Pathophysiology of Obstructive Sleep Apnea Syndrome in Childhood

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Introduction

Obstructive sleep apnea syndrome (OSAS) refers to a breathing disorder characterized by recurrent, partial, or complete episodes of upper airway obstruction, commonly associated with intermittent hypoxemia and sleep fragmentation [1, 2]. OSAS affects individuals of all ages, from neonates to the elderly. However, it is still not known whether OSAS represents a continuum of a disorder that places children at risk for the disorder also as adults [3], or whether OSAS during different stages of life comprises distinct clinical entities [4–7].

The structure and the neural control of the upper airway have evolved to serve three important physiological functions: (1) respiration (2) deglutition, and (3) speech. The upper airway is collapsible in order to accommodate these functions. The anatomic factors predisposing to OSAS differ over the lifespan. However, a smaller upper airway is noted in patients with OSAS in all age groups, and probably predisposes to airway collapse during sleep. Anatomic factors such as craniofacial anomalies, obesity, and adenotonsillar hypertrophy contribute to OSAS throughout life, yet a clear anatomic factor cannot always be identified. This suggests that functional factors altering upper airway neuromotor tone and the biomechanical properties of the upper airway could also play an important role in the etiology of OSAS [8, 9]. This chapter focuses on the anatomic, functional, and biomechanical aspects of the upper airway in the pathophysiology of OSAS during childhood as summarized in Table 35.1.

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Pharyngeal Development

The anatomy of the newborn pharynx is similar to the anatomy of other primates and mammals [10]. The uvula and epiglottis are in close proximity, creating a secure airway that allows for independent suckling and breathing. This anatomic relationship is maintained in other mammals throughout life, with discrete pathways for respiration and deglutition. However, in the human, at about 18 months of development the larynx descends to the level of the fifth cervical vertebrae. This anatomic formation develops because of the additional role of the human pharynx of phonation. For the purpose of deglutition, the pharynx functions as a flexible tube. The pharyngeal muscles, namely, the pharyngeal constrictors and tongue, force food from the oral cavity into the esophagus. For phonation, the pharynx functions as a muscular tube that can change its length and shape to alter the sounds generated by the larynx and passing through the pharynx. For respiration, the pharynx must remain as rigid as possible in order to allow air passage without collapse. However, despite the importance of respiration to sustain life, when one considers the muscles of the upper airway in the human, it becomes apparent that not one of these muscles has a primary function of pharyngeal dilation. It is speculated that the lack of such pharyngeal dilators in humans resulted from the absence of an evolutionary need in mammals and primates, because the anatomic orientation of the structures securing their upper airway is maintained throughout development, whereas in the human it is not.

Pharyngeal Anatomy

The pharynx is generally divided into three anatomic regions (Fig. 35.1):

1. *The nasopharynx*, located superior to the level of the soft palate and continuous anteriorly, through the choanae, with the nasal cavities.

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Table 35.1 Developmental aspects of obstructive sleep apnea syndrome

	Infancy	Childhood	Adolescence	Adulthood
Demographics:				
Estimated prevalence	?	2%	2%	4–9%
Peak age (years)	<1	2–8	12–18	30–60
Gender	M > F	M = F	?	M > F
Weight	Normal	Normal, may be underweight or obese	Mostly overweight and obese	Obese
Risk factors	Craniofacial anomalies Prematurity Gastroesophageal reflux Adenotonsillar Hypertrophy	Adenotonsillar hypertrophy Obesity	Obesity Adenotonsillar hypertrophy	Obesity Women-postmenopause
Level of obstruction	Nasopharyngeal Retropalatal	Nasopharyngeal Retropalatal	Nasopharyngeal Retropalatal Retroglossal?	Retropalatal Retroglossal
Anatomic findings				
Airway	Small?	Small	Small	Small
Craniofacial features	May have craniofacial anomalies: Midfacial hypoplasia Micrognathia	Majority normal	?	Retrognathia Micrognathia
Soft tissues	May have adenoidal hypertrophy; usually normal tonsils	Adenotonsillar hypertrophy Large soft palate	Adenotonsillar hypertrophy Other soft tissues?	Large lateral pharyngeal walls, tongue, soft palate, parapharyngeal fat pads
Functional findings				
Ventilatory drive: Normal subjects OSAS	High? ?	High Overall normal Some with subtle abnormalities	Moderate ?	Lower Studies conflicting
Arousability: Normal subjects OSAS	Low Very low	Very low Very low	Moderate ?	High High
Upper airway collapsibility: Normal subjects OSAS	Very low High	Very low High	Low High	Moderate High
Upper airway reflexes during sleep: Normal subjects OSAS	Brisk ?	Active Blunted	High Low	Low Low
Biomechanical findings				
Nasal resistance	?	Higher in OSAS	?	Higher in OSAS with obesity
Pharyngeal pressure drop	?	Higher in OSAS Lower after AT surgery	Higher in OSAS?	Lowered by MMA surgery
Pressure–area slope during tidal breathing	?	Sedated: more positive in OSAS Awake: more negative in OSAS		
Treatment				
Treatment of choice	Craniofacial surgery CPAP	Adenotonsillectomy	CPAP Weight reduction Adenotonsillectomy	CPAP Weight reduction
Treatment success	High	High	Moderate	Moderate

