Pediatric Rhinology

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ABSTRACT

The following review article highlights key topics in pediatric rhinology that are currently the focus in research and at conferences as well as in the interdisciplinary discussion between otorhinolaryngologists and pediatricians. In particular, congenital malformations such as choanal atresia or nasal dermoid cysts are discussed, followed by statements on the current procedures for sinogenic orbital complications and on the diagnosis and therapy of chronic rhinosinusitis in children. Furthermore, updates on the role of the ENT specialist in the care for children with cystic fibrosis and primary ciliary dyskinesia are provided.

Contents

Teaser

The care of children and adolescents suffering from rhinological diseases requires a high degree of interdisciplinary and interactive networking between multiple specialties, primarily ear, nose and throat medicine and pediatrics, but also human genetics, pulmonology, radiology, dermatology, neurosurgery, ophthalmology and many others. This interdisciplinarity is necessary not only to maintain the high standard of medical care, but above all to further develop innovative diagnostic and therapeutic concepts for children. Although there is no separate medical specialty defined for pediatric otolaryngology in Germany, the care of routine as well as complex clinical pictures for this patient collective takes place at the highest level. However, the lack of clearly defined interdisciplinary networking structures, as found in many other European countries, makes it all the more necessary to establish appropriate interdisciplinary care strategies on an individual basis. In general, the development of this network is primarily the responsibility of the core disciplines of pediatrics and otorhinolaryngology, which can jointly create a well-functioning care structure with a high degree of trusting communication. In this respect, the topic of Pediatric Rhinology fits ideally with this year's motto of the annual meeting of our professional society. "Crossing Borders" reflects the leitmotif and the approach to pediatric otolaryngology in a particularly fitting way.

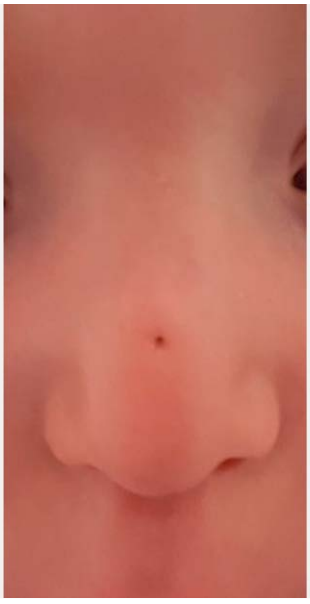
This paper does not claim to present a comprehensive compendium of all rhinological diseases of childhood, but rather focuses on specific areas for which innovations in diagnostics and therapy have emerged in recent years and which have been and continue to be regular topics of discussion at international meetings of pediatric otolaryngology. The European Society of Pediatric Otorhinolaryngology ESPO defines "Rhinology" as one of its six main topics, which underlines the importance of this subspecialty.

1. Congenital malformations

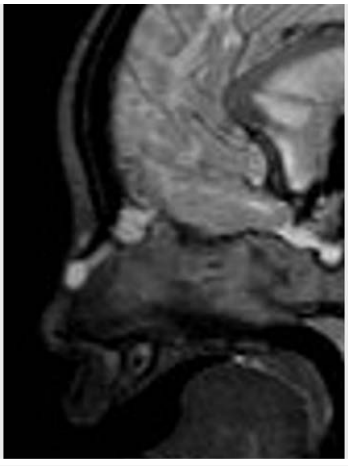
Congenital malformations include an extensive spectrum of rare and very rare disorders. Malformations of the nasal framework are usually clearly visible from the outside and require careful treatment planning and implementation. The focus is not only on remediation of the processes but also on cosmetic results in the context of the child's growing midface. Malformations of the internal nose can have significant functional implications and sometimes require urgent or even emergency care. As an example of frequently occurring malformations of the external nose, nasal dermoid cysts are described in this chapter. Innovations have been made in this area, particularly with regard to standardization of surgical approaches and optimization of reconstruction. As an example of malformations of the internal nose, choanal atresias are discussed. These can be syndromatic but also isolated. Therapy has become increasingly standardized in recent years with satisfactory surgical results and better long-term outcomes than 15 years ago. Pediatric lacrimal duct stenosis is a special topic because this clinical picture occurs very frequently in contrast to the other two examples. However, the ENT physician is needed for intervention only in complex cases, but then with the need for a high degree of expertise in midface surgery.

1.1 Nasal dermoid cysts

Congenital midline nasal lesions occur in one in 20,000 to 40,000 live births, making them rare malformations. Along with gliomas and encephaloceles, nasal dermoid sinus cysts (NDSCs) are among the most common congenital midline nasal lesions [1]. NDSCs manifest as a depression on the dorsum of the nose with a fistula opening in the median (▶ **Fig. 1**). Histopathologically, these are true cysts lined by keratinizing squamous epithelium with adnexal structures such as hair follicles, sebaceous glands, and glands. The adnex structures may be visible externally through the fistula opening, for example as a single medial hair. In contrast, nasal dermoids are spherical, sometimes minimally mobile lesions in the midline. NDSCs can visibly deform the cartilaginous and especially the bony framework of the nose. Typical in this case is a divergence of the two ossa nasalia at the junction with the cartilage (open roof deformity) as well as a tissue prominence in the supratip region (polly beak deformity) with a punctate retraction with fistula opening [2]. In NDSC, involvement of intracranial structures is reported with a frequency of 4–55 % in the literature [3, 4]. Clinically alone, purely intraosseous (frontonasal) NDSC cannot be differentiated from those with intracranial involvement; in this case, high-resolution, multiplanar cross-sectional imaging is always required. Intracranial involvement includes extradural as well as intradural extension. Intradural manifestations in particular are at increased risk of developing meningitis. The distinction between the different types is highly relevant before initiating surgical therapy, as the intracranial extension largely determines the extent and approach of the surgical intervention. In this regard, magnetic resonance imaging (MRI) is the modality with the highest precision and can best depict potential intracranial extension of NDSC [5]. High-resolution computed tomography (CT) is an alternative but tends to have poorer sensitivity and specificity compared to high-resolution MRI. However, preoperative radiologic misdiagnosis regarding intracranial extension is possible with both modalities, especially in children under the age of 3 years (▶ **Fig. 2**). Early excision of NDSC is the treatment of choice. Depending on the extent, different approaches have been established. These include vertical midline incision,



▶ **Fig. 1** Nasal fistula opening of NDSC (nasal dermoid cyst, nearly in the midline.



▶ **Fig. 2** MR imaging in sagittal section: presentation of an intracranial extradural fistula of a nasal dermoid cyst.

external rhinoplasty, Lynch incision, transverse incision, lateral rhinotomy, endoscopic techniques, and combined approaches [2]. In most cases, the open rhinoplasty approach offers the best cosmetic results as well as a favorable option for reconstruction of the nasal framework and nasal contour through osteotomies or the insertion of grafts to fill the defect [6] (▶ **Fig. 3**). In addition, the open rhinoplasty approach does not open the cartilaginous and bony nasal skeleton for surgery. After complete surgical removal, deformities of the upper lateral cartilage and nasal bones remain, depending on the extent of the lesion. For mild deformities, osteotomies can be used to medialize the bony flanks of the nose, and the defect is thus adequately reconstructed. For the reconstruction of larger defects, which cannot be sufficiently corrected by osteotomies, additional transplants are required. Ear cartilage is usually suitable for transplantation. Temporoparietal fascia, for example, can be used for additional splinting of the grafts under the thin skin [7]. Intraosseous dissections are possible with microdissectors under endoscopic view. The open rhinoplasty approach is not suitable for cranially located dermoid cysts or dermoids, such as those of the glabellar region. In these cases, vertical midline incision is a cosmetically acceptable alternative. In cases with intracranial extension, additional craniotomy via a coronal incision is required.

1.2 Choanal atresia

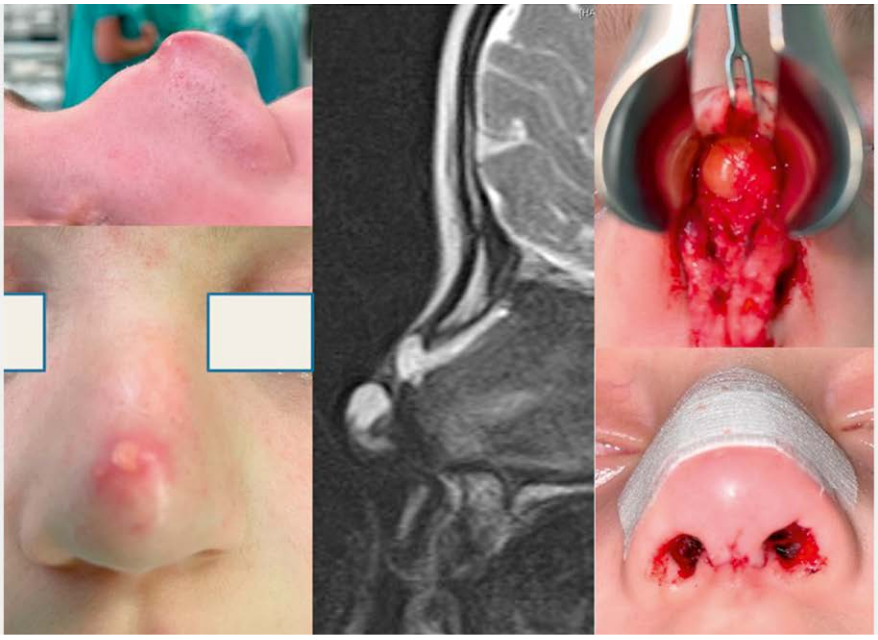
Choanal atresia (CA) is a rare disorder, occurring in one in 5,000–7,000 newborns [8]. A distinction is made between unilateral and bilateral choanal atresia (▶ **Fig. 4**). The unilateral atresias are more common. Female newborns are affected twice as often as males. In 30 % of cases, the choanal atresia is purely bony, in 70 % bony-membranous [9]. Purely membranous atresia has not been described to date. Congenital unilateral or bilateral CA is the most common among malformations of the nasal cavity and nasopharynx. The first 12 weeks of embryonic development are particularly relevant for the development of the face. The major part of this development occurs in the first 4 weeks. Over the years, various authors have formulated theories regarding the development of the atresia plate. There are four theories that have prevailed over the years and are widely accepted [10]:

1. Persistence of the buccopharyngeal membrane from the foregut.
2. Abnormal persistence or location of the mesoderm forming adhesions in the nasochoanal region
3. Abnormal persistence of the nasobuccal Hochstetter membrane.
4. Misdirection of cell migration of the neural crest.

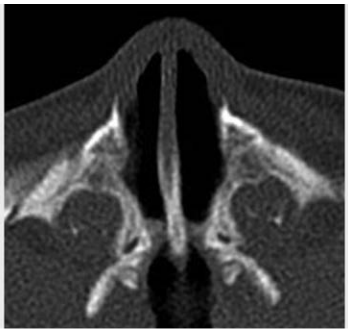
The clinical presentation is significantly influenced by two factors: whether unilateral or bilateral CA is present and whether there are associations with additional anomalies – as in CHARGE association – or craniofacial malformations [11]

Bilateral choanal atresia: Due to the ventral and cranial position of the larynx, newborns are obligate nasal breathers during the first 4–6 weeks of life. Bilateral CA is classically symptomatic immediately after birth, which results in dyspnea, stridor, and paradox cyanosis. This form of cyanosis occurs at rest and is relieved by crying. In addition, there are massive problems with food intake due to aspiration tendencies. Nasogastric tube insertion is not possible due to the CA-related nasal barrier. Affected individuals develop into respiratory emergencies and require very prompt treatment. The airway should be initially secured by intubation and surgical CA canalization should be performed within a few days.

