.

The parotid gland is the largest of the salivary glands. Its 5–6 cm long excretory duct (parotid duct; Stensen’s duct) crosses the masseter muscle, curves medially and then penetrates the buccinator muscle and the buccal mucosa to open into the vestibule of the mouth opposite the second upper molar. On average, the diameter of the parotid duct is 1.4 mm at the hilum, 1.2 mm as it runs through the buccinator and 0.5 mm at the ostium [1].

The body of the gland, which consists of serous lobules, lies in the retromandibular fossa, above and posterior to the masseter muscle and the lower jaw. It is important to remember that the facial nerve in children lies much more laterally than in adults, as the mastoid cells are not yet fully developed. In young children, the nerve is even a little larger in proportion to the surrounding structures [2], [3].

The seromucous submandibular gland lies on the hyoglossal muscle between the anterior and posterior bellies of the digastic muscle. The 5–6 cm long submandibular duct passes around the mylohyoid muscle, crosses the lingual nerve and then crosses the floor of the mouth to open through the sublingual caruncle. The average diameter of the duct is 1.5 mm along its entire course from hilum to ostium, narrowing to 0.5 mm at the ostium itself [1]. The sublingual gland, a mucouserous gland, lies in the sublingual fossa, in submucosal tissue superior to the mylohyoid muscle. Its excretory duct either empties into the submandibular duct or opens separately into the oral cavity on the salivary papilla [4]. There are no estimates...
of duct length or diameter in childhood to be found in the literature.

2 Physiology of the salivary glands

Healthy adults produce about 1.5 litres of saliva a day. Some 20–25% comes from the parotid gland, about 70–75% from the submandibular gland and 5% from the sublingual gland. The viscosity of the saliva depends on the individual proportions secreted by the different glands [5].

Taking the total production from all of the salivary glands, 0.3 to 0.5 ml of saliva is secreted per minute at rest, while 1.5 ml/min is produced under conditions of maximum stimulation. Hidas et al. [6] studied salivary flow in children and adolescents with attention deficit hyperactivity disorder (ADHD). The rate of total salivation at rest was 1.1 ml/min in the control group and therefore similar to the recognised normal values, while the flow rate in patients with ADHD with or without medication was significantly lower. Continuous secretion is activated by a weak parasympathetic stimulus and is important in keeping the mouth moist. Central nervous system (CNS) regulation arises in the salivary nuclei of the medulla and pons and is transmitted via the autonomic nervous system. The major salivary glands are innervated by both parasympathetic and sympathetic nerves. However, unlike in other organs, they do not act antagonistically to each other. Both systems stimulate saliva secretion, albeit in different ways. Parasympathetic stimuli lead to the rapid production of a copious watery secretion that is rich in enzymes. At the same time, there is vasodilatation. In contrast, sympathetic stimulation induces the secretion of a smaller quantity of slimy viscid saliva associated with vasoconstriction. The salivary centre may be affected by external factors acting through higher CNS centres (the sight, smell or thought of food). Two reflexes are involved: a simple unconditioned reflex and an acquired conditioned reflex. The simple reflex is triggered by oral chemoreceptors and baroreceptors. The parasympathetic component stimulates saliva secretion at the receptor level. Muscarinic receptors are important here, also in the pharmacotherapy of functional disorders. In addition, dehydration, lack of sleep and anxiety may inhibit saliva production.

Saliva consists of up to 99.5% water. Protein, electrolytes, and various bactericidal and antimicrobial factors make up just 0.5%. Roughly speaking, two characteristic secretory compartments can be distinguished: the first is the fluid serous saliva, which contains bactericidal substances such as thiocyanate, proteolytic enzymes (lysozyme) and antibodies such as IgA, as well as α-amylase to digest starches, while the second is the mucus secretion or the mucous component of saliva, which prevents the oral mucosa from drying out and makes chewing and swallowing considerably easier. It also improves the sense of taste and clarity of speech [5].

A continuous flow of saliva with this composition protects against wound infections and caries. Bacteria and food residues are washed away, so to speak. Calcium phosphate ions contribute to the remineralisation of the teeth. The bicarbonate in saliva acts as a buffer for acids from food and bacterial metabolism and this also helps to prevent tooth decay. The pH is higher with an increased salivary flow and this may possibly protect the oesophageal mucosa by buffering any acid reflux. Recent studies also credit saliva with an effect on the gland itself, at least a paracrine one (e.g. leptin) [7]. In a comparative study of the minor salivary glands, Sonneson demonstrated that even in preschool children, a high density of glands and mature innate immunity existed, which further adapts as the children grow up [8]. Studies on children's saliva are particularly relevant to dental problems. It appears that the quality (protein content) rather than the quantity of saliva is important for caries prophylaxis. In a group of four- to six-year-olds, Bhalla et al. showed that tooth decay was inversely proportional to the proline content, but not to the total quantity of saliva produced [9]. Medicines used for oral asthma therapy, such as β2-agonists and cortisone, may reduce salivation [10]. A protein-deficient diet or chemotherapy for cancer during childhood even leads to a persistent functional impairment of the salivary glands, which may have lasting effects on the immune defences in the adult and be associated with significantly greater pathological conditions of the teeth [11], [12].

3 Clinical examination and imaging

A careful history is the first decisive step in the diagnosis of salivary gland conditions. In infants and young children it is, of course, extremely important to question the parents. As with adult patients, a relatively small number of cardinal symptoms are to be found for a large number of possible diagnoses. Most conditions affecting the salivary glands give rise to painful or painless swelling of the gland. In addition, there may be xerostomia (dry mouth), sialorrhoea (drooling) and facial palsy and, of course, corresponding generalised symptoms whenever there is an infection. The differential diagnosis to be considered in children includes infections of the salivary glands, autoimmune and systemic diseases and lymphadenopathy of various origins. Tumours and drug-induced disorders tend to be rare. Clinical examination often provides a first provisional diagnosis, for example, a ranula can easily be identified on inspection. Assessment of the saliva being secreted also indicates whether there is an acute suppurative infection (creamy yellow) or a more chronic recurrent process (flocculent secretion). Salivary stones and tumours can also usually be palpated. Imaging or laboratory tests are usually required to define the condition and sometimes confirm the diagnosis. ENT surgeons in Germany are fortunate to have ultrasound scanning available as an excellent method for assessing the three major paired salivary glands in children. As the required depth of penetration is small, frequencies of
7.5–12 MHz are suitable for scanning children to depict and anatomically classify infections, stones and tumours as well as lymph nodes. The salivary gland ducts (Stensen’s and Wharton’s ducts) can only be seen when an obstructive disease or an acute suppurative infection is present, either on initial examination or secondary to a secretory stimulus (vitamin C). Colour Doppler mode allows the internal perfusion of space-occupying lesions, the circulation in the glands themselves and non-perfused cysts to be identified. This helps to characterise lesions more precisely, especially haemangiomas and arteriovenous malformations. Conventional sialography and X-rays have no place in diagnostic investigations during childhood. In young children, sialography can anyway only be performed under sedation. Magnetic resonance imaging (MRI) and computed tomography (CT) are reserved for certain situations requiring the further workup of space-occupying lesions or processes that exceed the ultrasonographic limits of the salivary glands and extend into the para- or retropharyngeal spaces or to the base of the skull or mastoid. MRI focuses mainly on questions of soft tissue, nerves and dural infiltration, while MR sialography may be used to examine the ducts or MR angiography to demonstrate the topography of the vascular supply. On the other hand, CT scans can be used to assess bony structures and is also useful for determining the extent of large abscesses, especially in the para- and retropharyngeal spaces. Sialendoscopy, with its direct visualisation of the ducts, can fill any diagnostic gaps in obstructive salivary gland disease.

Fine needle aspiration biopsy can be used to obtain tissue for ascertaining the type of tumour and whether it is benign or malignant and material for further microbiological investigation in the case of infection. It is important to detect the pathogen by direct means or by polymerase chain reaction (PCR). Indications for fine needle aspiration are limited in children and must be considered very carefully, as the procedure usually requires general anaesthesia. Depending on the indication, an open biopsy or complete resection of a space-occupying mass can be performed for histology. The workup of an infection/inflammation includes, of course, a full or differential blood count and C-reactive protein or procalcitonin (in cases of sepsis). Antinuclear antibodies (ANAs), SS-A or SS-B (Sjögren’s syndrome antibodies to duct epithelium, formerly Ro and La) and angiotensin converting enzyme (ACE) levels may be indicated in rare childhood systemic diseases such as Sjögren’s syndrome or sarcoidosis. The determination of the salivary secretion rate is only of secondary importance in childhood.

### 4 Congenital salivary gland diseases

Apart from conditions that affect the saliva composition (e.g. sticky saliva in Prader-Willi syndrome) or cause an inability to swallow and lead to drooling (see below), hypoplasia or aplasia of the salivary glands is a rare occurrence and can affect just one, several or even all of the salivary glands. Aplasia of the salivary glands may occur in isolation or be associated with other malformations of the first branchial arch. These include hemifacial microsomia, Treacher Collins syndrome and other congenital malformations of the face.