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2. *The oro*pharynx, located between the level of the soft palate and the larynx, communicating anteriorly with the oral cavity, and having the posterior one-third of the tongue as its anterior border. Based on a midsagittal view (Fig. 35.1a, b), the oropharynx is subdivided into retropalatal (bounded by the level of the hard palate and the caudal margin of the soft palate) and retroglossal (bounded by the caudal margin of the soft palate to the tip of the epiglottis) regions. In infants and young children, the oropharynx includes mostly the retropalatal region, since the soft palate and the epiglottis are in close proximity. The anterior oropharyngeal wall is

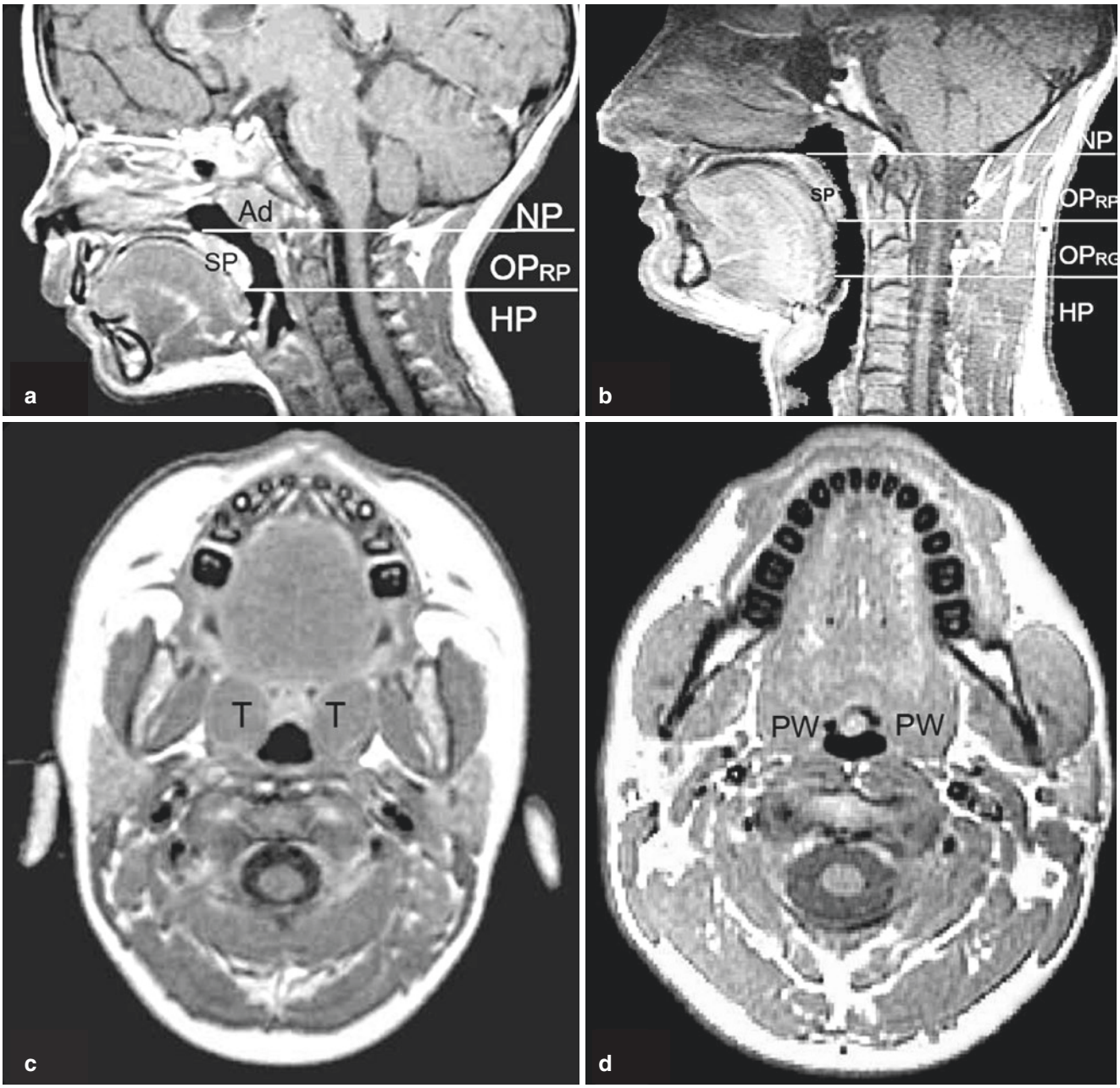

Fig. 35.1 Normal airway. A midsagittal MRI of the head of a child (**a**) and an adult (**b**) are shown. The airway is shown in black. Note the three main anatomical regions of the upper airway in the child: nasopharynx (NP), oropharynx adjacent to the retropalatal region (OP_{RP}), and hypopharynx (HP). The adult airway differs from that of the child by having, in addition, an oropharyngeal segment that is retroglossal (OP_{RG}). This anatomic difference is related to the descent of the larynx during the first 18 months of life. An axial MRI of the head at the retropalatal level of a child (**c**) and an adult (**d**) are shown. The airway is shown in black. The lateral pharyngeal walls (PW) in the child are formed mainly by the palatine tonsils (T). In the adult, the tonsils are usually absent or minimal in size and the PW is formed by a combination of muscles (see text for details). Ad, adenoid; SP, soft palate. (From Arens et al. [7]. Reprinted with permission from Oxford University Press)