Unilateral choanal atresia: Typical complaints of unilateral CA are unilateral nasal obstruction, persistent mucous rhinorrhea, and in most cases septal deviation to the affected side. The diagnosis is often possible directly after birth, but occasionally not until adolescence or even adulthood. Other comorbidities such as an ogival palate or facial hypoplasia are not uncommon. Surgical treatment should be performed from 6 to 12 months of age. Certain authors consider the optimal time for surgery to be between 6 and 12 years of age. This is based on the fact that the topographic conditions have increased by more than twofold by that time. This is expected to reduce the number of revision surgeries. Unilateral CA should be treated surgically in any case, otherwise secondary diseases such



▶ **Fig. 3** NDSC: preoperative aspect from lateral and frontal, MR imgaing in sagittal section: presentaiton of a purely intraosseous (fronto-nasal) NDSC, intraoperative presentation of the cystic part via an open rhinoplasty approach, picture at the end of surgery.



▶ **Fig. 4** Computed tomography scan in axial section: presentation of bilateral choanal atresia.

as recurrent sinusitis, middle ear ventilation disorders or otitis will almost inevitably occur [12, 13].

1.2.1 Syndromes/congenital anomalies

Pagon et al. [14] first mentioned the acronym CHARGE association in 1981, which is characterized by a variety of congenital anomalies and is inherited in an autosomal dominant manner: "**C**oloboma of the eye", "**H**eart defects", "**A**tresia of the nasal choana", "**R**etardation of growth and/or development", "**G**enital and/or urinary abnormalities", "**E**ar abnormalities and deafness". Studies [15] report that 7–29 % of patients with CA have CHARGE syndrome. Other patients are notable for other congenital anomalies such as tracheomalacia, laryngomalacia, subglottic stenosis, or other specific syndromes such as Treacher-Collins syndrome, Apert syndrome, or Pfeiffer syndrome. Overall, associated malformations are present in 49 % of patients with CA, especially bilateral CA [16]. In the case of syndromal disease and nasal obstruction, CA should be specifically sought [11].

1.2.2 Diagnostics

The diagnosis is usually based on clinical aspects. Typically, diagnosis begins in the delivery room by transnasal insertion of a thin suction catheter into the nasopharynx. CA should be suspected if advancement of the catheter beyond 3 to 3.5 cm is not possible. This would be the distance after which the choana should usually be reached in the newborn. Attention must be paid that the catheter does not roll up in the inferior nasal meatus and feign or obscure CA. Nasal obstruction can be objectified by use of a puff plate or laryngeal mirrow (▶ **Fig. 5**). Normally, a precipitate approximately 1.5–2 cm in size develops anterior to each nasal ostium. A definitive clinical diagnosis of CA can be verified endoscopically. Nasal endoscopy with a thin flexible endoscope should be performed after careful aspiration and decongestion of the mucosa. This allows direct visualization of the choanal region and confirmation of the suspected diagnosis [13]. The diagnostic imaging modality of choice for surgical planning is the computed tomography (CT). It allows detailed visualization of the osseous structures and determination of the extent of ossification and the size of any membranous atresia present. Typically, the dorsal vomer shows thickened and the ipsilateral lateral nasal wall bulges. In addition, anatomic norm variations are visualized, which are of great importance to the surgeon. Alternatively, high-resolution magnetic resonance imaging (MRI) is available, which provides similar, detailed information but only indirectly depicts the bone structures. Advantages are the avoidance of radiation exposure and the still possible visualization of skull base abnormalities. Despite the existing controversial dis-

▶ **Fig. 5** Respiration mirror according to Ernst Glatzel to check the air patency of the nose.

cussions about computed tomography in childhood, this imaging procedure should be performed in choanal atresia.

1.2.3 Therapy

Surgical approaches represent the therapy of choice. Various techniques have been described in this regard. However, the evidence for advantages and disadvantages of these techniques has not been based on randomized prospective studies [17], so there is no clear consensus regarding the technique to be used since surgical treatment was first described in the mid-19th century. Endoscopic techniques have existed for more than 20 years and are preferred by most surgeons today. Surgical treatment options include transnasal perforation, transpalatal resection, transnasal endoscopic perforation, and transnasal endoscopic choanalplasty [18].

Transnasal puncture is considered obsolete, but historically it was the first method used in CA. It was described by Carl Emmert in 1854 and consisted of a blind retropalatal puncture performed with a curved trocar. Later, a 120 ° endoscope or mirror was used to examine the area of atresia. After puncture, the opened choana was dilated with Bougies or Blakesley until the lumen was sufficiently large. Unfortunately, the opening of the stenosis with this technique is usually temporary and therefore often requires revision surgery [10]. In addition, there is a risk of complications, especially with blind puncture, due to injury to the septum, lateral nasal wall, nasal vault, or clivus [13].

In transpalatal resection, the mucosa of the hard palate is elevated in a local flap and the entire thickness of the bone in the region of the bony atresia is removed with the diamond drill. Despite a lower incidence of re-stenosis, complications of this technique are still common. These include the development of a malformed, high-arch palate, crossbite, nasopalatal fistulas, and dehiscence. For these reasons, this method is not recommended for children under the age of 6 years. With the advent of endoscopic techniques, the number of transpalatally performed operations has decreased [19].

Transnasal endoscopically assisted perforation is technically comparable to the blind puncture described above, but with additional endoscopic control. This reduces the complication rate with regard to damage to the adjacent tissue. In premature infants, even small rigid optics may be too large to allow transnasal endoscopic choanalplasty. In these cases, transnasal endoscopically assisted perforation is the method of choice for treatment of bilateral CA. However, transnasal endoscopic revision choanalplasty is then usually required at a later time as soon as anatomic conditions allow.

Transnasal endoscopic choanalplasty is considered the surgical technique of choice by most surgeons and is based on endoscopic resection of the atresia plate and posterior septum (vomer), creating a united bilateral choana ("single choana"). Primarily, "cold" instrumentation is used for bone resection. In the case of medialized medial pterygoid plates, the diamond drill can be used. In addition, the successful use of the CO_2 laser and balloon dilators has been described [20–22]. The authors of the paper prefer the use of a narrow diamond drill with reduced speed (10,000 rpm). If possible, the mucosa should be preserved as a pedicled flap that is then replaced on the exposed bony walls of the neochoans at the end of the procedure to accelerate epithelialization of the wound surfaces and thus prevent re-stenosis [23]. The success rate of transnasal endoscopic choanalplasty, as measured by the occurrence of re-stenosis or the need for revision surgery, was 65 % in a meta-analysis by Strychowsky et al. [24]. Risk factors for re-stenosis include associated congenital anomalies, reflux of gastric contents into the nasopharynx, and neonatal age less than 10 days. Navigation systems may be used to facilitate orientation in the presence of altered anatomy [25]. In addition to the anatomic requirements, the success of the surgical procedure is influenced by the following additional factors [26]: adequate resection of the posterior septum (vomer), avoidance of bony edges and large areas of exposed bone, avoidance of stents, performance of adequate postoperative follow-up.

1.2.4 Prognosis

The insertion of stents is controversial among experts. The advantages of using stents are the slightly lower incidence of re-stenosis, satisfactory air patency in the initial postoperative period, and support of re-epithelialization during the healing process of the neochoanae. For this purpose, stents are inserted for up to 16 weeks [24] and must be changed regularly. Disadvantages of their use may include pressure-induced mucosal damage, granulation and scarring, bacterial colonization, ulceration, and mechanical blockage of mucus secretion [27]. In the meta-analysis by Strychowsky et al. it was found that most complications after surgery for CA were due to the use of stents. In addition to those previously mentioned, these are mainly nasal entrance stenosis. In addition to stenting, the use of mitomycin C has been described in the prevention of granulation formation, re-stenosis, and to reduce the revision surgery rate [28]. Nevertheless, it is recommended only in complex cases due to its potential carcinogenicity and the lack of clinical efficacy data.

In their article published in 2019, the International Pediatric Otolaryngology Group (IPOG) makes the following recommendations for the postoperative management of CA [20]:

Use of medications:

- Proton pump inhibitors (PPIs) are recommended by 63.4 % of IPOG members, with a usual prescription duration of up to two months.
- Prescription of antibiotics is controversial, with 46.4 % of members prescribing oral or intravenous antibiotics and 53.6 % not prescribing them.

- Intranasal corticosteroids are frequently used (71.4 %), whereas systemic corticosteroids are not (28.6 %).
- 0.9 % saline solution should be applied topically after surgery (100 %), with 82.1 % of members recommending a duration of four weeks. Rinsing the nose one to three times per day is recommended (75 % of members).

1.2.5 Follow-up

Clinical follow-up should include flexible or rigid nasal endoscopy (96.4 %). The timing of the first postoperative follow-up examination is in the first two weeks in 75 % of members. "Second-look" surgery under general anesthesia is performed in selected patients by 50 % of members and systematically by 25 %. Reasons for preventive postoperative examination under general anesthesia include bilateral choanal atresia, syndromic choanal atresia (such as CHARGE association), low weight, and young age. The majority of members (64.2 %) reported that the timing of this procedure should be within the first month after the initial surgery. Postoperative imaging is not recommended, even for revision surgery (96.4 %). Objective assessments of nasal breathing are rarely performed and are almost impossible in neonates and infants. The duration of follow-up should be long, at least one year (100 %). Some centers perform follow-up examinations into adulthood. Surgical outcome is considered stable after 6–12 months (73.3 %). However, delayed re-stenosis has also been described, so parents and patients should also be informed about possible delayed recurrence.

1.3 Infantile lacrimal duct stenosis

1.3.1 Introduction

Nasolacrimal duct obstruction (NLDO) is the most common cause of persistent lacrimation or ocular discharge in children. It occurs in up to 20 % of all newborns and causes symptoms in approximately 6 % of those affected during the first year of life [29]. Nearly 90 % of cases resolve spontaneously or with conservative treatment [30]. A distinction is made between congenital and acquired NLDO. NLDO in the pediatric age group are almost always of congenital origin due to a lack of canalization of the distal end of the lacrimal duct with persistence of a membranous bar at the level of Hasner's valve [31]. The incidence of congenital NLDO is higher in children with craniofacial anomalies and Down syndrome. The causes of acquired NLDO are not well understood yet.

1.3.2 Therapy

Treatment of NLDO in children is predominantly conservative by compression or massage of the lacrimal sac and, if necessary, application of topical antibiotics in case of discharge. Rarely, irrigation of the lacrimal duct is required [32]. After 12 months of age, the likelihood of spontaneous healing decreases and most patients are treated by probing or intubation of the nasolacrimal drainage system [33]. In refractory cases, surgical therapy should be considered. These cases are very rare and generally limited to children with craniofacial dysmorphia or trauma.