A recent study from Norway looked at 21 patients with Treacher Collins syndrome [13]. In addition to ultrasound scans, it analysed salivary secretion. Almost half (48%) of the patients had abnormalities of the salivary glands. The pathology included dysplasia in six cases and aplasia in four. The salivary secretion rate was reduced in almost all the patients, although there was no correlation with subjective or ultrasound findings.

Matsuda et al. reviewed 43 cases of salivary gland aplasia appearing in the literature since the first case was reported by Gruber in 1885 [14], [15]. Nineteen more cases have been reported since 1999, of which at least five exhibited bilateral aplasia of the lower jaw and parotid gland [16]. A few of the case reports show a combination of aplasia and hypofunction of the salivary glands with other ectodermal malformations of the tear passages, skin appendages, and teeth. A familiar form seems to be inherited as an autosomal dominant with great variability of the phenotype [17]. One of the best-known conditions is the lacrimo-auriculo-dento-digital (LADD) syndrome, characterised by malformations including aplasia of the tear ducts, aplasia of the salivary glands, deafness and malformations of the ear as well as abnormalities of the teeth and limbs. Hypoplasia or aplasia of the salivary glands is often not recognised until late, since these patients, unlike those with acquired xerostomia, do not complain of their symptoms. Patients usually present with massive tooth decay associated with a dry mouth, difficulty swallowing and drinking copious amounts of fluid. Early diagnosis (on clinical examination, ultrasound, MRI and possibly scintigraphy) can result in appropriate and early prophylaxis against sequelae (teeth) and considerable relief of the symptoms.

And finally, juvenile recurrent parotitis may also be viewed as a genetic malformation of the gland [18]. Because of its topicality and new information on the treatment of this condition, it will be addressed in a separate section (see 5.2.8).

Polycystic (dysgenetic) disease of the parotid gland was described von Seifert et al. (1981) as a very rare entity that is independent of recurrent parotitis and congenital sialectasia [19]. They reported the case of a six-year-old girl who, like her father, suffered from this condition and therefore assumed an autosomal dominant inheritance. The cause is thought to be a defect in the interactions between activin, follistatin and TGF-β, leading to a developmental disorder of glandular tissue (salivary glands, pancreas and kidneys) in the mouse model [20].

Ranulas, benign tumours of the sublingual gland, may already occur before birth and large ones can cause direct respiratory problems during and after delivery. A congenital defect in the mylohyoid muscle is discussed in connection with plunging ranulas. These lesions have been
observed in siblings and are more common in certain ethnic groups [21], [22], [23]. An ex utero intrapartum treatment (EXIT) procedure can be carried out electively in such a situation that could possibly even be life-threatening. During a caesarean section, the ranula is decompressed and the airways held open before the umbilical cord is cut. Only then is delivery completed [24]. Only 5% of all salivary gland tumours occur in childhood. Congenital tumours such as sialoblastomas are even less common [25], [26]. The difficulty in the histological diagnosis has led to various synonyms being used in the literature, depending on the cell type: embryoma, congenital basal cell adenoma, etc. As a rule, tumours arise in the perinatal period or can already be identified on ultrasound scans during pregnancy. The parotid and submandibular glands are most often affected. Histology shows sialoblastomas to be malignant tumours arising from the embryonic epithelial anlage and they show a wide range of differentiation. These tumours were first described in 1966 [27]. Up to 2010, a further 26 cases were reported in the literature, which have occasionally also been associated with hamartomas or hepatoblastomas [28]. T1-weighted MRI shows an isointense tumour with heterogeneous contrast enrichment. A high mitosis rate, necrosis and anaplasia on histology are considered to be unfavourable prognostic features [29]. The treatment of choice is complete resection of the tumour, although this is not always possible because of infiltration into the surrounding structures, including the base of the skull. Tumour residues usually respond well to adjuvant chemotherapy or in cases that have already metastasised, to neo-adjuvant chemotherapy [30]. As for rhabdomyosarcomas, several courses of treatment are given (e.g. ifosfamide 3 g/m² on days 1 and 2; vincristine 1.5 g/m² on day 1; actinomycin D 1.5 g/m² on day 1; doxorubicin 30 mg/m² on days 1 and 2) [31]. Radiotherapy at this age is associated with possible adverse effects on bone growth and not inconsiderable mutagenicity.

Local recurrence was described in 10 of the 26 cases reported, so that patients should be monitored closely. At an average follow-up of 46 months (10 days to 43 years), 18 patients (69%) were still alive. Thus the prognosis is still relatively good [28].

5 Salivary gland infection/inflammation

Inflammatory diseases are the most common conditions besides benign tumours that affect the salivary glands of children and adolescents [32]. The most important viral pathogens are the mumps virus and cytomegalovirus [33], which will be looked at in more detail in the following section. In addition, there are acute bacterial infections and chronic inflammation, as well as autoimmune diseases. It must also be mentioned that the saliva itself plays an important role in many more viral, bacterial and other diseases. The paper presented by Weidauer to the 72nd annual meeting of the German Society of Otorhinolaryngology, Head and Neck Surgery in Hamburg is of particular interest in this context [34]. According to this presentation, saliva is a reservoir of the microorganisms involved in persistent bacterial infections of the oral cavity (dental plaque), as well as of the normal oral flora with pathogenic potential, and a vector for Helicobacter pylori. In certain infections, viruses and bacteria can be demonstrated in the saliva for a long time, even without any symptoms (mumps, cytomegalovirus, human herpes viruses, HIV, rabies, hepatitis B) or are found only transiently (pertussis, diphtheria, Haemophilus influenzae, Epstein-Barr virus, adenoviruses, herpes simplex virus type 1, influenza and parainfluenza viruses, measles and rubella viruses). Organisms with oncogenic potential, such as Epstein-Barr virus, human herpes virus 8, human papilloma virus and Helicobacter pylori are of particular relevance.

5.1 Viral sialadenitis

5.1.1 Mumps

The mumps virus is an encapsulated RNA virus (15,384 nucleotides) of the paramyxovirus family, with a diameter of 200 nm. The RNA codes for six structural proteins and at least two other proteins. The capsule consists of a two-layered lipid membrane, which means that the virus is susceptible to disinfection with ether or alcohol. The virus is stable for several days at 4 °C [35]. So far, twelve genotypes (A–L) of the mumps virus have been identified, with different regional distributions [36]. The disease is transmitted by droplet or contact spread. The incubation period is 15–24 days. Patients are already infectious two days before the onset of symptoms [37]. The virus can be detected in the saliva for seven days before the start of symptoms and for nine days afterwards. Virus replication usually takes place in the upper respiratory tract and in the salivary glands. Nevertheless, parotitis is not one of the first or even essential steps in the course of the infection. Replication takes place in the duct epithelium of the parotid gland and leads to oedema and a local inflammatory reaction with lymphocyte and macrophage infiltration [38].

About one-third of mumps infections are asymptomatic. The cardinal symptoms of parotitis with fever are seen in 60–70% of all infections and in 95% of symptomatic patients. The gland remains swollen for about one week. There is bilateral involvement in 90%, although the swelling may not be seen at the same time on both sides. Complications of parotitis are rare: sialocele with further recurrent swelling has been reported [39]. The submandibular and sublingual glands may also be involved in 10% of cases. Problems with lymphatic drainage may cause bilateral cervical oedema or, in rare cases, supraglottic oedema [40]. The disease can also spread to other organs, giving rise to epididymitis in 30% and bilateral orchitis also in up to 30%. Infertility as a result of mumps infection is, however, a rare complication [41]. Oophoritis
The infection rate in the population is 40% to 100% [51]. Cytomegalovirus is a member of the herpes virus family. The choice of treatment must be determined on a case-by-case basis, especially for paediatric patients, but an initial monitoring with appropriate antiretroviral medication would appear to be possible in most cases. Radiotherapy and surgery are indicated in selected cases [55].

5.1.3 HIV and the salivary glands

HIV infections may also primarily involve the salivary glands, especially the parotid. The clinical picture is often one of unilateral swelling, pain and inflammatory changes in the gland, sometimes analogous to acute parotitis. On the other hand, there may just be a painless enlargement of the gland. Ultrasound scans show hypoechoic and anechoic structures, which correspond histologically to epithelial cysts and lymph nodes. In these cases, HIV testing should be added to the diagnostic tests and further cytological or histological workup considered [54]. Hobbs et al. suggested a three-stage classification in paediatric patients: persistent generalised lymphadenopathy (PGL), benign lymphoepithelial lesions (BLEL) and benign lymphoepithelial cysts (BLEC) [55]. Benign lymphoepithelial lesions in HIV are similar to those in other salivary gland diseases (sarcoidosis, Sjögren’s syndrome, chronic recurrent parotitis) and are probably the expression of an autoimmune reaction [56]. Whilst BLEL is thought to be a separate histological entity with no transformation into BLEC, the generalised lymphadenopathy is probably the precursor of BLEC. The management of benign lymphoepithelial cysts includes a watch and wait policy, repeated fine-needle aspiration (also to confirm the diagnosis) or drainage, highly active anti-retroviral therapy (HAART) [57], [58], [59], sclerotherapy (ethanol, picibanil, tetracycline, doxycycline, etc.), radiotherapy (8–24 Gy) and surgery with extracapsular dissection or total parotidectomy [60].