formed primarily by the tongue and soft palate, while the posterior wall of the oropharynx is formed by the superior, middle, and inferior constrictor muscles [11, 12]. The lateral pharyngeal walls (PW) (Fig. 35.1c, d) are formed by several different soft tissues, including muscles (hyoglossus, styloglossus, stylohyoid, stylopharyngeus, palatoglossus, palatopharyngeus, and the lateral aspects of the superior, middle and inferior pharyngeal constrictors [13, 14]); lymphoid tissue, primarily the palatine tonsils (noted more in children, Fig. 35.1c) [15]; and adipose tissue (lateral parapharyngeal fat pads).

3. *The hypopharynx*, located posterolateral to the larynx, and communicating with the cavity of the larynx through the auditus. This includes the pyriform recesses and the valleculae.

Anatomic Considerations

Anatomic determinants of OSAS in children can be discussed in relation to broad age categories—infants, children, and adolescents.

Infancy

Infants are predisposed to obstructive events and oxygen desaturation during sleep because of high nasal resistance, reduced airway stiffness, and a highly compliant chest wall with reduced functional residual capacity [7, 16]. Spontaneous neck flexion can also result in airway obstruction in premature infants [17]. Nasal occlusion results in a switch to oral breathing only in a minority of infants [18] and therefore obstruction of the nasal passages from respiratory infection, craniofacial syndromes or choanal stenosis can result in significant OSAS. Upper airway obstruction may also occur as a result of airway edema, laryngospasm, and airway edema from gastroesophageal reflux disease (GERD). Intrinsic softness of the larynx from laryngomalacia in infants has been demonstrated to be associated with obstructive sleep apnea with improvement after supraglottoplasty [19]. OSAS in infancy is notable for its association with several important risk factors: (1) craniofacial anomalies, (2) altered soft tissue size, and (3) neurological disorders.