Historically, refractory saccal and postsaccal lacrimal stenoses have been treated by external dacryocystorhinostomy (DCR). This procedure was first described by Toti in 1904 and is a highly effective procedure for correcting NLDO. With the introduction of rigid nasal endoscopes and fiberoptic light delivery systems, the endonasal approach has been greatly improved, especially in the pediatric patient population, thanks to better illumination and magnification. Endoscopic DCR (EDCR) has undergone many changes over the years in the field of pediatrics, among others, for example, in the context of preservation and shape of a mucosal flap [34]. EDCR has become the surgical treatment option of choice in many centers thanks to its many advantages over external DCR [35–37]. The endonasal approach allows drainage of an obstructed lacrimal sac and system without the need to make an incision in the face and thus without creating a scar. In addition, there is less surgical trauma to the medial lid angle and orbital tissue and less risk of bleeding. The pediatric endoscopic instrumentation is specifically designed for optimized surgical access and also allows correction of intranasal causes of epiphora (i. e., membranous and bony obstructions, adhesions, mucosal abnormalities, inferior turbinate hyperplasia). Similar to the treatment of choanal atresia, the use of silicone stents, both in external and endoscopic DCR, is controversial. In some centers, their use is systematic; in others, they are targeted and used only when canal stenosis is suspected or during revision surgery [38]. The goal is to ensure permanent patency of the DCR ostium. However, there is evidence that stent placement increases the risk of granulating inflammation and thus failure of surgery. To prevent obstruction of the DCR ostium by granulation tissue, the use of mitomycin C or 5-fluorouracil has been described as an alternative to stenting. In a meta-analysis, Cheng et al. [39] investigated the efficacy of using mitomycin C during EDCR and concluded that it may help to reduce the rate of occlusion of the created ostium. The authors of the paper favored a generous ablation of the os lacrimale and a planar opening of the lacrimal sac to minimize the risk of restenosis and recommended that the use of mitomycin C be limited to individual cases (for example, complex recurrent situations). Pediatric EDCR differs from adult EDCR because of the anatomic setting. In children, the nasal cavity is relatively narrow with proportionally voluminous turbinates. The presence of septal deviation complicates the endoscopic procedure, as septoplasty is usually avoided due to its potential impact on facial growth. Despite the narrow nasal anatomy in young patients, systematic reviews have shown that endoscopic DCR allows similar success compared to the external procedure [40]. Therefore, it represents the procedure of choice.

2. Therapeutic aspects of acute and chronic rhinosinusitis

Inflammatory diseases of the nasal cavity and paranasal sinuses are common. Acute rhinosinusitis in particular is one of the most common clinical pictures in children. Therapy is usually coordinated by pediatricians or general practitioners. The otolaryngologist is usually not the first contact in the care of uncomplicated acute rhinosinusitis in children. The acute upper respiratory tract infection (common cold), usually virally induced, is associated with nasal obstruction, with nasal secretion, and sometimes accompanied by headache or facial pain and cough. The disease is usually self-limiting and due to its short-term duration, purely symptomatic therapy is sufficient. Only when symptoms persist or recur, further di-

agnostic and therapeutic measures are indicated. Acute bacterial rhinosinusitis is rare compared to the viral form, so the administration of antibiotics is usually not necessary. The ENT speciatist is usually only consulted in the context of complications of acute rhinosinusitis. Here, orbital complications are significantly more common than intracranial complications, especially in younger children. The inflammatory complications of the cranial bone (sinugenic osteomyelitis) is even less frequent in comparison [41]. For this reason, the present chapter focuses on orbital complications. Chronic rhinosinusitis is much less common in children compared to the acute form. The current innovations in therapy are addressed and distinguished from the routine care of adults with chronic rhinosinusitis. At conferences, isolated sphenoid sinus pathologies are often discussed in separate sessions, which is why a targeted literature search was performed for this purpose. Finally, the chapter concludes with an update on pediatric allergology, including focal aspects that deliberately go beyond the topic of "rhinology" to include other clinical pictures that must be recognized as comorbidities by the otolaryngologist in order to provide patients with further targeted therapy.

2.1 Sinogenic orbital complications

2.1.1 Causes and forms

The most common cause of orbital complications in pediatric rhinology is acute rhinosinusitis, most commonly ethmoidal sinusitis [42]. Acute rhinosinusitis is a common condition in children, whereas, in comparison, orbital sinogenic complications are very rare. They occur more frequently in children than in adults. The ethmoid cells, unlike other sinuses, develop in early childhood and act as the initial site for orbital manifestations of inflammation. The term of orbital complication summarizes clinical pictures of different severity. They are subdivided according to their localization and severity. Internationally accepted and most commonly used is the classification according to Chandler [43], although it is quite controversial, as discussed below. For example, Chandler introduced the term "cellulitis", which is still used in international terminology, although it would be better replaced by other terms such as "inflammation". The individual subtypes of orbital complication may manifest sequentially, one after the other, but not necessarily in every case. In this context, preseptal cellulitis or preseptal eyelid edema (Chandler I) represents the mildest manifestation of the disease and is the most common sinogenic orbital complication in children and adults, accounting for approximately 60–75 % [44, 45]. It is an inflammatory edema of the upper and/or lower eyelid. An inflammatory reaction within the internal orbital structures is not found, so strictly speaking it is not really an orbital but rather a preorbital complication. The cause of such a manifestation may be dentogenic in addition to sinusitis or may have other causes such as insect bites, lacrimal inflammation, or skin disease [46]. An escalation is the periostitis (in international language orbital cellulitis, Chandler II), in which the inflammation spreads to the orbital fat tissue. Symptoms are not only a swollen upper and/or lower eyelid as in the pre-septal form, but also diplopia and a protrusion in the further course of the disease. The clinical picture is already much more severe with an increased risk of further complications. Visual acuity is usually still normal but may also worsen as the disease progresses. The next stage is the subperiosteal abscess between the bony orbital wall and the periorbit (Chandler III). The pathomechanism here is most likely to be spread of infection from the ethmoidal cells via the thin lamina papyracea, via the bony channels of the anterior and posterior ethmoidal arteries, or via venous drains from the orbit. Finally, orbital phlegmon (Chandler IV) follows, an extremely severe disease with massive protrusion of the bulb, diplopia, often complete ophthalmoplegia and rapid visual loss up to blindness. Often in clinical practice, orbital complications without abscess formation are referred to as phlegmon, but usually there is preseptal inflammation or periostitis with inflamed tissue. These should not be mistakenly referred to as orbital phlegmon. In the maximum case of an orbital complication, there may be a continuation to intracranial, primarily to the cavernous sinus (Chandler V, still counted as an orbital complication under Chandler, but is de facto already an intracranial complication). This disease has a high long-term morbidity and also a significant mortality [47].

2.1.2 Diagnostics

The key diagnostic question is to distinguish preseptal cellulitis, which is usually easy to treat, from the other orbital complications according to Chandler II to V. Clinical appearance and laboratory values are already indicative in this regard [48]. Patients with orbital involvement are significantly more likely to have general symptoms such as fever and clinically manifest acute purulent rhinosinusitis. Diplopia, ophthalmoplegia, and exophthalmus occur exclusively with orbital and not the preseptal manifestation. Optimal imaging is controversially discussed in the literature. A valid diagnosis can only be made by cross-sectional imaging. The indication for computed tomography is given very cautiously in children, since any radiation exposure should be avoided if possible. Nevertheless, a majority of the authors of the peer-reviewed articles use computed tomography as the imaging modality of choice. Without question, however, MRI can provide equivalent, and in many cases better, information for diagnosis and treatment planning. CT cannot answer the question of exact abscess extension and involvement of the cavernous sinus or other intracranial extension in particular. The anatomic landmarks that are commonly visualized via CT in the case of surgery may also be indirectly visualized on MRI. Therefore, the authors suggest MRI as the imaging of choice for diagnosis and treatment planning in orbital complications of sinusitis [49]. In reality, the availability of an MRI examination can be a critical argument, as it is not available in every hospital around the clock. Especially in emergency situations and outside regular working hours or outside maximum care medical situations, this may lead to the need to use alternative imaging modalities. In many of the publications reviewed, imaging is not performed in the case of a clinically clear preseptal problem (Chandler I). Only in the case of a refractory, prolonged or progressive course or a suspected complication, imaging is performed in the Chandler I situation. From the Chandler II stage onward, imaging must be performed to rule out abscess formation, as the literature is clear on this point. In case of doubt, a generous decision should be made to perform imaging.

2.1.3 Therapy

In the current literature, several authors discuss the adequate therapeutic approach especially of Chandler I and II manifestations. The conflict between the indication for early surgical intervention of the initial focus in the paranasal sinuses and the extension of con-

servative therapeutic measures is controversially discussed between ENT physicians and pediatricians. On the one hand, the therapy depends on the stage of the disease, but also on the dynamics and the response to the therapy already in progress, if any. In the case of anatomical skull anomalies or odontogenic inflammation, indications for surgery are made very early, except in the absolute initial stages of the disease. In sinogenic orbital complications of children with normal cranial anatomy, the recommendation is for conservative treatment with systemic antibiotic therapy in stages Chandler I and II. In stage Chandler I, oral therapy in an outpatient setting is conceivable after good parental education if there are no systemic signs of inflammation and orbital involvement can be safely excluded. On the other hand, progression may occur even in these selected cases, so that close monitoring is required and, if improvement fails to occur, intravenous therapy must be rapidly started [50]. In stage Chandler II, antibiotic therapy is always given intravenously. If there is no response to therapy after 48 hours at the latest, sinus surgery should be performed. Imaging is recommended prior to this, as a lack of response to antibiotic therapy may indicate a change to a higher Chandler stage or abscess, which must be taken into account when planning surgery. From stage Chandler III (clinical/radiological) onwards, surgery should be performed early. If visual acuity worsens, emergency surgery is required [51]. During the surgical procedure, the acute sinusitis as initial focus is drained in the sense of endoscopic endonasal surgery. In case of an intraorbital pressure problem (protrusio, diplopia, …) the lamina papyracea is removed two-dimensionally and the periorbit is incised medially. In this way, sufficient pressure relief can be ensured to counteract visual acuity deterioration [52]. If intraorbital abscess is present, the abscess must also be drained. Depending on the location, this is also done endonasally endoscopically in most cases or in some cases (for example, when the abscess is located in the lateral part of the orbit) via a transfacial approach. As an example, an otolaryngologic paper by McDermott et al. [53] from Columbus, Ohio, US, summarized their findings on a cohort of 168 children with orbital complications according to Chandler I to III. All patients received initial intravenous antibiotic therapy. Ampicillin plus sulbactam was usually administered. Approximately half of the hospitalized children suffered from intraorbital inflammation (Chandler II). Relative to the entire cohort, surgery was required in 49 % of patients after unsuccessful drug therapy. In Chandler I cases, 30 % of children ultimately underwent surgery, and the numbers were similar in Chandler II with 29 % of children operated on. The Chandler III cases almost all underwent surgery. Compared with other publications, the surgical indication in the present work was rather generous. The approach is not uniform in international comparison; for example, Santos et al. [46], pediatricians from Portugal, published a case series with 122 cases of children with Chandler I and II complications. The therapeutic approach consisted of antibiotic therapy, and systemic glucocorticosteroids were also administered as a single shot in 16 % of cases. Only 2 children underwent surgery due to abscess development. Although the data from these exemplary studies are divergent, a review of the current literature nevertheless reveals uniform basic principles for the treatment of orbital complications. In general, inpatient intravenous therapy is indicated even in incipient cases [54]. This is supplemented by local decongestant measures; this may include a single shot of steroids. In Chandler stage I and II cases, reevaluation is performed 48 hours after initiation of therapy, and, of course, earlier in the case of rapid progression with therapy. The likelihood of surgical indication is higher for Chandler II than for Chandler I [55]. In most cases, the latter subgroup can be treated conservatively only [44]. Whereas about 15 years ago and in the years before, surgical acute therapy was performed in almost half of the cases, nowadays this is only the case in an average of 20 % of the patients [56]. In cases of Chandler III and higher, the surgical indication is given immediately. Data in the literature show that patients in stages III and higher usually do not benefit from prior one to two days of conservative therapy; on the contrary, delaying surgery in these cases is risky [53, 57]. Prognosis is good with adequate diagnosis and therapy; 95 % of cases achieve complete healing without long-term damage [58]. Although these data seem very positive, any orbital complication (Chandler II and above) is a severe condition that can only be successfully treated by consistent inpatient therapy. Even in the case of pure phlegmonous eyelid edema, i. e., a preorbital manifestation (Chandler I), inpatient admission for intravenous therapy and monitoring of the course is necessary in many cases. Even if the prognosis is good considering the treatment recommendations, severe and permanent neurological complications such as permanent visual loss, epilepsy, and focal neurological deficits or even death occur in rare cases [59]. The best way to prevent such courses and to improve the outcome is an early and correct diagnosis and an adequate interdisciplinary therapy.