5.1.2 Cytomegalovirus

Cytomegalovirus is a member of the herpes virus family. The infection rate in the population is 40% to 100% [51].
5.2 Bacterial sialadenitis in childhood

5.2.1 Neonatal suppurative parotitis

Neonatal suppurative parotitis has been described as a particular form of acute sialadenitis occurring immediately after birth. There is typically a warm red swelling around the affected gland. In a recent review, Ismail et al. collected 44 cases reported in the literature since 1970 [61]. The infection was unilateral in 77% and a similar percentage of the affected patients were boys. Purulent secretions were expressed from the papilla of the parotid duct in all but two patients. Only half of the patients had a raised temperature. The leucocyte count was elevated in 44%. Other laboratory tests were not particularly helpful.

The organisms isolated were *Staphylococcus aureus* (in 61% of cases), with three patients (7%) having MRSA (methicillin resistant *staphylococcus aureus*) [62], other Gram-positive cocci (25%), Gram-negative rods (16%) and anaerobic bacteria (11%). Blood cultures were positive in 32%.

Possible modes of infection are bacteria ascending via the parotid duct and haematogenous spread. As the infection was unilateral in 77%, a similar percentage of the affected infants became dehydrated through inadequate breast-feeding, with ascending duct infection related to decreased salivary flow [63]. Other risk factors were high ambient temperatures, excessive sucking and feeding via a nasogastric tube [64]. In addition, the rate was considerably higher in premature babies (32%) than otherwise described. Premature birth is therefore a risk factor [65]. The majority of the patients were successfully treated with a combination of an anti-staphylococcal drug and an aminoglycoside or a third-generation cephalosporin. The duration of antibiotic therapy was between seven and 21 days, depending on the bacterial colonisation, comorbidity and spread of infection. Only 23% required surgical drainage. Most patients have an excellent prognosis with respect to morbidity and mortality; as a rule, it is very favourable. Parotid fistulas, facial nerve palsy, septicemia, meningitis or mediastinitis occur only rarely [66].

5.2.2 Suppurative parotitis and parotid abscesses in children and adolescents

Older children and adolescents very rarely have suppurative sialadenitis. In a centre for paediatric ENT, Stong et al. treated only 17 patients with acute suppurative parotitis, and a further four patients with an acute exacerbation of juvenile recurrent parotitis, over a period of five years [67]. It must be assumed that most children with these conditions are treated by their general practitioners or in an ENT practice. The mean age of the eight boys and 13 girls was 6.5 years (6 months to 15 years). Typical symptoms were painful unilateral or bilateral swollen parotid glands and purulent secretion from the parotid duct; 62% of the patients had to be admitted to hospital with severe dehydration, leucocytosis and fever. Over half of the children admitted had serious comorbidities (cystic fibrosis, leukaemia, HIV, diabetes and infantile cerebral palsy). In two (10%) patients, an abscess developed in the gland during the course of the disease.

Treatment of acute suppurative parotitis consists of gland massage, sialogogues and antibiotic therapy to cover *staphylococci* and *streptococci*, in particular. Antibiotic resistance testing is only needed in cases of treatment failure. Ultrasound scanning is the imaging method of choice to perform after clinical examination. CT is rarely indicated, but may be used to determine the extent of an abscess. Apart from abscesses, the complications of acute parotitis include facial palsy and extensive phlegmonosis of the throat causing difficulty in breathing [68]. Parotidectomy is required only in rare cases [32]. Saarinen et al. from Finland reported on ten children (aged 2–16 years) who were treated within a ten-year period and calculated an incidence of 0.7 cases per million inhabitants [69]. The treatment of choice was incision and drainage of the abscess (Figure 1). Considerations in the differential diagnosis of an abscess include infected cysts or fistulas of the first branchial arch. Even though the most common pathogens comprise a mixed flora of *staphylococci*, *streptococci*, anaerobic bacteria and *Haemophilus influenzae* [70], the possibility of tuberculosis and atypical mycobacterial infections should also be considered [71]. Samples should therefore be obtained before treatment and sent for microbiological tests. Salivary stones should also be ruled out.

5.2.3 Obstructive sialadenitis in childhood

Also in childhood are stones frequently the cause of obstruction in the excretory ducts. As a rule, idiopathic inflammatory stenosis and radiiodine-induced stenosis are found only in adults [72], [73], [74], [75], [76], [77], [78]. In our own patient population, we have also seen iatrogenic stenosis after surgical procedures on a frenulum of the tongue or ranula. One adolescent patient had traumatic papillary stenosis of the parotid duct, which is rarely seen in children and adolescents, but caused in this case by excessive bruxism. Salivary stone disease is seldom seen in children [79]. In their literature review of reports published since 1860, Reuther and Hausamen found 21 cases of submandibular gland stones in children aged between three weeks and 15 years [80]. In Japan, thirty-two cases in children below the age of ten were described up to 1994; in 29 of them, stones had formed in the submandibular gland [81].

In their study population, Zenk et al. described 39 patients below the age of 21. The youngest patients with confirmed stones in the parotid gland were a five-year-old girl and a three-year-old boy. Parotid stones are less common in adults as well [82].
As in adults, the symptoms are characteristic. There is usually recurrent swelling of the affected gland, which may be associated with pain. Sialolithiasis may also present for the first time as an acute bacterial infection of the gland. Management priorities are treating the sialadenitis and looking for the stone. The treatment of salivary stones in children today is basically not different from that in adults. As a rule, younger children require a general anaesthetic for the procedure because they are unable to cooperate. The decisive factors in selecting the therapeutic option are the site size, and mobility of the stone.

Sialendoscopy can be used initially to investigate both the parotid and submandibular ducts to determine the presence of a mobile stone, or one that can be mobilised, in the distal duct system and right up to the hilum (Figure 2). In this case, the stone can then be extracted using a Dormia basket [83], [84]. Stones that have impacted anywhere up to the hilum in the submandibular gland can usually be removed transorally without problem [85] (Figure 3). Extracorporeal shockwave lithotripsy (ESWL) is an excellent method for disintegrating or destroying impacted parotid stones, irrespective of their site and size. The stone fragments may pass spontaneously or a repeated attempt can be made to remove the stone endoscopically [86], [87], [88]. ESWL is also suitable for use in children (Figure 4). A combined endoscopic and transcutaneous approach to stone removal can be used as an alternative [89]. Lithotripsy is also indicated for submandibular stones lying proximally. New intracorporeal methods with laser lithotripsy have been reported in a few adult study populations, but have not yet become established in routine clinical practice, partly because of possible adverse effects and partly because they are time-consuming and relatively expensive [90].

If it is not possible to relieve the symptoms with these methods, then the only remaining option is surgical excision of the gland with all its known risks [91], [92].

5.2.4. Pneumoparotitis

Idiopathic recurrent pneumoparotitis is a rare condition with painful swelling of the affected gland [93]. In this case, patients blow air into the excretory ducts of the parotid gland. It has been described in wind instrument players and glass blowers [94]. However, it can also be associated with diving, dental treatment or recovery from an anaesthetic (coughing fits) [95]. It may also be self-induced in adolescents with psychosocial disorders [96]. It remains unclear whether the cause involves an open parotid duct ostium or a weak buccinator muscle in combination with already dilated ducts. We ourselves can report on a 13-year-old boy who developed the recurrent parotid swelling of pneumoparotitis as a result of blowing up balloons. The diagnosis is made using ultrasonography (Figure 5), where numerous mobile echogenic reflexes with a comet-tail artefact are apparent. The air inclusions can also be seen clearly on CT. Available treatment includes symptomatic measures such as gland massage,
Figure 2: Sialendoscopy performed on a 13-year-old girl to detect a stone in the hilum of the right submandibular gland (see screen) that could not be clearly demonstrated with ultrasound scanning.

Figure 3: a) Ultrasound scans showing two hilar stones, measuring 4.4 mm and 4.7 mm, in the left submandibular gland of 14-year-old girl, before treatment. The hypoechoic changes in the parenchyma of the gland are regarded as the expression of chronic obstruction. b) Transoral stone extraction with marsupialisation of the duct under local anaesthetic in the same patient. c) Four months after the stone extraction, the patient is free of symptoms and has no new stones. The ultrasound scan shows a normal gland parenchyma (MMH: mylohyoid muscle, GSM L: left submandibular gland). d) A neo-ostium with no signs of inflammation can be seen in the left posterior floor of the mouth.
Figure 4: a) Pre-operative ultrasound scan of a 5-year-old girl with a stone measuring almost 9 mm (+...+) in the right parotid gland (DS: Stensen’s duct; GP: parotid gland; UK: lower jaw; MM: masseter muscle). b) Extracorporeal shockwave therapy under general anaesthetic. c) No stones or symptoms one year after the intervention, with an unremarkable ultrasound appearance of the right parotid gland. d) A 3-year-old boy after lithotripsy of a stone in the left parotid, showing petechial haemorrhages into the skin as a typical adverse effect of lithotripsy. These will be resorbed within a few days.
sialogogues, analgesics and antibiotic therapy, if necessary. The most important thing is to avoid the underlying trigger. Psychiatric treatment or behavioural therapy should also be considered for patients with self-induced disease. Surgical procedures such as duct ligation, duct repositioning into the tonsillar fossa and even excision of the gland have been described, but are indicated only in exceptional cases [97], [98].