Common Pediatric Disorders Affecting Upper Airway Size and Associated with Obstructive Sleep Apnea Syndrome

I. *Craniofacial Anomalies*:
- Apert syndrome
- Crouzon syndrome
- Pfeiffer syndrome
- Treacher-Collins syndrome
- Robin sequence
- Stickler syndrome
- Nager syndrome
- Hallermann–Streiff syndrome
- Goldenhar syndrome
- Rubinstein–Taybi
- Down syndrome
- Beckwith–Wiedemann
- Achondroplasia
- Klippel–Feil syndrome
- Marfan syndrome
- Choanal stenosis
- Mucopolysaccharidoses (Hurler, Hunter)

II. *Neurological Disorders:*
- Cerebral palsy
- Syringobulbia
- Syringomyelia
- Myasthenia gravis
- Möbius syndrome
- Arnold–Chiari malformation
- Poliomyelitis

III. *Miscellaneous Disorders:*
- Obesity
- Polycystic ovary syndrome (PCOS)
- Prader Willi syndrome
- Melanocortin-4 receptor deficiency
- Congenital hypothyroidism
- Sickle cell disease
- Laryngomalacia
- Subglottic stenosis
- Airway papillomatosis
- Face and neck burns
- Gastroesophageal reflux

IV. *Postoperative Disorders*:
- Post-adenotonsillectomy leading to naso- and or oropharyngeal stenosis
- Post-pharyngeal flap: leading to naso- and/or oropharyngeal stenosis

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Craniofacial Anomalies

The relationship between craniofacial structure and OSAS is most compelling in infants with distinct craniofacial anomalies seen with craniofacial synostosis, such as Crouzon, Pfeiffer, and Apert syndromes [20, 21]; and with mandibulofacial dysostoses, such as Robin sequence [22–25] and Treacher-Collins syndrome [26]. Altered facial skeletal development, especially the association of maxillary and/or mandibular hypoplasia, may lead to airway narrowing due to crowding of adenoid, tonsils, and other soft tissues within the mid and lower face skeletal boundaries. Decreased neuromotor tone may further reduce airway size by inducing glossoptosis and hypopharyngeal collapse during sleep. Children with craniofacial anomalies may present with OSAS soon after birth and during the first years of life. In some cases, OSAS does not occur until the child is older and

develops adenotonsillar hypertrophy in conjunction with the narrow upper airway. Some craniofacial syndromes, such as Down syndrome, are also associated with hypotonia, which can contribute to upper airway obstruction. Children with associated central nervous system abnormalities may also have central hypoventilation.

Down syndrome is the most common genetic disorder associated with craniofacial anomalies. OSAS is present in 30–60% of these patients [27–30]. Anatomic factors related to the Down syndrome phenotype, including midfacial and mandibular hypoplasia, glossoptosis, adenoid and tonsillar hypertrophy, laryngotracheal anomalies, and obesity, are the most common causes for OSAS in this group [31, 32]. Reduction in neuromuscular tone may also play a role in the development of sleep-disordered breathing in these children.

Altered Soft Tissue Size

The size of the upper airway soft tissues (tonsils, adenoid, fat pads, and musculature) are determined by genetic factors. In addition, the size of these tissues may be affected by inflammation, infection, and infiltration by various metabolic or storage components. Finally, abnormal neuromotor tone may further alter the shape of upper airway musculature, predisposing to airway narrowing and collapse during sleep.

Inflammatory changes leading to adenotonsillar hypertrophy are seen in some infants prior to 1 year of age, leading to the full clinical spectrum of OSAS [33, 34]. Macroglossia can significantly reduce upper airway size. It commonly occurs in infants and children with Down syndrome, as well as in infants and children with various storage and metabolic disorders, such as mucopolysaccharidosis [35] and Beckwith–Wiedemann syndrome [36]. In patients with glossoptosis, the tongue may prolapse posteriorly and occlude the airway. Glossoptosis is commonly seen in patients with a small and retroposed mandible as in the Robin sequence [22–25], or in conditions associated with poor upper airway muscle tone such as Down syndrome [27–32]. Anomalies of the soft palate, such as cleft palate and velopharyngeal insufficiency, are not usually associated with OSAS. However, the surgical repair of these malformations by palatoplasty and pharyngeal flap, respectively, are associated at times with a moderate degree of OSAS [37, 38].