2.2 Chronic rhinosinusitis in children

There are numerous epidemiological data on chronic rhinosinusitis (CRS) in adults. However, this is not the case in the under-18 age group, and little information is available on more differentiated age subgroups such as children under 6 years, under 12 years, and adolescents. The main reason for the weak data situation is that a clinical differentiation between a true CRS, the clinical picture of a pharyngeal tonsillar hyperplasia including its sequelae and an allergic rhinitis is difficult due to the overlapping symptomatology. In the medical care structure, which for infantile CRS is represented by ENT physicians as well as pediatricians in private practice and also general practice, a diagnostic rigid or flexible nasal endoscopy, which would be helpful to differentiate a CRS, is not part of the routine. As a result, the diagnosis of pediatric CRS is usually a clinical diagnosis of exclusion. These limitations in making a valid diagnosis must always be kept in mind when considering all data on pediatric CRS, both epidemiology and diagnosis and treatment. Immunologically, pediatric CRS differs from the adult form. While adults are predominantly characterized by an eosinophilic form of inflammation, pediatric CRS is usually characterized by a non-eosinophilic, neutrophilic or lymphocytic cell infiltrate. Nevertheless, eosinophilic inflammatory patterns do exist in children. Eosinophilic CRS may manifest with or without polyps, often as a more severe course than the neutrophilic form, and has an association with bronchial asthma and allergic rhinitis [60]. In summary, the common neutrophilic CRS can be distinguished from the less common eosinophilic form in children. In addition, the specific CRS forms such as allergic fungal sinusitis, CRS in the context of nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NERD),

CRS in the context of primary ciliary dyskinesia and cystic fibrosis, and CRS in the context of primary immunodeficiencies must be distinguished [61].

2.2.1 Epidemiology

Despite all limitations, publications on the prevalence of CRS in childhood can be found in the literature. A study by Sidell et al. [62] analyzed a US registry containing data on approximately 42 million school children. The diagnosis of CRS was documented in 4 % of children, or 1.7 million individuals, within the collective considered. These figures represent at least an approximate value, although it must be assumed that the diagnosis was not usually made on the basis of endoscopic examination methods. A study from Sweden is interesting in this regard. Here, a nationwide program is used, in which initially about 4,000 newborns were included, who have to answer questionnaires regularly – among other things on health questions (Swedish population-based birth cohort Barn (Children), Allergy, Milieu, Stockholm Epidemiological Study (BAMSE)). 3,112 16-year-olds participated in a questionnaire survey, of whom 1.5 % reported symptom combinations that may indicate CRS according to the EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) 2007 criteria. The diagnosis was then partially validated via a targeted telephone interview and finally verified via specialist nasal endoscopy, so that in the end 0.3 % of the adolescents from the cohort actually had CRS [63]. Although data on CRS in children and adolescents are much less accurately collected and only indirect evidence of the prevalence of CRS can be elicited, there is a trend that the condition appears to have a much lower prevalence than in the adult population. Nonetheless, the quality of life limitations are comparable to those in adults.

2.2.2 Etiology

In terms of predisposing factors, genetic influences and environmental influences contrast with each other. Epidemiological studies clearly show that CRS has a high familiary incidence and is particularly common in first-degree relatives. Although it must be mentioned again at this point that the diagnosis was most likely made false positive in a significant percentage, the familial clustering found is an indicator of a genetic predisposition [64]. Initial studies of genetic alterations in people with CRS (children and adults) are yielding interesting data on possible genetic variants associated with the disease [65, 66]. Here, however, it remains open whether clear mutational patterns can be identified in the future and, in the best case, can be used prognostically, diagnostically, or therapeutically. Anatomic variations within the nose have some influence on the development and maintenance of CRS in adults. These variations are also found in children, for example conchae bullosae or enlarged cells in the agger nasi, but the affected patients do not suffer from CRS. Anatomic variants are generally less common in children than in adults and are found, if at all, in older children or adolescents. This is because the paranasal sinus system does not mature until later in adolescence [67, 68]. In addition to genetic causes, environmental factors play some role in the development of CRS, although only isolated traceable associations can be demonstrated. Acute or recurrent viral infections could theoretically contribute to the development of CRS in childhood. The viral or bacterial infections result in mucosal edema, mucus overproduction and retention, and consequent ostia obstruction, initiating a vicious cycle of self-perpetuating processes. Although the pathomechanism would be comprehensible, it has never been demonstrated to date that viral infections are actually causative for CRS [61]. Exposure to tobacco smoke has been shown to limit mucociliary clearance and epithelial regeneration. Passive or active tobacco smoke exposure is a known risk factor for the development of CRS [69]. Although the association between passive smoking and rhinosinusitis has been demonstrated primarily for the acute form, it is likely that the development of chronic rhinosinusitis is also related to tobacco smoke. Evidence has also shown a worse postoperative outcome in children with smoke exposure after paranasal sinus surgery, as well as higher recurrence rates and worse functional scores (poorer quality of life, lower symptom reduction, poorer olfaction). The lack of clear pathophysiological evidence of a link between tobacco smoke exposure and the primary development of CRS is compensated by the data on the acute course and poorer success rate of standard therapies in exposed children [70, 71]. Also, a clear evidence of an etiopathologic role of allergic rhinitis in the development of pediatric CRS is not unequivocal upon a precise review of the literature. The frequency of co-occurrence of CRS and allergic rhinitis is undoubtedly present, often in association with comorbid bronchial asthma; however, the other way round, allergic rhinitis probably does not play a demonstrable role in the development of CRS [72]. The role of adenoid vegetations in the development and persistence of CRS is of particular interest. As mentioned at the outset, there is great overlap between the sequelae of enlarged adenoids and CRS, making the syndromes sometimes difficult to distinguish clinically. Co-occurrence is common. Several studies have shown that the symptoms of CRS are significantly improved after removal of the adenoids, but due to the independent nature of both diseases they do not disappear completely. Here, the adenoids probably play a role primarily as a reservoir of germs [73, 74]. In cases of refractory CRS in childhood or rapidly recurring symptoms of acute or chronic rhinosinusitis, a congenital immunodeficiency must be excluded [75]. The special forms of CRS associated with cystic fibrosis and primary ciliary dyskinesia are addressed separately in the corresponding chapters of this paper.

2.2.3 Diagnostics

Diagnostically, the distinction between CRS and the recurrent acute form or allergic rhinosinusitis is not easy, sometimes not possible. Symptoms such as nasal obstruction, chronic mouth breathing, infection-independent snoring, recurrent cough or olfactory disturbances are non-specific. In addition, especially olfactory disorders are usually not registered or communicated by children. The diagnostic procedures in children are identical to those in adults. The main focus is on taking a medical history and clinical endoscopic nasal examination. The latter is particularly relevant for verifying the diagnosis and differentiating it from symptoms of adenoid hyperplasia. There is still controversy about the indication and type of imaging. Computed tomography (CT) and magnetic resonance imaging (MRI) are both suitable to obtain relevant additional information supporting the diagnosis of CRS. In the case of suspected complications of acute exacerbations of CRS, CT or/and MRI scans are indicated. In these cases, CT imaging can be considered espe-

cially when orbital complications of the disease are suspected and need to be clarified. MRI is more informative in cases of involvement of the orbital structures for evaluation of intracranial involvement or involvement of the cavernous sinus [49]. Imaging is also indicated prior to surgery, usually involving computed tomography. Minimizing radiation exposure is a relevant factor when discussing the indication and type of imaging. However, CT and MRI are also only one of several components in the diagnosis of CRS and, standing alone, cannot verify the diagnosis [76, 77]. Allergy testing should be performed as a standard procedure in children with CRS, and here we refer to the relevant chapter of this paper. A conventional skin test (prick test) is not age-related, but should not be performed in children younger than 6 years for compliance reasons. In principle, olfactory tests can be performed, but they are complicated by the fact that children often do not yet know the odorants to be identified or are unable to verbalize them. Therefore, the validity of an olfactory test is limited in the younger age groups [78]. Specific causes such as cystic fibrosis or primary ciliary dyskinesia must be carefully excluded in children with CRS.

2.2.4 Non-surgical therapy

Also regarding the therapy of pediatric CRS, the data situation in the literature is incomplete. Drug therapy is predominant compared to surgery. Only limited useful data exist on the use of antibiotics in the therapy of CRS. Nevertheless, they are frequently used. The EPOS group summarized in its 2020 guidelines on this topic that placebo-controlled prospective trials of antimicrobial therapy for pediatric CRS exist. However, in most studies, therapeutically effective conservative measures such as nasal lavage or inhalations were given in addition to oral or intravenous antibiotic therapy, so the effect of antibiotic therapy alone cannot be evaluated without doubt. As in studies on the treatment of CRS in adults, the short-term administration of an antibiotic seems to intercept only acute exacerbations, but shows little effect on the chronic process. EPOS postulates that short-term or long-term (up to 4 months) oral antibiotic therapy seems to have no effect on CRS. It has not been shown to be efficient as a sole therapy in any double-blind placebo-controlled trial, but only in combination with other measures that are also effective. This is also the case for intravenous antibiotic therapy approaches, which have only been investigated in small studies and are also again limited in their evaluability by other measures performed at the same time, such as adenotomies or parallel saline irrigation of the maxillary sinus [79]. In summary, there is currently no evidence for efficacy of short- or long-term antibiotic regimens (oral or intravenous) in the treatment of children with CRS. However, further studies are needed in any case to draw clear conclusions on this issue. Since the long-term administration of antibiotics in particular can also be associated with a number of relevant side effects, no recommendation is made in this regard at the current time. Exceptions to this are children with cystic fibrosis or primary ciliary dyskinesia, in whom different therapeutic regimens are used than in CRS children without these underlying diseases. Data on the efficacy of intranasal steroids in children are also inconclusive. However, they are undoubtedly an integral part of all therapeutic algorithms in the treatment of CRS in children. The safety profile of intranasal steroids has been shown to be favorable, and systemic effects of mometasone have been ruled out in both adults and children. Since therapeutic effects of intranasal steroids have been shown to exist in adults and to stand up to meta-analysis [80], these results can be extrapolated with a high probability to pediatric conditions and therapeutic regimens as well. Given the favorable safety profile and the high likelihood of existing efficacy, intranasal steroids are recommended as the standard therapeutic agent for pediatric CRS in any case. Without question, systemic steroids are also highly effective [81] but should be used with caution due to their side effect profile. Nasal lavage with saline has been evaluated as effective in several studies. In an older but formally sound study, 3- to 16-year-old patients with CRS received nasal lavage with hypertonic and isotonic saline. A few patients did not tolerate the therapy because of nasal burning. The other patients tolerated the therapy and benefited clinically. Both concentrations (0.9 % and 3.5 %) resulted in a reduction in postnasal drip, but after application of hypertonic saline, there was a decrease in sinus shadowing and a reduction in coughing [82]. The addition of antibiotics to nasal irrigation did not produce any relevant additional benefits. Other studies have also found saline irrigation to be effective, in various combinations and dosage forms [83]. Saline lavage is among the most commonly used therapeutic measures worldwide and has become established as a fixed conservative therapeutic measure due to its reliable efficacy. On average, up to 70 % of patients report symptom improvement and improvement in quality of life with nasal rinses [84].