![Sonographic imaging in an 11-year-old boy with recurrent pneumoparotitis after blowing up balloons with mobile hyperechoic reflections with acoustic shadowing (LUFT=AIR), which correspond to air inclusions in the duct system (MM: masseter muscle, UK: lower jaw, GP: parotid gland).](image1)

5.2.5. Postoperative sialadenitis

Unilateral parotid gland swelling arising immediately postoperatively (sometimes called ‘anaesthesia mumps’) usually resolves spontaneously within 48 hours [99] and can also rarely occur in children. The incidence is one patient in 1,000–3,000 surgical procedures. The underlying cause is thought to be an imbalance between secretion and obstruction [100], [101]. Dehydration and intraoperative medication, the duration of the operation and the positioning of the head are all thought to play a part [102].

5.2.6 Tuberculosis (TB) and mycobacteria other than tuberculosis (MOTT)

Infection with mycobacteria is particularly relevant to the parotid gland and worth mentioning once again here, since from both an anatomical and developmental point of view, this gland contains numerous lymph nodes, which correlate with disease. On the other hand, the disease may spread from the cervical lymph nodes to the salivary glands. The incidence of tuberculosis is falling in developed countries, but infections with MOTT are on the increase [103]. In children, the incidence is 7.7 per million inhabitants up to the age of 18 and as high as 23 per million inhabitants up to the age of four [104].

![Ultrasound scan of an atypical mycobacterial infection in the inferior pole of the left parotid gland (RF +...+), prior to surgical excision, in a 2-year-old girl (MSCM: sternocleidomastoid muscle; GLP: parotid gland).](image2)

Even though surgical treatment is basically superior, it can still be debated whether medication is more appropriate for lymph nodes in the parotid gland or in the region of the submandibular gland, because of the risk of facial nerve injury [106]. If a decision is made for pharmacotherapy, this should definitely take the form of a combination therapy with at least one macrolide antibiotic and rifampicin or ethambutol for a period of up to six months [110], [111].

Figure 5: Sonographic imaging in an 11-year-old boy with recurrent pneumoparotitis after blowing up balloons with mobile hyperechoic reflections with acoustic shadowing (LUFT=AIR), which correspond to air inclusions in the duct system (MM: masseter muscle, UK: lower jaw, GP: parotid gland).

A prospective study showed that simple incision and drainage more often led to postoperative fistulas (91%) than complete excision (50%) [107]. In a retrospective study, disorders of wound healing were seen in 20% of patients after complete excisions and in 79% following drainage [108].

On the other hand, surgical excision has been shown to be superior to pharmacotherapy (clarithromycin and rifabutin) given for 12 weeks. The cure rates were 96% and 66%, respectively [105]. At follow-up, the aesthetic results in surgical patients were subjectively rated better [109]. Even though surgical treatment is basically superior, it can still be debated whether medication is more appropriate for lymph nodes in the parotid gland or in the region of the submandibular gland, because of the risk of facial nerve injury [106]. If a decision is made for pharmacotherapy, this should definitely take the form of a combination therapy with at least one macrolide antibiotic and rifampicin or ethambutol for a period of up to six months [110], [111].
six months, the rest after a year at the latest. These authors did not report any complications. There are, however, no placebo-controlled trials on observation alone and patients have to put up with a fistula that persists for a relatively long time. In principle, these children also have to be regarded as infectious. If the microbiology shows an infection with *Mycobacterium tuberculosis*, triple therapy with rifampicin, isoniazid and pyrazinamide for six months is indicated [113]. In these cases, it is important to check whether there is involvement of any other organs, especially of the lungs. The disease is notifiable and contact tracing should be performed to find, inform and examine all persons who have been in close contact with patients with open TB.

5.2.7 Other granulomatous and inflammatory diseases

When considering granulomatous inflammation, the differential diagnosis is important: sarcoidosis, cat-scratch disease, Kikuchi lymphadenitis and, less commonly, tuberaemia and actinomycosis. In addition to demonstrating the pathogenic organism, histology is important in the diagnosis of persistent lymphadenopathy, in order to rule out benign tumours and malignant changes. Actinomycosis is due to gram-positive microaerophilic bacteria, often triggered by trauma or dental treatment. The salivary glands can also be affected by the usually painless necrotising infection, which often leads to fistula formation [114]. Antibiotic therapy with Penicillin is the treatment of choice [115]. Sarcoidosis (Besnier-Boeck-Schumann’s disease) is seldom seen in childhood. Asymptomatic involvement (swelling) of the salivary glands alone does not require any treatment. The child should in any case be referred for further paediatric assessment and systemic therapy (cortisone) if necessary. Necrotising sialometaplasia is a particular form of inflammation, which may rarely be found in children and adolescents. The World Health Organization (WHO) classifies this condition with six other lesions of the salivary glands [sialadenosis, oncocytic changes, benign lymphoepithelial lesions, salivary duct cysts (retention cyst, ranula, and dysgenetic polycystic disease), chronic sclerosing sialadenitis (Küttnér’s tumour) and changes of the salivary glands with HIV infection] [116]. The disease may appear in all locations where there is salivary gland tissue and very often on the hard and soft palate. Painless ulceration, possibly caused by ischaemia following mechanical irritation, occurs in most cases and may give rise to the suspicion of malignancy [117]. In children, it may also present as a simple swelling without any necrosis [118]. Histology shows inflammation and granulation tissue, which heals spontaneously after 6–12 weeks [119].

5.2.8 Juvenile recurrent parotitis

The disease is seen clinically as an acute swelling of the affected gland, which usually affects only one side and is associated with symptoms of varying degree. The swelling appears independently of meals or season of the year. There may be reddening of the skin over the affected gland and a raised temperature or mild fever. The swelling usually persists for 24–48 hours, but may sometimes last for 1–2 weeks or rarely even months. The acute episodes (flares) appear punctuated by symptom-free intervals ranging from days to years. Hyposecretion of the gland with very viscous saliva can also be demonstrated in the intervals and, typically, flocculent secretions can be expressed at this time. Purulent secretion similar to that of acute bacterial parotitis is rare and, if seen, is found only in the acute phase.

In his review of more than 5,000 cases of chronic sialadenitis, Seifert reported chronic recurrent parotitis in 27% [120]. He distinguished between a juvenile and an adult form. The adult form is about ten times more common than the juvenile form. It affects mainly women and is usually unilateral. Changes are seen in the distal part of the excretory duct with pronounced stenosis and dilatation. Juvenile recurrent parotitis (JRP), which was first described in 1909 [121], occurs between the ages of 4 months and 15 years and mostly affects boys. As a rule, there is duct ectasia of the small intraparenchymal excretory ducts. Similar changes can usually also be found on the asymptomatic side. Ussmüller divided the disease into three stages on histological grounds (stage I: initial inflammatory stage; stage II: advanced inflammation with lymphatic follicles; stage III: very rare immunological end stage with complete lymphatic transformation of the gland) [122]. JRP is generally self-limiting, it goes into spontaneous remission at puberty and may even completely resolve [123]. Most patients are free of symptoms by the age of 22 [124].

The aetiology of JRP is probably multifactorial. As early as 1945, Hamilton Bailey proposed the presence of a congenital or acquired abnormal dilatation of the duct [125]. Stasis of the secretions could lead to recurrent secondary inflammation [126]. Initial inflammation is due to a reduced flow of saliva, resulting in changes to the excretory duct epithelium of the salivary gland with metaplasia, strictures, and stenosis. Metaplasia of the duct epithelium would result in a more mucous secretion. It is still not clear whether the well-documented hyposecretion, which can also be demonstrated in the contralateral clinically normal gland, is cause or effect. Other authors view the lymphocytic infiltration seen on histology to be the cause of damage to the duct walls [127]. Weakness of the surrounding connective tissue leads to the typical duct ectasia. This theory clearly explains the presence of ectasia without any signs of obstruction. The fact that changes in the ducts are also found in asymptomatic glands also supports this assumption [124], [128], [129].

In addition, genetic factors seem to contribute to the aetiology, without any specific gene or definite correlation having been found to date. Familial disease, in the sense
of an autosomal dominant inheritance, has frequently been reported in the literature [18]. Wittekindt et al. published a case report relating to this, which involved identical twins with chronic recurrent parotitis in childhood [130]. Reid et al. reported a family where four members had the disease and two others had asymptomatic changes [131]. An interesting finding in JRP, as well as in Sjögren’s disease and other conditions affecting the oral mucosa, is that the levels of metalloproteinases (MMP2 and MMP9) are increased in the saliva [132], [133]. Analogous to the lymphocytic infiltration, this also ties in with the underlying cause of JRP being autoimmune disease [134], [135].