Neurological Disorders

Various central nervous system disorders have been associated with OSAS in young infants. All induce pharyngeal hypotonia and predispose to sleep-disordered breathing and airway obstruction. Common causes include cerebral palsy, increased intracranial pressure, brain stem compression/dysplasia such as Arnold Chiari malformations, recurrent laryngeal nerve palsy, palsies of the cranial nerves, and syrinx [39–42].

Childhood

In preschool children, the incidence of OSAS is estimated to be 2% [43, 44], whereas primary snoring is more common and is estimated as 6–9% in school-aged children [45]. Although the exact mechanism for OSAS in children is not fully understood, important anatomic risk factors have been identified, and are linked to the anatomical structures surrounding the airway that affect airway size, shape, dynamics, and mechanics.

Anatomical Assessment of the Upper Airway

Physical examination of the upper airway is important and should be performed in each child as part of the general assessment. However, in order to more thoroughly evaluate the airway, endoscopy [46] and imaging techniques such as lateral neck radiographs, cephalometrics, fluoroscopy, acoustic reflection, computerized tomography, and MRI are helpful [47–52]. The above modalities have all demonstrated that the upper airway of children with OSAS is smaller on average than that of the normal child.

MRI is a particular powerful tool because (1) it provides excellent upper airway and soft tissue resolution; (2) it provides accurate, reproducible quantification of the upper airway, and surrounding soft tissue structure; (3) imaging can be performed in the axial, sagittal, and coronal planes; (4) volumetric data analysis including three-dimensional reconstructions of upper airway soft tissue and craniofacial structures can be performed [15, 47, 53–55]; (5) dynamic images provide four-dimensional data of the size and shape of the airway during breathing [56, 57]; and (6) it does not expose subjects to ionized radiation. On the other hand, several limitations should be noted: (1) young children need to be sedated to avoid motion artifact; (2) studies in sleep are limited in the MRI environment because of noise, arousals, and movement artifact; and (3) MRI is expensive and not always available.

Airway Size

Using MRI, Arens et al. [47] studied the upper airway in 18 children with moderate OSAS (age 4.8 ± 2.1 years) with an apnea/hypopnea index of 11.2 ± 6.8 and compared these findings to 18 matched controls. MRI was performed under sedation with intravenous pentobarbital, and axial and sagittal T1- and T2-weighted sequences were obtained (Fig. 35.2a, b). The volume of the upper airway was smaller in subjects with OSAS in comparison to controls (1.5 ± 0.8 cm^3 vs. 2.5 ± 1.2 cm^3, $p < 0.005$). This finding was later reproduced by other investigators [58, 59] using similar techniques.

Region of Vulnerability and Overlap Region

In order to determine the anatomic region of maximal narrowing in children with OSAS, Isono et al. performed upper