2.2.5 Surgical therapy

Surgical measures must be differentiated between adenotomy in the sense of removing the bacterial reservoir (indirect effects) and functional endoscopic sinus surgery in the sense of direct control of the disease. In general, adenotomy is considered first-line surgical therapy for the treatment of pediatric CRS. In addition to improving the obstruction of nasal breathing, the germ reservoir and biofilm formations relevant to CRS are removed. At this point, it is important to reiterate the often difficult differentiation between adenoid hyperplasia and CRS as the cause of a corresponding symptomatology, as well as the great overlap in the clinical presentation of both diseases. Since adenotomy can be considered a therapeutic step in the treatment of CRS in any case, it is considered a much minor surgical procedure preceding paranasal sinus surgery in order to subsequently reassess the remaining symptomatology of CRS and to reevaluate the therapeutic regimen in a more targeted manner. In a consensus paper, the American Academy of Otolaryngology, Head and Neck Surgery (AAO HNS) recommends adenotomy as an effective first-line therapy in children younger than 12 years with CRS. No consensus was found in older children (13 years and older) [85, 86]. Functional endoscopic sinus surgery is usually used when adenotomy and/or adequate drug therapy have not improved symptoms. Numerous studies exist on the effectiveness of sinus surgery in children. Some suggest that a combination of drug therapy and surgery provides better symptom control over the ten-year course than drug therapy alone [87–89]. In older children, functional sinus surgery is more effective than adenotomy alone. The success rate of functional endoscopic sinus surgery is considered very high at almost 90 % in a review article [90]. While

it was not uncommon in the past to perform so-called second look surgery to clear the nasal cavity after sinus surgery, this measure is increasingly out of fashion. It has not been shown that second look surgery leads to a reduction in revision rates [91].

2.3 Sphenoid sinus pathologies

Small case series on isolated sphenoid sinus pathologies have been published repeatedly in recent years. The reason for this is certainly the rarity of these pathologies and the relatively large number of differential diagnoses. Usually, the leading symptom of chronic isolated sphenoid sinus pathologies is a persistent headache with projection to the center of the skull. However, other non-specific headache localizations are also possible. Other symptoms, also non-specific, include nasal obstruction, nosebleeds, or new-onset snoring [92]. Depending on the extent of the process, visual impairment may also occur. In acute isolated sphenoid sinus pathologies, the symptomatology is often still combined with fever and impaired general condition [93]. The most common causes of chronic sphenoid sinus processes are chronic inflammations with an isolated manifestation pattern and their complications such as mucoceles or pyoceles. In addition, a variety of benign and malignant neoplasms are also found. Meningocele or encephaloceles occur more frequently in the ethmoid roof in childhood, but can also be found in the sphenoid sinus [94]. Nowadays, therapy is almost exclusively endonasal endoscopic with opening of the ostium and sanitation of the process or taking a biopsy in case of suspected tumor. If visual impairment occurs, therapy must be induced very quickly to prevent further deterioration. Some authors report recovery of visual acuity with early remediation, at least for acute changes. The treatment sequence usually begins with imaging to evaluate for pediatric headache or other non-specific symptoms, in which sphenoid sinus shadowing emerges as a usually incidental finding. Magnetic resonance imaging (MRI) is usually performed for headache evaluation and is the most informative technique for delineating sinus pathology. There is disagreement about the need for additional computed tomography. Some authors suggest ultra-low-dose CT scans. In case of visual impairment, both CT scan and MRI should be performed in an emergency. The minimum requirement here would be a CT scan if an MRI is not available in the emergency situation.

In the case of acute courses of the disease, inflammatory changes are usually the reason. These are therefore primarily treated with antibiotics. If there are no other symptoms besides headache, especially no visual impairment, only drug therapy can be applied at first. Surgical procedures are indicated in all other cases immediately or in case of failure of exclusively conservative treatment. Most pathologies in the pediatric sphenoid sinus are benign, usually inflammatory changes. This justifies an initially minimally invasive procedure. If, as is always the case in meningocele or encephalocele, defects of the skull base are present, reconstruction is required, which can be challenging in the sphenoid sinus. Clear exposure of the dural defect is a prerequisite for defect coverage. Intradural placement of, for example, fascia or other materials is optimal as the first step of reconstruction, followed by multilayer coverage with fibrin materials. Optimal is the placement of a nasoseptal flap, even in children. Concern has repeatedly been expressed about whether extensive sinus surgery in general, and especially in unilateral surgery, might have an effect on cranial and facial growth in adolescence [95]. This could not be confirmed by Lee and colleagues [96]. Rather, the pathologic process itself leads to a change in pneumatization and anatomy [97].

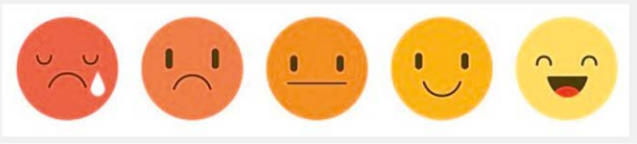
2.4 Pediatric allergology

Rhinologic allergic diseases are among the most common diseases in pediatrics and have a significant impact on the quality of life in affected children. Although the exact cause of allergic disease in children is not fully understood, genetic predisposition, environmental factors and lifestyle changes play an important role. As in adults, it is by all means not “only” an inflammation of the nasal mucosa, but a systemic, immunological disease with increased occurrence of further autoimmune diseases and multiple comorbidities.

In the following, the different clinical manifestations in children will be discussed, as well as the minimal diagnostics often desired by parents and children. This chapter deliberately includes a small excursus on comorbidities of allergic rhinitis. The ENT physician is often the first contact for the clarification of allergic rhinitis. In this context, a rough knowledge of comorbid diseases is necessary to expand the anamnesis in a targeted manner and to initiate further treatment, if necessary. Therefore, this chapter will briefly discuss new therapeutic approaches in allergic bronchial asthma and food allergies.

2.4.1 Clinical manifestation of allergic inhalation diseases in children

Correct diagnosis is critical for effective management of rhinologic allergic disorders in children. Young children require an adult to communicate their history. Children who grow up with allergic diseases often lack comparison to life with a healthy respiratory system. Therefore, the attending otolaryngologist should be alert for clinical manifestations or disease combinations that may indicate the presence of an allergy and, if such symptoms are present, specifically supplement an allergologic diagnosis. All symptoms are non-specific and can also occur in non-allergic children. However, persistence of symptoms or a combination of many symptoms is suggestive for the presence of an underlying allergy. Clinical symptoms or diagnoses suggesting an underlying rhinologic allergic disease in children are (seasonal) conjunctivitis, atopic dermatitis, recurrent tympanic effusions with consequent speech developmental delay, rhonchopathy, obstructive sleep apnea, chronic mouth breathing, bronchial asthma, infectious sinusitis without and with orbital complications, and recurrent otitis media in school-aged children and adolescents despite prior adenotomy. It is more likely that children of allergic family members acquire allergies as well. The cumulative incidence for pollen sensitization is twice as high



▶ **Fig. 6** Analogue scale for toddlers for classification of their complaints, according to EUFOREA.

in female children of parents with atopic disease than in female children of parents without atopic disease. In boys, it is even almost three times higher [98]. With the above diagnoses and/or positive family history for allergies, the implementation of allergic screening is crucial to detect the possible underlying allergic disease at an early stage and to prevent chronification. An attempt to allow younger children to describe their symptoms by means of an analogue scale was suggested by EUFOREA (European Forum for Research and Education in Allergy and Airway Diseases), an international non-profit organization focusing on research and education, patient information regarding allergic and inhalation diseases. https://www.euforea.eu/) [99]; see ▶ **Fig. 6**.

Allergic rhinitis in children: In Germany, 37.1 % of 3- to 17-year-olds are sensitized to the SX1 allergen mixture (timothy grass, rye, birch, artemisia, cat and dog hair, house dust mites, and the Cladosporum). Boys (42.6 %) are initially more frequently affected than girls (31.3 %). These data come from the so-called KiGGS wave 2 study, a long-term observational study on the health of children and adolescents in Germany conducted by the Robert Koch Institute [100, 101]. The percentage of new cases with allergic rhinitis increases between the ages of 3 and 12 years at a constant rate of ≈ 2 % per year (EUFOREA) [99]. The KiGGS study assumes 11 % of medically diagnosed children and adolescents with hay fever. The fact that there is a significant discrepancy between the identified sensitizations (37.1 %) and the medically diagnosed patients (11 %) is not questioned much in the KiGGS study. The missing nasal provocation tests, the insufficient determination of allergen thresholds and last but not least the lack of specialists for allergology in Germany compared to other European countries are to be mentioned here. Ultimately, therefore, the actual number of allergic children in Germany is unknown. However, the prevalence of respiratory allergies has been increasing across countries since the 1980s and has just recently stagnated in Germany [102]. Clinically, patients with "hay fever", i. e. pollen allergy, are mostly distinguished from patients with mite and mold allergies. The latter are referred to in English as "blockers", i. e. patients with obstructed nasal air passage, while pollen allergic patients are "sneezers and runners". The further distinctions into intermittent-persistent, mild and moderate/severe allergic rhinitis are well known and reference should be made to the continuously updated comprehensive international guidelines [103, 104].