Besides the hypothesis of an allergic origin for the disease, postviral changes (e.g. mumps) and immune deficiencies (IgG3 subclass deficiency) have been suggested [136], but there is no concrete evidence for any of these. Recent publications [137], [138] focussing intensively on the composition of saliva and on analyses of the secretion rate have concluded that the most likely pathogenesis of JRP is a congenital malformation of the excretory ducts, triggered by a bacterial infection. Albumin, IgA, lactoferrin and kallikrein in the saliva were all significantly higher than in the control group. The increase may be due to leakage in the salivary ducts even during the symptom-free intervals, which would also explain the higher concentrations of serum proteins and repeated demonstration of antibacterial substances. Nevertheless, no acute or healed tissue damage can be seen under the light microscope. There is, therefore, no concrete evidence of active infection. On the other hand, bacteria have also been demonstrated in swabs taken between the acute episodes [124], which serve to perpetuate the disease.

The provisional diagnosis of chronic recurrent parotitis is based primarily on the history of repeated painful swelling of the gland and on the clinical examination. Even in the symptom-free interval, flocculent secretion can usually be expressed from the excretory ducts. Diagnostic imaging can then confirm the diagnosis. For a long time, sialography was the method of choice to demonstrate stenosis and strictures in adults and duct ectasia in the juvenile form. Pooling of contrast medium in the dilated interlobular portions of the ducts is consistent with sialectasis [139]. Even when the disease is clinically restricted to one side, imaging usually shows contralateral involvement. The extent of the radiologically detectable sialectasis does not correlate with the clinical symptoms [124]. However, the further development of ultrasound scanning, MRI and CT means that conventional sialography no longer has a place, at least in Germany. Apart from the radiation exposure, there is a risk of contrast medium allergy. It is also extremely difficult to perform sialography in young children, who are generally not very cooperative. B-mode ultrasonography is a non-invasive method that is straightforward to use in children as well. It is easy for experienced ENT surgeons to recognise the typical, almost pathognomonic, picture of JRP with hypoechoic and anechoic areas in the parotids, which are consistent with sialectasis and enlarged lymph nodes (Figure 7). Ultrasound scanning is an excellent means of monitoring the condition and shows any parenchymal changes much more clearly than sialography [140]. Other possible reasons for a lymph node enlargement should, however, be considered in the differential diagnosis. A very similar picture is seen with Sjögren’s disease and sarcoidosis, but the clinical history and age of the patient are usually completely different [141].

MRI and MR sialography are excellent ways of visualising salivary gland parenchyma as well as the excretory ducts. The latter can be seen without contrast enhancement in a special T2 weighting [130]. With alternative methods available, however, the time and effort required for this type of imaging in children mean that it is only worth considering for paediatric patients in exceptional cases. CT is, in our opinion, not indicated because of the high radiation exposure and little additional benefit.

Examining affected glands with the new method of sialendoscopy shows the duct epithelium to be whitish in colour with an atrophic appearance. Blood vessels, usually clearly visible in the duct walls, are few or cannot be seen at all. The actual duct ectasia is central and
therefore not accessible with the sialendoscope. This method alone is therefore not suitable for the diagnosis of JRP.

To date, there is no causal treatment for the condition. The aim of treating flares is to relieve the acute symptoms and prevent further parenchymal damage. It is expedient to give analgesics and antibiotics at this time. Amoxicillin is often used in combination with a penicillinase inhibitor, although penicillin alone, a cephalosporin or a macrolide antibiotic should suffice, since staphylococci are not usually encountered. It is debatable whether the natural course of disease is actually altered by such treatment [124], [142], [143]. Sialagogues, the local application of heat, gland massages and probing the duct may all be used additionally to promote the flow of saliva. There is no firm scientific reason to give prophylactic antibiotics to prevent acute episodes.

Radiotherapy, which was being recommended 30 years ago, is certainly obsolete these days [144]. Diamant et al. reported parotid duct ligation as a therapeutic alternative and occlusion of the duct with sodium amidotrizoate (Ethibloc®) has also been described [145], [146]. Furthermore, based on the results of animal studies, the intraductal administration of tetracycline has been recommended as a possible and effective measure [134]. However, it should be noted that tetracycline in childhood may damage the teeth and should not be given to children below the age of 14. Maier et al. irrigated the duct with aprotinin (Trasylol®), a kallikrein inhibitor, with short-term success [147]. Surgical excision of the whole gland, with all its possible complications, is seen as the last resort. Irrigation, e.g. with normal saline or cortisone solution, has therefore also been indicated for a long time, especially in children, as in reports on sialoraphy it had been established that this diagnostic measure alone led to a clear improvement in the symptoms [72], [123], [148]. A simple instillation of normal saline or penicillin into the excretory ducts also often led to the relief of symptoms [149].

All the invasive therapeutic options have ultimately to be considered in the light of the fact that conservative measures, with a watch and wait policy, result in up to 92% of all children being free of symptoms within a follow-up period of five years [142], [143]. Based on the results of irrigation with normal saline and cortisone solution, a promising method of treating both JRP and chronic recurrent parotitis in adults has been developed in association with sialendoscopy (Figure 8). The largest study published to date, by Shacham et al., reported on 65 children whose ducts had been irrigated and dilated with about 100 ml saline solution during sialendoscopy [150]. At the end of the procedure, the gland was irrigated with an additional 100 mg of hydrocortisone via the endoscope. One inclusion criterion for this study was at least two acute episodes within a year – so patients with little in the way of symptoms were also
included. At follow-up of 6–36 months, 95% of all the patients had no symptoms after just one treatment session. Quenin et al. reported a success rate of 87% in 10 patients with 17 treated glands [151]. Out of 14 patients in Milan who underwent a single treatment session, five (36%) had recurrent symptoms within 20 months and had to be treated again [152].

The first retrospective study comparing conservative management in 21 patients with JRP and sialendoscopic therapy in another 15 patients showed that there was a significant improvement in both the frequency and intensity of the gland swelling. The difference between the groups was not significant, but there was a tendency towards a more rapid relief of symptoms in the group treated with endoscopy, irrigation and cortisone [72].

Definitive results can only be expected from a prospective study.

Based on current experience and findings in the treatment of juvenile recurrent parotitis, we recommend the following treatment strategy [153]:

1. For mild symptoms or after a single episode: conservative symptomatic treatment, antibiotic therapy with analgesia and measures to reduce the swelling. Prophylactic antibiotics are not indicated, nor are they effective. It is worthwhile massaging the gland and giving sialagogues in the intervals.

2. For severe symptoms and repeated episodes of swelling: a minimally invasive procedure with sialendoscopy and duct irrigation as well as the intraductal application of prednisolone in normal physiological saline solution (100 mg/100 ml), instilling 30–40 ml in each gland. Children require a general anaesthetic.

3. Complete parotidectomy: as the last resort, for persistent symptoms after failure of the previously mentioned measures or with the rare stage III disease (immunological end stage with complete lymphatic transformation).

5.2.9. Juvenile Sjögren’s syndrome

Sjögren’s syndrome is an autoimmune disease characterised by progressive lymphocytic and plasmacytic infiltration, mainly of the salivary glands and lacrimal glands. According to Vitali et al. [154], there are six criteria for the diagnosis of Sjögren’s syndrome: ocular symptoms, oral symptoms, objective ocular signs (Schirmer’s test), histologically detectable lymphocytic infiltration (>1 focus of 50 lymphocytes/4 mm²), objectively verifiable findings in the salivary glands (<1.5 ml saliva/15 min, positive imaging) and autoantibodies. Sjögren’s syndrome is confirmed when at least four of these are present together with at least positive histology or serology.

Sjögren’s syndrome occurs considerably more often in women than men (9:1); the onset is usually between the ages of 40 and 50. Juvenile Sjögren’s syndrome is rare or underdiagnosed. Children and adolescents often have predominant recurrent swelling of the parotid gland at the onset as well as during the course of disease, whilst ocular and oral symptoms are less common. Systemic extraglandular manifestations (vasculitis, cryoglobulinemia, autoimmune hepatitis, alveolitis, neuropathy and B-cell lymphomas) are also seen less often during the course of disease [155], [156]. Sjögren’s syndrome may occasionally give rise to life-threatening situations, such as hypocalcaemic paralysis due to renal tubular acidosis. In addition, it may involve the central nervous system and liver [157], [158]. A total of 81 patients aged between four and 16 (mean 10 years of age) were reported in the literature from 2000 to 2010 [159]. Swelling of the parotid gland was found in 65%, xerostomia in 22% and ocular symptoms in 33% of the cases. Rheumatoid factor was positive in 54%, SS-A (ro) in 67%, SS-B (la) in 62% and antinuclear antibody in 72%. Nikitakis et al. gave higher figures for xerostomia (64%) and ocular symptoms (72%) in 95 patients studied in the period 1995–2002 [160]. Here, too, the cardinal symptom was enlargement of the parotid gland (74%), which showed the typical changes seen on ultrasound (Figure 9).