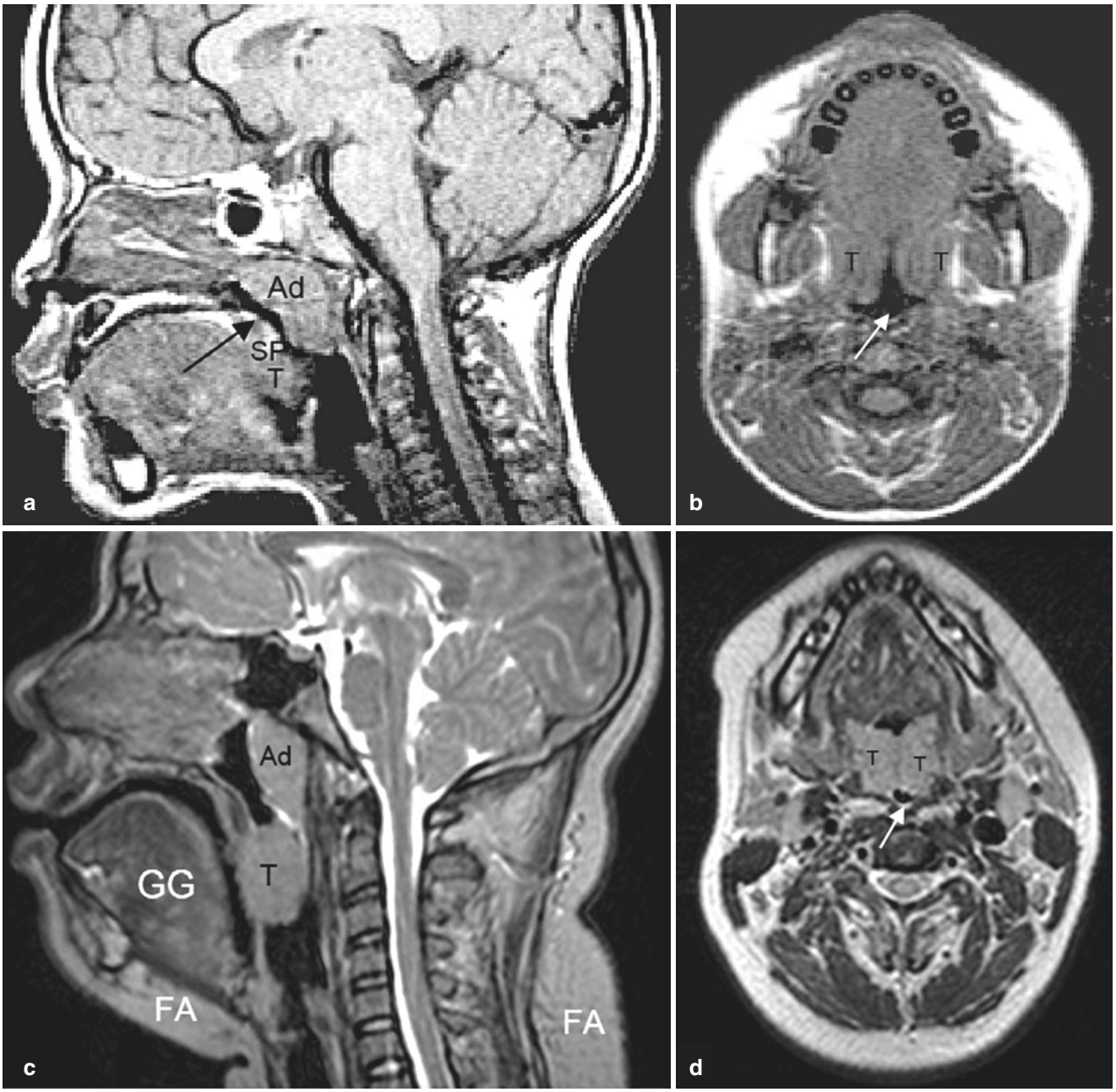

Fig. 35.2 Mid-sagittal image of a non-obese young child with OSAS (**a**). Black arrow points at narrow nasopharynx and overlap region between adenoid (Ad), soft palate (SP), and tonsils (T). Axial image of the same subject (**b**); white arrow points to a narrowed oropharyngeal airway by two tonsils (T). Mid-sagittal image of an obese adolescent with OSAS (**c**). Note complete occlusion of nasopharynx in the overlap region by large adenoid (Ad), soft-palate and tonsils (T). Axial image of the same subject (**d**); white arrow points to a very small oropharyngeal airway between both tonsils (T)

airway endoscopy under general anesthesia, evaluating discrete levels of the upper airway including the adenoid, soft palate, tonsil, and tongue [46]. The minimum cross-sectional area was found to be at the level of the adenoid and the soft palate. These findings, along with high closing pressures noted at these points in the same study, suggest that the superior upper airway segments are most involved in children with OSAS. These findings are supported by two recent studies evaluating upper airway shape with MRI. Arens et al. [53] showed that airway narrowing in children with OSAS occurred along the upper two thirds of the airway, and was maximal in the region where the adenoid overlap the tonsils and soft palate—"the overlap region" [53] (Fig. 35.3). Similar findings were noted by Fregosi et al. [59], who