2.4.2 Minimal diagnostics of inhalation allergens

Total IgE is a non-specific inflammatory marker that is elevated in Th2 inflammation but also in infections especially with parasites and immunological diseases. Inconspicuous values do not exclude allergic disease, but the relation of total IgE to specific IgE is a helpful parameter. In patients with low specific IgE (sIgE) and low total IgE, serologic allergy tests may be considered false negatives if sIgE was considered in isolation [105]. "Blockers," i. e., patients with nasal obstruction, nasal speech, tubal dysfunction, and speech developmental delay, should be screened for sensitization/allergy to house dust and storage mites, molds, and pets. In this regard, diagnostic testing for specific IgE in total extract is more sensitive than determination of IgE levels to major allergen components, and prick testing is more sensitive than serologic testing [106]. In addition, combined house dust and storage mite sensitizations occur more frequently than "only" isolated house dust mite or sole storage mite sensitizations [107]. "Sneezers or runners", i. e. patients with rhinitis, sneezing and itching, often with seasonal symptoms, should receive initial screening for the common pollen allergens in addition to the above mentioned diagnostics. In Germany, in addition to grasses and birches and their relatives (hazel, alder, oak, beech, etc.), the non-PR-10-related tree pollens are to be distinguished diagnostically, for example ash and sycamore, possibly also the cypress family as important pollen allergens [108]. "Sneezers and runny noses" are usually diagnosed earlier in contrast to patients with obstructed nasal air passage, especially since they also frequently complain of concomitant pruritus and conjunctival involvement. Nevertheless, allergic rhinitis is often trivialized and only about two-thirds are presented to a physician for this condition [109]. Only about 10 % of those affected receive adequate treatment [110]. This concerns both the time-consuming education regarding a necessary allergen reduction in the home environment and the correct use of nasal sprays for local therapy with nasal glucocortiocide sprays (e. g., approved: Mometasone from 3 yrs, Fluticasone from 4 yrs, combination preparations for seasonal rhinitis from 12 yrs e. g. Dymista, Ryaltris). According to Wartna et al. [111], costumized medication is preferable to continuous therapy in children. The only curative therapy, allergen immunotherapy (AIT), which has been shown to reduce asthma development, is presented in detail and with health economic evaluation of therapeutics in the current German guideline [112].

Prior to therapy, a combined diagnosis by means of cutaneous and serological testing is helpful; especially before oral immunotherapies (SLIT), the allergen components should also be determined in order to select the correct AIT. Grass or house dust mite allergic patients may show very complex sensitization patterns with major allergens not included in all preparations. For complementary or sole drug therapy of allergic rhinitis, reference is made to the extensive international, European and the German guidelines mentioned above [113].

2.4.3 Comorbidities and new therapeutic approaches

Patients suffering from allergic rhinitis frequently show further comorbidities. The best known are atopic dermatitis and allergic bronchial asthma. In the following, particular attention will be paid to the diseases that are mostly presented to the ENT physician in addition to the pediatrician, before other specialties are consulted.

Regarding allergic bronchial asthma, epidemiological studies show that over an observation period of 10 years, about 40 % of patients with allergic rhinitis develop bronchial asthma. Boys are also affected more frequently than girls. If bronchial asthma already exists, 60–70 % of this group also show allergic rhinitis. Therapeutically, allergen immunotherapy is recommended across all therapy levels in controlled bronchial asthma, see updated National Health Care Guidelines for Asthma [114]. Since inhaled glucocorticosteroids (ICS) such as fluticasone, beclometasone, and budesonide have a measurable, albeit small, effect on body length growth in clinical trials, the lowest amount of ICS should always be used. In contrast to the German NVL (National Health Care Guideline), inhaled steroids are already recommended by the international expert forum of the Global Initiative for Asthma GINA as needed in children under 5 years of age and, if necessary, as continuous therapy from 6 years of

age (GINA, 2022). In severe persistent asthma (stages 5 and 6), the following biologics have been approved: from the age of 6. From the age of 6, omalizumab (monoclonal antibody against human immunoglobulin E), dupilumab (monoclonal antibody with blockade of the cytokines interleukin-4 and interleukin-13 by inhibitory binding to the alpha chain of the interleukin-4 receptor) and mepolizumab (monoclonal antibody against interleukin-5), and from the age of 12, tezepelumab (monoclonal antibody against thymic stromal cells). For isolated pediatric allergic rhinitis, none of the preparations is approved as sole therapy, although rhinitis is successfully co-treated with the comorbid asthma.

In the context of sIgE- and non-sIgE-mediated food allergies, pediatric patients rarely develop secondary food allergies to pollen in infancy, but cross-allergies with symptoms of an oral allergy syndrome do occur. Primary sIgE-mediated food allergies with anaphylaxis are much more common. These can vary greatly in children depending on their age. Infants and toddlers are more prone to vomiting, coughing, and vigilance reduction, while older children may show prodromes with sudden onset of rhinitis, cough, hoarseness, perioral itching, and/or itching in the palms or soles, usually quickly followed by the well-known other generalized symptoms of anaphylaxis, for details see updated guideline Anaphylaxis [115]. Important anaphylaxis-inducing foods in young children include cow's milk and egg. Unlike in "adult allergy," these food allergies often resolve by school entry, whereas fish and nut allergies occurring in childhood usually persist. In the case of nuts, the causes of more severe anaphylaxis are mostly special types of proteins. Important major allergens of these proteins for diagnostics are peanut ara h 2, cashew ana o 3, hazelnut cor a 14 and cor a 9, walnut jug r 1. For peanuts, an approved commercial oral allergen immunotherapy (AIT) is currently available for the first time from 4 to 17 years of age. AIT for infants (1–3 years) is in study phase III as an epicutaneous application. The initial data of epicutaneous AIT look promising [116]. Both preparations are expected to reduce the rate of anaphylaxis associated with accidental consumption of trace amounts of peanuts in children. Consumption of peanuts without complications remains unachieved.

Children and adolescents presenting to the otolaryngologist with dysphagia should also have non-IgE mediated eosinophilic esophagitis (EoE) considered. EoE is a chronic immune-mediated disease of the esophagus. Approximately 2/3 of patients show specific sIgE to allergens without definite evidence that clinical symptoms manifest to match this specific IgE. However, in one third of the patients (in children more frequently than in adults) the abstinence from cow's milk and/or other primary foods such as gluten-containing cereals, nuts or eggs can resolve EoE symptoms. Newly included in the German AIT guideline is the observation that oral immunotherapies may lead to an initial manifestation of EoE (approximately 2.7 %) [117]. Inflammatory gastrointestinal as well as acute and chronic recurrent diseases and open wounds of the oral cavity are now considered contraindications for sublingual immunotherapy (SLIT). Since the initial description of EoE (1993), there has been a rapid, 20-fold increase in the incidence of EoE in children, with a first peak of manifestation in infancy (up to 3 years of age) and the second peak in adolescents. Boys are also two to three times more likely to develop the disease. Infants frequently show food refusal, vomiting, abdominal pain and failure to thrive, while in adolescents the bolus impaction is a compelling indicator. Often, there is already a prolonged clinic with dysphagia and adaptive strategies, e. g., long chewing, copious drinking at meals, etc. The diagnosis may be characteristic endoscopically in the full picture (so-called trachealization of the esophagus), but is mostly made histologically (at least 6 tissue samples from different sections of the esophagus and the detection of > 15 eosinophils per high-resolution visual field). Therapeutically, in addition to abstinence from possible triggering foods, proton pump inhibitors and topical corticosteroids (e. g., orodispersible Budesonide-Jorveza) are used. Anti-IL-5 (mepolizumab, reslizumab) and anti-IgE (omalizumab) were found to be without therapeutic benefit. Still in trial is dupilumab, which according to initial results may be therapeutically useful [118].

Regarding allergic rhinitis and cognitive/mental disorders in children, a large number of studies demonstrate the reduced performance of students suffering from allergic symptoms [119–122]. However, attention-deficit/hyperactivity disorder (ADHD) also shows a frequent comorbidity to allergic rhinitis [123]. Schans et al. [124] were able to show in a large meta-analysis that ADHD is frequently observed in atopic diseases and that the probability of developing ADHD is 30 to 50 % higher in allergic patients compared to control subjects. This was true not only for bronchial asthma and atopic dermatitis but also for allergic rhinitis alone, although the heterogeneity of study data in rhinitis studies was considered substantial. Whether this is a secondary phenomenon or a causal relationship is unclear. Much studied serological parameters were inconclusive, however, in a pilot study with a small collective, Gao et al. [125] demonstrated for the first time altered brain activities in resting functional neuroimaging for patients with allergic rhinitis compared to a control group. Fuhrmann et al. [126], using an AOK cohort for Germany with 41,484 children, showed that children who received antihistamines in the first two years of life (N = 5540) but did not show atopic dermatitis had a 35 % increased risk of developing ADHD. Children with atopic dermatitis and antihistamines even showed a 47 % increased risk of later developing ADHD. The authors critically discuss that also sleep disturbances and the need for antihistamines could be first signs of ADHD not yet diagnosed at that age. Overall, however, the early administration of antihistamines is critically evaluated. It should be noted that the majority of antihistamines prescribed in these studies were first-generation antihistamines, which are currently no longer recommended. Second-generation antihistamines are generally recommended for children because they are less likely to be absorbed by liquids, are less likely to shorten REM sleep, and have fewer central nervous side effects. Second-generation antihistamines with the lowest brain penetration are bilastine (approved from six years of age) and fexofenadine (30mg, approved from six years of age) [99].

3. Systemic diseases with chronic sinusitis as a leading symptom

The care of patients with cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) is one of the core tasks of pediatric ENT specialists, despite the rarity of these two diseases. Both diseases require a high degree of interdisciplinarity already in the diagnostics, but also in the course of therapy. In the care of these patients, close

consultation and optimally coordinated logistics between the disciplines involved are absolutely essential. On the part of otorhinolaryngology, a high degree of understanding of the clinical presentation and the complexity of the patients concerned is required. This is a basic prerequisite for the development of a trustful cooperation with the pediatric pulmonologists and for the establishment of a successful interdisciplinary CF/PCD consultation.

3.1 Management of the paranasal sinuses in cystic fibrosis

Cystic fibrosis (CF) is caused by biallelic pathogenetic variants in the CF transmembrane conductance regulator (CFTR) gene. The resulting dysfunction of CFTR affects not only the epithelial cells of the lung, but also the mucosa of the genital tract, gastrointestinal tract, and upper respiratory tract, including the paranasal sinuses and middle ears. Impaired chloride transport causes impaired mucociliary clearance in the paranasal sinuses, resulting in chronic persistent and exacerbating infections and problematic microbiotic colonization. Formally, the paranasal sinuses are involved in every CF patient, which is also radiologically comprehensible. However, the clinical picture of chronic rhinosinusitis associated with CF (CF-CRS) is not symptomatic at all in a relevant number of cases or at least only slightly symptomatic and may be an "incidental finding" in the course of cranial imaging. The relationship between the expression of CF-CRS and the pulmonary dynamics of the disease has not been finally elucidated, but it is suspected that manifest CF-CRS also negatively affects pulmonary function. With increasing options for drug therapies in CF, new algorithms are also emerging for affected patients with a sinunasal manifestation to weigh therapy between conservative management and surgery.

3.1.1 Conservative therapy

Conservative approaches to sinunasal problems for people with CF are diverse, but high-quality studies with large case numbers are lacking compared with therapy for lung disease [127]. The following list summarizes the most common approaches [128–132]:

- regular rinsing of the nasal passages with saline solutions
- sinunasal inhalation with isotonic and hypertonic saline solution
- Sinunasal inhalation with dornase alfa
- Topical therapy, sinunasal inhalation, or oral therapy with steroids.
- Sinunasal inhalation or systemic therapy with antibiotics
- Therapy with CFTR modulators

For sinunasal inhalation, systems with pulsed delivery of inhalate such as the Pari Sinus are preferred in order to achieve good sinuidal deposition. In recent years, a number of so-called CFTR modulators have been approved for the treatment of cystic fibrosis, with positive effects on lung function, body weight and quality of life.