As the ocular and oral symptoms are not as pronounced in children as in adult patients, the usual criteria have a lower sensitivity to the presence of juvenile Sjögren’s syndrome. This disease should always be considered, however, when there is recurrent swelling of the salivary glands without any other relevant symptoms [156]. Recurrent conjunctivitis also suggests Sjögren’s syndrome, as do elevated amylase levels, renal tubular acidosis, leucocytopenia, ANAs, a positive rheumatoid factor and hypergammaglobulinaemia. Taking a cut-off of >1 focus/4 mm², the histological findings of the minor labial salivary glands are often negative. The sensitivity is greatly increased by using a score of >0 focus/4 mm² [161]. As in adults, the biopsy of the parotid gland is of considerably more diagnostic use in children. McGuirt et al. reported on six patients: biopsy of the minor salivary glands was negative in four of them, while parotid biopsies performed in all patients were positive [162]. The treatment of juvenile Sjögren’s syndrome is largely symptomatic. As in adults, the aims are to replace the function of the affected glands (sialagogues, artificial saliva and tear substitutes) and reduce the sequelae (dental care, etc.) [163]. The management of juvenile Sjögren’s syndrome should be discussed in detail with a paediatric or general medical rheumatologist. To date, no studies on systemic therapy of juvenile Sjögren’s syndrome are to be found in the literature [161], so that recourse has to be made to the experience gained in treating adults. This is based on the administration of corticosteroids, with cyclosporin A given in severe cases [164]. Immunosuppressant therapy may control the symptoms of the disease and reduce the lymphocytic infiltration and fibrosis of the salivary glands. Studies have shown a partial success of the anti-B-cell antibody rituximab in adults, but, even though the circulating B cells are clearly suppressed, antibody-producing B cells remain in the glands. Rituximab is currently recommended for systemic involvement [165], [166]. Gene therapy approaches and stem cell transplantation are still in the animal study stage [167], [168].
Figure 9: a) Sjögren’s syndrome in a 10-year-old girl with only the symptoms of non-specific bilateral parotid swellings. Ultrasonography showed typical hypoechoic cloud-like changes in all three major salivary glands. b) Left parotid gland (GP: parotid gland; MM: masseter muscle, UK: lower jaw). c) Left submandibular gland (GSM LI: left submandibular gland; MMH: mylohyoid muscle). d) Left sublingual gland (GSL: sublingual gland; UK: lower jaw; MB: floor of the mouth). In this case, the biopsy to confirm the diagnosis was taken from the sublingual gland. e) Dense lymphocytic infiltration of the sublingual gland parenchyma with the formation of lymphoepithelial lesions (reproduced with the kind permission of Prof. Agaimy, Department of Pathology, and Erlangen, Germany).
6 Salivary gland tumours in children and adolescents

6.1. Ranula

Histologically speaking and according to the WHO classification, ranulas and salivary gland retention cysts belong to the group of tumour-like lesions [116]. As mentioned previously, these lesions may already be present at birth. Ranulas are extravasation mucoceles, arising from either the ruptured and then blocked main excretory duct of the sublingual gland, or the numerous subsidiary ducts or the acini [169]. In so-called plunging ranulas, the accumulation of secretions extends into the soft tissues of the neck. Pre-existing gaps in the floor of the mouth or directly in the mylohyoid muscle predispose to these lesions [21], [22], [170]. Ranulas can usually be diagnosed on visual inspection and confirmed by an ultrasound scan. Conservative methods, including sclerosis (OK-432) and injection with botulinum toxin A, have been described with mixed results [171], [172], [173], [174]. Complete excision of the sublingual gland is the surgical procedure with the best results for recurrence rate, but it also carries the highest risk of complications [175]. In a retrospective study on 13 children carried out by our research group, we also found that removal of the sublingual gland was associated with the lowest rate of recurrence (<2%) [176]. On the other hand, extensive marsupialisation of a ranula is a viable alternative. The success rate is well over 85% and the gland can still be removed later if there is a recurrence.

6.2 Haemangiomas and vascular malformations

Haemangiomas are the most common vascular tumours in childhood. Following a growth phase, the vascular epithelium often undergoes spontaneous involution that may last for months or even years. Haemangiomas account for almost 60% of tumours in children, of which 80% occur in the parotid gland (Figure 10) and 18% in the submandibular region, while 2% are associated with the minor salivary glands [114]. Vascular malformations are pathologically anomalous structures arising from an abnormal development and morphogenesis of arterial, venous and/or lymphatic vessels. Section 2 of this book takes a closer look at the classification, diagnostic investigation and treatment of haemangiomas and vascular malformations.

6.3 Epithelial salivary gland tumours

On the whole, salivary glands tumours are rare in children and adolescents. Seifert and co-workers estimated the incidence to be 4% in patients up to the age of 20 [177]. They reported 80 epithelial salivary gland tumours in the register, corresponding to 2.5%. Of the 53 benign tumours (66%), 52 were pleomorphic adenomas. The 27 malignant tumours (34%) consisted of twelve mucoepidermoid carcinomas, five acinus cell carcinomas and ten showing other histology. Three of them, however, were adenoid cystic carcinomas, making this type of cancer the third most common. Cunningham et al. analysed malignant head and neck tumours in children over a period of 20 years [178]. Malignant lymphomas were present in 60% of the 241 children with cancer. Salivary gland carcinomas were very rare, accounting for only 2.5% overall. The Surveillance, Epidemiology and End Results (SEER) database also records rhabdomyosarcomas of the salivary glands in 8% of 113 cases [179]. Recent studies from China, with 119 patients, confirm the distribution of the different histological findings. Tumours were benign in 73% of the patients (n=87), with pleomorphic adenomas of the parotid gland, submandibular gland and minor salivary glands in all but three patients, [180]. Most tumours (77%) arose after the age of ten years [181]. An older review article [2] shows that the majority (85%) of tumours arise in the parotid gland with 48% of them being benign; 11.7% of tumours are found in the submandibular gland, with benign lesions accounting for two-thirds or more [179], [182]. A further 3.2% arise in the sublingual gland, all of which are benign. Conversely, the incidence of malignant lesions in adults increases from the parotid gland to the sublingual [183]. Lymphomas occur primarily in the parotid gland, representing some 2%-5% of all salivary gland neoplasms. About one-third of these lymphomas are mucosa-associated lymphoid tissue (MALT) lymphomas, another third are follicular lymphomas and the remaining third are diffuse large cell B lymphomas [184]. However, when children present with a firm solid swelling of the salivary gland, a higher suspicion of malignancy is needed than in adults. Local pain and especially facial palsy are further indications of possible malignancy. In addition to the clinical examination, ultrasonography, MRI and possibly CT are required to determine the extent of the lesion and any local metastasis. The following section takes a closer look at the most common benign and malignant tumours.

6.3.1 Benign epithelial tumours

A retrospective analysis of the Hamburg tumour register with a total of 549 surgical specimens from children showed adenomas in 47 cases (12%) [185]. 71% of these were pleomorphic adenomas, less commonly a Warthin’s tumour, oncocytoma, basal cell adenoma, inverted ductal papilloma and other rare benign tumours. The pleomorphic adenomas most commonly seen usually occur between the ages of 11 and 18. They are found in the parotid gland, the submandibular gland and also in the minor salivary glands [186]. Treatment of these benign tumours consists of complete surgical resection. Tumours in the superficial part of the parotid gland can be removed with a superficial parotidectomy (lateral lobectomy), whilst tumours in the deep lobe require complete parotidectomy [187]. There is no information on how often a superficial...
Figure 10: a) Unclear findings on ultrasonography of the left parotid gland of a 12-year-old girl. MRI showed a space-occupying lesion with high signal intensity in the T2 weighted scan and (b) a hypointense, inhomogeneous structure taking up contrast medium in an enhanced T1 weighted scan (c). The diagnosis of an atypical pleomorphic adenoma seemed most likely. After extracapsular dissection of the tumour (d), histology showed a cavernous haemangioma with cystic, partially thrombosed vascular clefts with residual acini in between them (e: reproduced with the kind permission of Prof. Agaimy, Department of Pathology, Erlangen, Germany).

parotidectomy or a extracapsular dissection is performed at this age, although, on the basis of the currently available data, such a procedure is, in principle, also considered possible, depending on the site of the tumour [188]. Surgery must aim for a complete resection of the tumour, without any residual disease, whilst preserving the facial nerve [183]. Submandibular gland resection is indicated for tumours in the submandibular gland, with complete local resection for the small salivary glands. As in adults, recurrences may occur if any tumour has been left behind and carcinomas may develop in longstanding pleomorphic adenomas.

6.3.2. Malignant epithelial tumours of the salivary glands

As mentioned previously, malignant epithelial salivary gland tumours are rare, mostly presenting around the age of 14 [189]. Girls seem to be affected more often than boys. The site tends to be the parotid gland more often than the submandibular gland, the sublingual gland and the minor salivary glands [186]. In principle, all tumours of the recognised WHO classification can, just as in adults, occur histologically. Low-grade or intermediate-grade mucoepidermoid carcinomas are the malignant tumours most frequently described in childhood [190], followed by acinus cell carcinomas (Figure 11) and aden-
oid cystic carcinomas. These three types of cancer account for 80–90% of malignant salivary gland tumours in children and adolescents. Adenocarcinomas, basal cell carcinomas and squamous cell carcinomas of the salivary glands are less common.

The treatment of choice is surgical removal of the tumour with a superficial or total parotidectomy, combined if necessary with neck dissection [114]. As for adenomas, total parotidectomy is preferred for tumours in the deep lobe [191]. But it is well known that the extent of the resection impacts the recurrence rate. A study from the Mayo Clinic found the recurrence rate of mucoepidermoid carcinomas to be 48% after simple enucleation, 31% after lateral parotidectomy and 0% after total parotidectomy [192]. In view of these results, it can certainly be argued that total parotidectomy should be performed for all parotid gland malignancies in childhood.

When the facial nerve has been infiltrated by tumour, it must also be resected to obtain an R0 resection and appropriate rehabilitation measures carried out [193]. Removal of the gland, with or without neck dissection, is indicated for cancer of the submandibular or sublingual gland. Malignancy of the minor salivary glands requires complete resection (clinically extending into healthy tissue). Neck dissection in children with salivary gland cancer can be considered in the same way as for adults. Such a dissection is indicated whenever abnormal lymph nodes are picked up on clinical examination or imaging. Elective neck dissection should be carried out whenever there are undifferentiated or large tumours (T3–4) and in certain individual cases [32], [194]. Given the 36% incidence of cervical node metastasis (N+) [191], with predominantly poorly differentiated tumours, it is our opinion that neck dissection can be considered as a basic elective procedure.

Postoperative radiotherapy for children is, of course, indicated in selected cases only (R1 resection, perineural invasion, advanced tumour stage, and poorly differentiated tumour) [195]. Nevertheless, it must be remembered that radiotherapy in children may affect growth of the skull bones and even cause osteoradionecrosis, trismus, dental problems, visual disorders and, in particular, radiation-induced second malignancies [191]. The indication for chemotherapy is found mainly in palliative situations or following recurrence, especially when surgery and radiotherapy are no longer possible [196].

Kupferman et al. carefully analysed the risk factors and the prognosis of childhood epithelial salivary gland cancer in a large population of 61 patients over a long follow-up period (median: 114 months) [191]. They found that 72% of the cases had T1 or T2 tumours and only 7% were classified as T4. Metastasis to the cervical lymph nodes (N+) was present in 36% of the cases. The five- and ten-year overall survival rates were 93% and 84%, respectively, with figures of 85% and 80% for disease-free survival. Seven patients died, five of them from the primary cancer. Univariate analysis of their data showed that patients aged more than 14 years, of non-Caucasian descent, with undifferentiated tumours, and with perineural invasion had a significantly worse disease-specific survival rate. The age, histology, ethnic origin and positive cervical lymph nodes were statistically related to poorer overall survival. Mucoepidermoid carcinomas have a relatively favourable prognosis, even when they arise as second malignancies (e.g. following treatment of lymphoma) with a 5-year survival rate of almost 94% or even better [197], [198]. A similarly good outcome, with a disease-specific survival of 88.4%, is also achieved with cancer of the minor salivary glands, if small, well-differentiated tumours are completely resected [199]. On the other hand, the survival rate falls with the corresponding risk factors, e.g. to 30–50% with undifferentiated tumours. Just like adult patients with such cancer, these children have to be followed up long-term over 10–20 years [200].

7 Systemic causes of salivary gland swelling

Systemic diseases, whose pathogenesis is not primarily related to salivary gland disease, may also cause swelling of the salivary glands in children. Today, many of these diseases can be treated successfully, so that changes in the salivary glands may not be seen so often. These diseases include hormone disorders such as hypothyroidism, diabetes mellitus and disorders of the pituitary gland [201]. The submandibular gland in particular may be enlarged in cystic fibrosis [202]. Nutritional disorders (obesity, malnutrition, hyperlipoproteinemia and vitamin deficiencies) may cause salivary gland enlargement.
Bulimia or anorexia must also be considered, particularly in adolescents with bilateral parotid swellings. The actual pathological mechanism for the swelling is not known. Ultrasound scans show homogeneously enlarged glands similar to those seen with sialadenosis [203]. Medications responsible for drug-induced enlargement of salivary glands are not often prescribed for children.

8 Sialorrhoea

Sialorrhoea (excessive salivation or drooling) impacts strongly on the mental state of the patient and is therefore a medical condition that needs to be clarified and treated. Sialorrhoea carries a social stigma, due to the impossibility of holding the saliva in the mouth and is usually found in association with an underlying neurological disease. In the long term, drooling leads to a considerable reduction in the quality of life of the affected children and their families. The indication for treatment depends on the quantity of saliva produced and the individual situation of the child or adolescent. Patients with mild sialorrhoea, but of normal intelligence and perhaps with a slight speech impediment, feel socially incompetent and rejected. At the other end of the scale are children with physical and learning disabilities, who have profuse sialorrhoea. They wear 10–15 bibs a day to catch the saliva, need frequent changes of clothes, and often need to be looked after in care facilities. These patients dribble all the time, and over everything. Consequently, they are often socially isolated and receive less loving care and attention. The complexity of sialorrhoea and the many possibilities for treatment make interdisciplinary management essential. A team consisting of an ENT surgeon, dentist and orthodontist as well as a maxillofacial surgeon, neurologist or paediatric neurologist and speech-language therapist should agree on the best possible treatment. Together, they must consider whether spontaneous improvement is likely and, if not, they must decide which therapeutic modality to use, in particular, whether surgery is required [204], [205].

Increased salivation, in the sense of sialorrhoea, is physiological up to the age of four years. Excessive salivation in children over the age of four, who are awake, must, however, be considered pathological. The most common reason for drooling is a neurological disorder, with an incidence of 10% to 30% [206]. Peripheral disorders of the trigeminal or facial nerves can also lead to drooling. With neurological disorders, difficulty in swallowing is a much more prominent feature than the hypersecretion of saliva. A lack of lip closure is a prime feature [207]. Centrally regulated sialorrhoea may be caused by raised intraluminal oesophageal pressure, but is far more often due to interruption of the first (oral) phase of swallowing. Uncoordinated movements of the tongue impede the transport of saliva from the mouth to the oropharynx. Sialorrhoea has been studied particularly well in children with Down’s syndrome. General muscular hypotonia and relative macroglossia with a wide mouth opening have a deciding aetiological role [205]. Drug-induced hypersalivation, especially due to neuroleptic agents, can be distinguished from sialorrhoea of neurological origin. Alpha-adrenergic and muscarinic receptors in particular are involved in the pathophysiology of neuroleptic-induced salivation [208].

Idiopathic hypersalivation is another form of sialorrhoea of unknown origin. A study by Johnson et al. showed that children who are developing normally may also show delay in saliva control. This problem is usually self-limiting without any treatment, as the child continues to develop [209].

Besides the obvious causes, important cofactors impacting on sialorrhoea include the current emotional status, ability to concentrate, disorders of occlusion, tooth damage and posture. Dental or gingival damage naturally increases salivation, whilst inclining the head forward obviously encourages saliva to flow out of the mouth under the force of gravity.

In addition, patients with difficulty in nasal breathing and wide-open mouths tend to salivate more. Treatment with anticonvulsants also promotes hypersalivation [205]. Gastro-oesophageal reflux may be a problem in children and it has been suggested that reflux may induce hyperstimulation of the salivary glands with increased saliva production [204]. Even though an effect on drooling has not yet been confirmed for anti-reflux therapy, such treatment has led to considerable improvement in a few cases [210].

A rough estimate of the severity of the sialorrhoea is the minimum required to assess and compare different therapeutic approaches and outcomes. The problem with sialorrhoea is that it undergoes extreme temporal variation. Blasco et al. divided the various methods for quantifying the degree of drooling into three categories [210]:

1. Basic clinical estimation (e.g. the number of bibs or T-shirts required)
2. Drooling severity scales and frequency based on systematically timed observations [211].
3. Volumetric measurement of saliva for absolute quantification of the saliva flow using special external or intraoral collection devices [212], [213]

However, none of these different methods can replace the long-term observations of the parents or carers. The best semiquantitative measure is the number of bibs or T-shirts required during the course of a ‘typical day’, a ‘bad day’ or a ‘good day’. Interestingly, numerous surgical procedures have been reported in the literature of English-speaking countries, while conservative treatment is preferred in German and European sources. The problems of drooling also seem to be perceived differently in different societies. Before beginning any specific treatment of sialorrhoea, the potentially exacerbating factors first need to be corrected. Dealing with tooth decay, resecting hypertrophic tonsils or correcting malocclusion often leads to a distinct
improvement in the symptoms. The treatment of sialorhoea always requires interdisciplinary cooperation between dentist, ENT surgeon, orthodontist, maxillofacial surgeon and neurologist or paediatric neurologist.