The first of these modulators, which became available under the compound name Ivacaftor, increases the opening probability of the CFTR channel. Thus, Ivacaftor can act in those people with CF who either have too few CFTR channels and/or express a sufficient number of a functionally reduced channel protein at the cell surface. The best known mutation that results in a near absence of CFTR protein opening is G551D. However, this mutation is found in only about 3 % of affected individuals in Germany [133]. Therapy with Ivacaftor significantly reduces sweat chloride levels in people with G551D as a measure of impaired CFTR function, improves the one-second capacity reduced in cystic fibrosis, and increases the body weight typically low in this disease. Regarding the situation of nasal and sinus manifestations of CF, there are a number of encouraging reports. For example, Sheikh et al. [134] saw improvement in sinus changes with Ivacaftor in all twelve patients they studied. In a prospective multicenter study, symptoms as assessed by the Sino-Nasal Outcome Test (SNOT-22) improved after initiation of ivacaftor therapy.

By far the most dominant mutation in the CFTR gene in Germany is F508del, which is carried by approximately 85 % of affected individuals on at least one allele [133]. On the one hand, this mutation leads to a defective folding and thus tertiary structure of the CFTR protein, which is therefore degraded in the endoplasmic reticulum before it reaches the cell surface. Second, the conductance of the channel is also disturbed in the F508del mutant. Substances that have a corrective effect on the folding of the protein, such as Lumacaftor, Tezacaftor and Elexacaftor, combined with Ivacaftor as a functional enhancer, have also enabled several modulator-based therapeutics to be developed for people with F508del. Even the combination of Lumacaftor and Ivacaftor, which was only moderately effective in terms of improving lung function, showed positive effects in sinunasal imaging by MRI [135, 136]. The highly effective combination of Elexacaftor, Tezacaftor, and Ivacaftor was even able to cause regression of nasal polyps in some cases in an observational study of 34 affected individuals between the ages of 12 and 60 years [137]. In another study by Beswick et al. [138] in 30 patients, the symptom score and a CT score improved with therapy with Exelxacaftor, Tezocaftor, and Ivacaftor.

Our personal experience with the use of CFTR modulators over the longer course is consistent with the study results described above. However, people with CF and chronic rhinosinusitis may experience increased sinunasal secretion formation and solution, especially at the beginning of modulator therapy. It is possible that this secretion formation plays a role in the reported adverse events with modulator therapy such as frequent headaches and increased obstructed nasal breathing. We therefore recommend that patients with sinunasal symptoms optimize their nasal therapy scheme before starting modulator therapy and continue it consistently in the first weeks after starting modulator therapy.

3.1.2 Surgical remediation of CF-CRS

A US database included 50,000 children under 21 years of age with CF who required inpatient therapy for pulmonary exacerbations from 2003 to 2016. One in five children suffered from clinically manifest CF-CRS, i. e., symptomatic and thus in need of therapy. In the overall view over the 14 years of observation, it was found that the incidence of CF patients with clinically manifest CRS increased and was approximately 25 % in 2016. The diagnosis of CF-CRS was made clinically and radiologically. In contrast, the proportion of patients who required functional sinus surgery was declining, amounting to only 11 % in recent years. It was noticeable that mainly patients with comorbidities (gastrointestinal, hepatic, etc.) showed an indication for surgery. Consequently, there is a need for studies to analyze to what extent CF patients with comorbidities benefit from

sinus surgery. Indirectly, however, it can be stated that CF-CRS does not necessarily require surgical treatment [139].

Another retrospective analysis from the United States looked at a cohort of approximately 11,500 children younger than 18 years with CF who received outpatient or inpatient care in eight different US states between 2006 and 2015. 18.7 % of patients underwent sinus surgery at least once. Indications for surgery varied widely among the eight included hospitals. There were no clear indication criteria for when initial surgery and when surgery at all seemed appropriate. All the more the authors conclude that a better recording of the surgical criteria and finally a definition of uniform indications is necessary [140].

Hughes and Adil published two meta-analyses on the role of endoscopic sinus surgery in patients with CF-CRS in 2015 and 2021 [141, 142]. Here, several reviews were combined. The authors found that paranasal sinus surgery can significantly reduce patients' sinunasal symptom burden and thus improve quality of life. A reduction in required i. v. antibiotic doses was not clearly demonstrated. Also inconclusive were the effects of surgery on lower respiratory tract disease manifestations, with most included studies showing no improvements in pulmonary function tests. In contrast, moderate evidence was found that sinus surgery following lung transplantation achieved a clinical benefit in patients with CF-CRS with or even without polyps. Especially after extensive surgery and postoperative consistent nasal lavage, graft infections were reduced, there were less frequent cases of bronchiolitis obliterans, and in some papers even a survival benefit due to Pseudomonas eradications was observed. In general, patients with severely impaired pulmonal function prior to transplantation were not eligible for sinus surgery due to anaesthesiologic reason. Thus, transplantion had to be performed before sinus surgery. Conversely, genetically identical bacteria have been detected in the nose and lungs in Pseudomonas recolonizations in transplanted lungs, emphasizing the importance of the paranasal sinuses as a reservoir of bacteria.

Due to the controversial data on the influence of sinus surgery on lung function in CF patients, studies on this topic are repeatedly published, as in 2021 by Kawai et al. CF patients in childhood and young adulthood (range between 4 years and 38 years) were analyzed retrospectively. The aim was to verify whether surgery could have a positive effect on lung function. For this purpose, patients were divided into 3 severity levels in relation to their relative forced exspiratory volume (%FEV_1). Pulmonary disease was defined as mild for values above 70 % and severe for values below 40 %. If the FEV_1 was between 40 % and 70 %, these cases were classified as moderate. A total of 188 surgically treated CF patients who underwent 427 operations were included. The median age of patients at the time of initial sinus surgery was 13 years, which is consistent with epidemiologic data from many other studies in the literature. The analysis showed that there was improvement in lung function in almost all patients except those with mild disease, who were part of a particularly good subgroup (FEV_1 better than 80 %). In those with severe and moderate disease, there was a generalized improvement in FEV_1 of 8 % and 3 %, respectively, which was sustained for up to 12 months on average. Patients with mild lung disease who had an FEV_1 between 70 % and 80 % also showed an improvement in FEV_1 of 7 %. This study was thus able to show that the indication for surgery can not only lead to a reduction of nasal symptoms such as rhinorrhea, obstruction, and olfactory dysfunction but can also be used as a tool to improve lung function, at least in the medium term [143]. The study is also worth mentioning because the high number of cases allowed a statistic evaluation of the FEV_1 differences, which are small in themselves.

An Italian study group analyzed the occurrence of mucoceles in patients with CF-CRS. The retrospective analysis included 34 patients with 53 mucoceles in a period between 2004 and 2020. The mucoceles could be correctly suspected by endoscopic otolaryngologic examinations in most cases and were finally confirmed by imaging. The majority of mucoceles involved the maxillary sinus, and only rarely the ethmoid or sphenoid sinus. All patients received surgery, no complications were noted, and all patients benefited from surgery in terms of a recurrence-free course with a mean follow-up of 85 months. The authors pointed out that mucoceles are not uncommon as a complication of CF-CRS and that endoscopic examinations can be used to screen for mucoceles with a high degree of certainty [144].

The question about the value of a second look intervention with debridement of wound coverage, transections of synechiae, and removal of secretion after functional sinus surgery in CF-CRS is repeatedly discussed. This may seem reasonable especially for children, since endoscopic postoperative nasal care is not as well tolerated as by adults and the surgical outcome can be positively influenced by appropriately skilled follow-up. A research group led by Z.M. Helmen investigated this question in a systematic study. In a retrospective analysis, 61 sinus surgeries in pediatric CF-CRS patients were analyzed between 2013 and 2016. Here, a second look was performed in 38 cases, on average after approximately 3 weeks. The preoperative severity of polyp manifestation in CRS was assessed by the Lund Mackay score and was the same in both groups (with and without second look). Thus, comparable baselines between the two groups can be assumed. The perioperative administration of systemic steroids and the extent of surgery were consistent in all patients. Synechiae (26 %), residual polyps (23 %), and rapid re-stenosis of the maxillary sinus ostiae (8 %) were found in the second-look procedure. There were no differences between the two groups in the need for and timing to administration of antibiotics due to re-exacerbations of CRS after surgery. However, re-exacerbation of pulmonary exacerbation occurred earlier in the patients without second look. There were also no significant differences in revision rates and time to revision between the groups. In conclusion, the benefit of second look intervention after paranasal sinus surgery for CF-CRS remains unclear, as no benefits of the procedure were seen in most comparative parameters, but at least a positive effect on pulmonary function was observed. Again, from these results, one can indirectly conclude that surgical indication considerations must include possible pulmonary improvements [145].

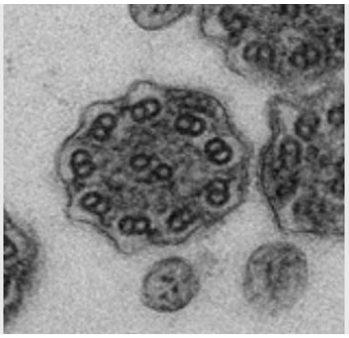
Because CFTR mutations can affect the development and maturation of paranasal sinus ventilation, adult CF patients can potentially be expected to have altered midface anatomy, which could also have implications for potentially requiring surgery and complication rates. Maggiore et al. investigated this hypothesis in a retrospective case-control study. They compared CT images of 103 adult CRS patients with CF with 100 CRS patients without CF who underwent sinus surgery. They found that the anatomy differed in

the CF group: the olfactory fossa protruded less deeply into the ethmoid bone on average and supraorbital pneumatization was also less pronounced. The authors explain this by the fact that the maturation of the sinus ventilation in adolescence is also dependent on a continuous air supply of the area and in the CF collective therefore the expansion of the air-containing spaces in the midface is reduced in comparison. The depth of the olfactory fossa is interpreted here as an expression of pneumatization of the frontal recess. Although CF patients underwent more extensive surgery on average than non-CF patients, there was no increased rate of complications such as olfactory fossa injury with CSF or orbital complications due to injury of the lamina papyracea [146].

In a German study, MRI screening was performed in 67 preschool children with CF to investigate the development of the paranasal sinuses and the prevalence of disease-specific changes compared with a control group of 30 children healthy at the sinuses. The children in the CF group were 2.3 years old and those in the control group were 3.5 years old. The study found that there were no differences between the dimensions and pneumatization of the paranasal sinuses between the two groups. Compared with the above-mentioned study by Maggiore et al. in adults, changes in the anatomy are not yet evident at this young age, but it is expected that these will develop as the sinuses mature in early adolescence. However, various pathologies were identified in the CF group via MRI. These included mucosal swelling (83 %), mucopyoceles (75 %), polyps (26 %), and deformities of the maxillary sinus wall (68 %). The authors conclude that routine MRI examination in CF children may provide valuable additional information on disease progression without radiation exposure and should be considered especially in future study designs [147].

3.1.3 Guidelines

In 2022, the Cystic Fibrosis Foundation (CFF) published guidelines for ENT care of CF children. In general, the evidence level of the available literature was not particularly high. In this regard, the committee only makes recommendations. In consultation logistics, the guidelines of the CFF should be followed. To prevent cross-infections, CF patients in the waiting areas should have as little contact as possible with other patients with resistant germs, for instance with other CF children. This can be achieved, for example, by very short durations of stay in the waiting areas, by wearing face masks, by surface and room disinfection in the examination centers, or by wearing gloves. In addition to screening for the clinical relevance of CF-CRS, otologic and audiologic status must also be obtained on a regular basis. Structured questionnaires should be used to assess the subjective severity of sinus disease. To what extent and at what time sinus imaging should be performed, and what type of imaging this should be, is not addressed. Basic drug therapy for CF-CRS includes saline irrigation, which has solid evidence of efficacy. Comorbid allergies need to be specifically identified and treated. Endoscopic paranasal sinus surgery has a firm place in refractory CF-CRS under sufficient conservative measures. In this case, the procedure differs in principle from non-CF-CRS patients, in whom drug therapy approaches also precede an indication for surgery, but in whom pulmonary status, in contrast to CF, plays a lesser role when it comes to the decision to operate. Perioperative nebulization therapy with, for example, dornase alfa or hypertonic saline should be consistently given to minimize perioperative inflammatory events in the mucosa of the paranasal sinuses. While the benefit of preoperative short-term steroid therapy has been proven in CRS patients without CF [148, 149], the study situation in CF-CRS is insufficient to make a corresponding recommendation. Also, the authors of the guideline agree that at the present time, the data on the relationship between sinus surgery and pulmonary function is still too controversial to justify the indication for surgery on pulmonary reasons alone. At the very least, no surgical procedures should be performed without the presence of nasal symptoms. Routine adenotomies or the use of balloon catheters for sinus ostial dilation are also not recommended [150].



▶ **Fig. 7** Transmission electron microscopy in primary ciliary dyskinesia: missing inner dynein arms and partially present outer dynein arms, regular central microtubular pair.

3.2 Updates on primary ciliary dyskinesia

In addition to cystic fibrosis, primary ciliary dyskinesia (PCD) is another genetic disorder in which chronic rhinosinusitis is one of the major symptoms. PCD is inherited in an autosomal recessive manner and has the so-called Neonatal Respiratory Distress Syndrome, situs inversus, recurrent middle ear infections, chronic cough and chronic sinusitis as leading clinical symptoms. Bronchiectasis develops in childhood and, together with chronic bronchitis, leads the disease course [151]. Due to the now more than 40 known mutations, various defects in the ultrastructure of the cilia arise, which lead to different changes in the function of the cilia [152]. In addition to completely motionless cilia, manifestations with hyper- or hypomotile cilia (altered beating frequency) or with uncoordinated cilia movement (altered beating pattern) are also found [153]. A common feature is insufficient mucociliary transport, from which the disease symptoms originate. The diagnosis of PCD is complex, which is why the disease is often diagnosed too late and a certain number of incorrectly diagnosed PCD patients can be assumed [154]. Diagnosis is based on clinical scores, the combination of which should lead to a suspected diagnosis of PCD. Widely used is the nasal NO screening. Decreased values in combination with a pathological clinical PICADAR (PrImary CiliAry DyskinesiA Rule) score have a high significance as a screening test for PCD in adults with unclear bronchiectasis [155]. Furthermore, transmission electron microscopy examination of the ciliary ultrastructure is among the more advanced diagnostic tests (▶ **Fig. 7**). However, there are also PCD forms with normal ciliary cytoskeleton. Another diag-

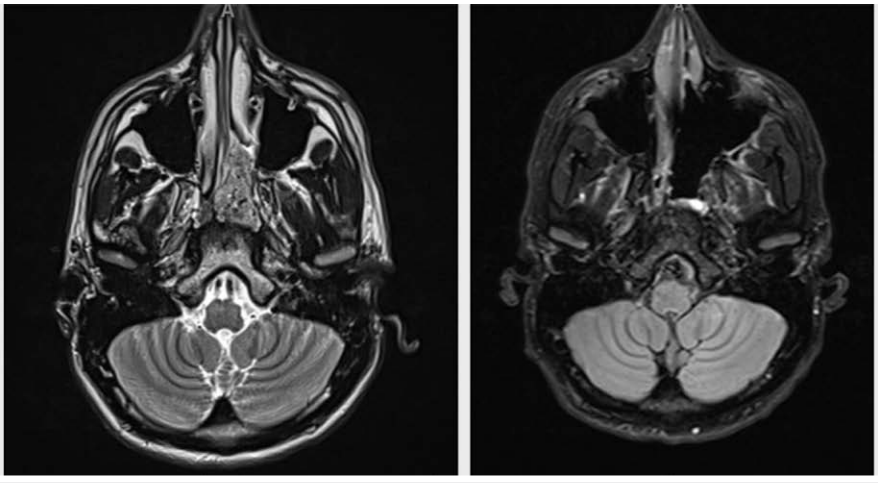
nostic component is high-speed video microscopy to identify the beating frequency and pattern, which requires a high level of expertise. In this regard, recent research is investigating the experimental use of patient-specific 3D in-vitro nasal mucosa models for long-term screening of motility disorder and testing of individual conservative therapeutic approaches [156]. Genetic diagnostics has been gaining importance for years. Many genetic defects have already been linked to corresponding defects in ultrastructure (defects in the inner and/or outer dynein arms or in the central microtubule pair). According to literature reports, gene mutations of DNAH5, DNAH11, DNAL1, and DNAI1 are associated with defects of the outer dynein arms, gene mutations of RSPH9, RSPH4, RSPH3, and RSPH1 are associated with defects of the radial axes. Mutations in the genes CCDC164, CCDC65, and GAS8 are associated with defects of the dynein regulatory complex. HYDIN codes for a central single tubulin instead of a microtubule pair. The advantage of genetic tests is that they are safe, reliable and, depending on the organizational structure of the diagnosing institution, also rapid, but the disadvantage is that they need high technical requirements and imply high costs [157–159]. They are already among the hallmarks of PCD diagnostics now and, despite the aforementioned obstacles, will gain in importance in the future as prices fall.

4. Juvenile nasopharyngeal angiofibromas

Juvenile nasopharyngeal angiofibromas (JNA) can present a therapeutic challenge. With optimal preparation, surgical repair is easily achievable in many cases. A prerequisite for adequate and patient-safe care is a high level of surgical experience, especially in identifying complicated cases. One's own surgical limitations as well as the limitations of the competence of the entire caring team must be well-known.

4.1.1 Genesis

JNA are very rare, benign, fibrovascular tumors that occur almost exclusively in male adolescents, most commonly between the ages of 9 and 19 [160]. Case reports of JNA cases in female adolescents exist in the literature, but these are extremely rare, and may even be questioned [161]. The incidence of JNA is approximately 1:150,000 [162]. They account for only 0.5 % of all head and neck neoplasms, making them a rare entity. The localization of origin of JNA remains controversial. Certainly, JNA do not arise in the nasopharynx itself, which is why the name of the disease is actually incorrect. Rather, the origin of JNA seems to be either in the sphenopalatine foramen at the border between the processus sphenoidale of the palate and the pterygoid process or in the pterygoid canal [163]. Due to their osteodestructive growth behavior and the critical localization of the space-occupying lesions, as well as the possible bleeding complications caused by strong vascularization, they are potentially problematic tumors despite their benign character. The cause of the development of JNA remains a subject of controversy. On the one hand, JNA are thought to be true neoplasms, but their histologic origin is controversial. It remains unclear whether vasoproliferative or stromal cell proliferation is involved. The high expression of sex hormone receptors suggests a histological similarity to erectile tissue [164]. On the other hand, other authors assume that an involutional disorder in the sense of a vascular malformation is present, which results from a lack of regression of arterial residues and receives a proliferation stimulus through hormonal and genetic influences. There are no reports in the literature of a clustered familial occurrence of JNA. Although the published data usually describe only a few cases, there is nothing to suggest an inherited disease, so that genetically, somatic rather than germline mutations are most likely to be assumed [165]. The associations of JNA growth with hormonal status have been extensively studied. Elevated levels of progesterone and estradiol have been detected in tissue biopsies of JNA, but not testosterone [166]. Regarding hormone receptor status, there are also numerous publications, but with differing results. Thus, it remains unclear whether androgen or estrogen receptors are more dominant [167]. In addition, P450 aromatase appears to have high activity in JNA, an enzyme that converts androgens to estrogens [168]. A clear correlation of JNA with a specific hormonal, genetic or molecular alteration has not been found to date. The typical age and predominance to the male sex, the rapid growth and the possibility of spontaneous re-



▶ **Fig. 8** Juvenile nasopharyngeal angiofibroms, left-sided, in a 17-year-old male patient, MR imaging in axial section, preoperative and 6 months postoperative.

gression in adulthood remain striking. In a literature review on the genetics and molecular pathology of JNA, Doody and colleagues [167] state that despite very low published case numbers, VEGF (vascular endothelial growth factor) and the Wnt/β-catenin pathway may be the most promising targets for future systemic therapies at the current time.

4.1.2 Therapy

The gold standard of therapy is complete excision of the mass, with preoperative embolization or other neoadjuvant measures if necessary. One of these is the oral administration of flutamide. This is an antiandrogenic substance with antineoplastic properties. Flutamide binds to the androgen receptor and is commonly used in the treatment of advanced prostate cancer. The antineoplastic effect is based on inhibition of DNA synthesis stimulated by testosterone. The data on the use of flutamide in the preoperative period before tumor resection of JNA is circumscribed; critically, insufficient evidence exists on the indications, efficacy, or tolerability when the drug is used in adolescents or young adults. A review article by Sitenga et al. [169] summarized papers on preoperative flutamide administration in JNA. This showed a mixed tumor response to the antiandrogen, with a tendency for the small tumors to show size reduction and the older, postpubertal patients to respond better than the prepubertal ones. Therefore, a general recommendation for administration cannot be made, but flutamide is at least an option to be considered in neoadjuvant therapy. The question of the benefit of preoperative embolization and the technique required for this must ultimately be investigated in prospective studies, but at this stage it can already be said that embolization in the context of tumor direct puncture appears to be advantageous compared with transarterial embolization. This is expressed in a lower recurrence rate, which may ultimately indirectly argue for a higher rate of complete removals. In addition, tumor puncture was associated with a lower complication rate. In general, the rate of recurrence in patients with embolized space-occupying lesions, regardless of the technique used for embolization, was lower than in cases without pretreatment. Embolization also has a positive effect on surgery time and blood loss [170]. In addition to the positive effects on blood loss and clarity during surgery, the angiography itself naturally depicts the relationships of the vascular architecture. This provides information about potential vascular inflows to be supplied, critical localizations of the tumor (affecting the vascular supply), and can thus also influence the choice of access route or other surgical steps [171]. While open surgical access and microscopic tumor removal via a Caldwell-Luc approach or (modified) midfacial degloving were more common a few years ago, the endonasal, endoscopic approach is preferred nowadays. The advantages are the significantly better visualization of the sometimes extensive tumors and a reduced blood loss due to the less invasive access route (▶ **Fig. 8**). In combination with preoperative embolization, endoscopic procedures hardly require any blood transfusions [172].

Conflict of Interest

The authors declare that they have no conflict of interest.

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