8.1 Conservative therapeutic approaches

Behavioural modification and biofeedback therapy

These therapeutic methods aim to trigger swallowing in response to an auditory signal [214]. In a study on EMG biofeedback, a significant reduction in salivary flow with a simultaneous slightly increased rate of swallowing could be achieved. The success of the method depends on improved coordination during the oral phase of swallowing, but it is very time consuming. Nevertheless, Rapp reported a sustained benefit in children with a mental age of between 18 months and 8 years [215].

Oral-motor therapy and orofacial regulation therapy

In 1978, McCracken reported on the treatment of three cases using a sensorimotor technique. Vibration was applied to the masseter as well as to the anterior belly of the digastric muscle and the lip area for two to three minutes [216]. Harris and Dignam also found this therapeutic technique to be successful [213]. However, the available reports on this method are ultimately concerned with small patient groups only. In Germany and South America, the literature focuses on the Castillo-Morales concept of orofacial regulation therapy [217], [218], [219], [220]. This method essentially involves the application of acrylic plates in the region of the palate and oral vestibule of the upper and lower lips, which function as active components stimulating the intra- and circumoral muscle, in combination with oral and facial physiotherapy. This treatment method can be started in infants as young as six weeks old. Its effects have been monitored particularly well in several studies on patients with Down’s syndrome. Here, improvement was seen in the symptoms of hypotonia with the resulting optimisation of swallowing and expression [218]. Furthermore, it reduced tongue protrusion with improved lip closure. Similar observations have also been made in children with central motor injury. An improvement in the spontaneous position of the tongue, coordination of tongue movements, eating, speech development, and drooling was seen in almost half of the cases (n = 71) [218], [220].

In summary, it can be said that although orofacial therapy at least reduces drooling, it can rarely return salivation to normal [205]. Treatment should always start before the age of four, otherwise the palatal stimulating plate is not tolerated and there is no guarantee of success. It is not known whether the stimulating plate is better used alone or with the additional physiotherapy [204].

Speech therapy

Even though experimental attempts have been made to reduce drooling with speech therapy, it seems to be too time-consuming and is only successful with continuous application [216].

8.2. Medication for sialorrhoea

The basis of many pharmacotherapeutic approaches to drooling is an anticholinergic effect. One of the oldest and best-known active substances is scopolamine, a cholinergic muscarinic receptor-antagonist, which causes a significant reduction in salivation, even in comparison with atropine [221]. Giving medication to children and adolescents has to be considered very carefully and is, at most, indicated in exceptional cases for a short time only. The best-known method of administration is the Scopoderm patch (Scopoderm TTS®), which can be affixed directly to the skin behind the ear, after the area has been cleansed with 70% alcohol. The patch can be left in situ for up to four days after which time it is replaced with a new patch. The onset of action is about 15 minutes after applying the patch [222]. Very good results have been achieved with Scopoderm patches in adults. Adverse effects, such as local allergic reactions, acute psychotic and confusional states, dry mouth, constipation, urinary retention, reduced sweating and flushing, may occur. Hypertension and glaucoma are relative contraindications [205].

An important recent addition is the use of botulinum toxin A to inhibit salivary gland secretion. Botulinum toxin inhibits the reuptake of the neurotransmitter acetylcholine from the synaptic cleft, thereby blocking signal transmission and reducing saliva production; this, in turn, leads to a considerable reduction of drooling [223], [224], [225], [226], [227], [228], [229]. However, it must be remembered that treating hypersalivation with botulinum toxin is currently off-label use, i.e. using an approved medicinal product for an indication not included in its marketing authorisation. In terms of prescribing freedom, however, the medicinal product may also be used for a non-approved indication when this is justified and medically necessary. On the basis of existing studies, its use in the salivary glands falls into this category. According to Ellies et al., the best way is to inject the toxin, under ultrasound guidance, into both parotid glands (21 units of Botox® each side) and both submandibular glands (10 units of Botox® each side). Improvement can already be seen three days after the injection [224], [225], [226]. Bothwell et al. used botulinum toxin A in a population of children with sialorrhoea associated with various neurological diseases. They injected 5 units of botulinum toxin into the parotid gland. All patients had a reduced incidence of hypersalivation after four weeks. Eight of the nine patients also showed a reduction in the objectively measured salivary flow; 55% of the parents were of the opinion that the treatment was successful. The reported adverse reactions included difficulty chewing, dry mouth,
and transient weakness of jaw closing - the last probably due to inaccurate injection into the masseter muscle [223]. The possibility of transient facial paresis should also be mentioned, although this has not been described in the literature with regard to the use of botulinum toxin. The effects of botulinum toxin A last 8–16 weeks and then the injections have to be repeated. Compared with anticholinergic medication (see above) the success rate is about the same.

8.3 Surgical treatment of sialorrhoea

Despite conservative methods as well as the use of medication and even acupuncture, surgical procedures may be indicated for drooling because of adverse drug reactions or treatment failure [230], [231], [232]. These operations essentially aim to reduce saliva production, change the outflow of saliva or involve a combination of the two. Transtympanic neurectomy of the tympanic nerve [233] often leads to recurrence and especially to a loss of taste sensation or possibly even to xerostomia [234]. For this reason, it is nowadays no longer performed. Distortion or even loss of the sense of taste is particularly serious for children and those with mental impairment, as oral sensations are often the only pleasures in their lives. Reduction in saliva production can obviously be achieved by resecting the gland. Here, the simplest solution for pronounced drooling is certainly to remove both submandibular glands (Figure 12). Simple ligation of the parotid and/or submandibular ducts have been described [235]. Instead of using ligatures, one research group occluded the parotid duct using Nd:YAG laser impulses, resulting in stenosis. With this procedure, they achieved symptomatic improvement in more than 90% of the 48 patients [236]. However, a manipulation of the parotid duct on its own is somewhat disputed in the literature, as the parotid gland produces only a small proportion of the saliva at rest, even though it is of greater importance when secretion is stimulated [205]. Other surgical techniques consist of rerouting the excretory ducts. For this, the parotid ducts and possibly also the submandibular ducts are dissected out from their usual anatomical positions and reimplanted in the tonsillar fossa. In 1967, Wilkie was the first to propose the procedure, which was subsequently named after him. The parotid ducts were implanted in the tonsillar fossae, in order to trigger a direct swallowing reflex on salivation [237]. Wilkie and Brody modified the procedure in 1977, by removing the submandibular glands during the same operation. Tonsillec- tomy is also carried out as part of the procedure, in order to prevent stenosis and recurrent infection of the excretory ducts or salivary glands [238], [239]. Even the rerouting of the parotid duct with autologous venous interposition grafts has been tried as a variation of Wilkie’s procedure [240]. Rerouting of the submandibular duct into the tonsillar fossa has also been described, a procedure that is associated with the risk of a ranula developing [241], [242], [243]. One obvious disadvantage of these operations is that the patient has to be admitted to hospital. In addition, there is a risk of a branchial cyst developing, as well as severe caries [243]. Rerouting the excretory duct into the tonsillar fossa is contraindicated in patients being aspirated. Figures from 67% to more than 90% have been reported for the success rates of the surgical procedures.

9 Parotidectomy in children: indications and complications

Overall, parotidectomy is very rarely indicated in children. In their analysis of 22 parotidectomies (six total), Xie and Kubba [244] demonstrated the different indications very well. Congenital abnormalities, atypical mycobacterial infections and tumours were each responsible for about one third of the patients requiring surgery. This is very different from the reasons seen in adults [32], [245]. Typical complications, such as transient or persistent fa-
Permanent facial palsy (House-Brackman VI) and Frey’s syndrome, occur about as frequently as in adult patients. We recommend the use of facial nerve monitoring and nerve stimulation during surgery in children. It is important to remember that the facial nerve may lie much more laterally in children than in adults, as the mastoid cells are not yet fully developed. In proportion to the surrounding structures, the nerve is even slightly larger in young children [2], [246]. There are no contraindications to this procedure. Transient facial weakness has been reported in 36% and persistent palsy in 11% of lateral or total parotidectomies [191]. Other authors give figures of 23% to 50% for transient paresis and complete recovery with time. The incidence of short-term facial nerve weakness is higher with total than with superficial parotidectomy (25% vs 16%) [32]. A mild Frey’s syndrome that did not require treatment was found in 19% of children following lateral parotidectomy [183], [244]. Hypertrophic scarring requiring treatment (14%) seems to be more common in children than in adults. Treatment is usually intrallesional injection of steroids. One study found the recurrence rate of pleomorphic adenomas in children to be 20% [2]. The authors attributed this to the smaller anatomical structures, which make capsular rupture and tumour seeding more likely. In contrast, Malone and Baker [247] found no recurrence in their patients after up to 20 years’ follow-up.

In principle, surgeons must be aware of the special features of parotidectomy in childhood that have been mentioned and discuss them in detail with the parents as well as with the children, if they are older. The surgeon should already have extensive experience in parotid gland surgery.

**Notes**

**Competing interests**

The authors declare that they have no competing interests.

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