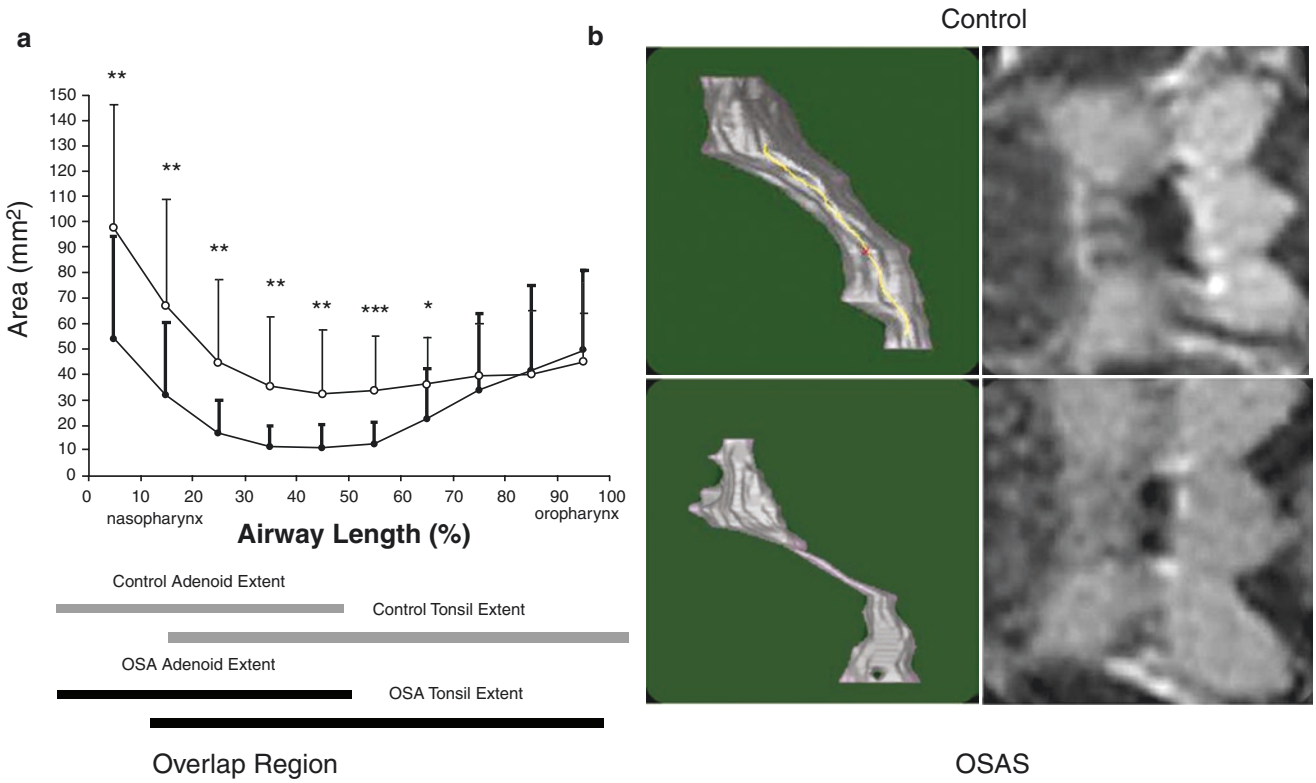

Fig. 35.3 Airway cross-sectional area from choana to epiglottis and the "overlap region." (**a**) Airway length versus cross sectional area in 20 control children (open circles) and 20 children with OSAS (closed circles). Data points are means ± SD. Horizontal bars show the regions of the adenoid and tonsils adjacent to the airway. Gray = controls, black = OSAS. *$p < 0.5$, **$p < 0.005$; ***$p < 0.0005$. Note that the *overlap region* of the adenoid and tonsils in both groups corresponds to the minimal airway cross sectional area. Modified from reference [53]. (**b**) 3D reconstruction of the airway and overlap region where the adenoid and tonsils overlap the soft palate in Control and OSAS

described maximal narrowing in the retropalatal region where the soft palate, adenoid, and tonsils overlap.

Airway Dynamics Depicted by MRI

Arens et al. used respiratory-gated MRI to demonstrate the dynamics of the upper airway during tidal breathing in sedated children with OSAS [56]. They showed that the maximum restriction in patients with OSAS occurred in mid-inspiration (Fig. 35.4), and that dynamic fluctuations in the airway overlap region were sixfold higher than in controls. They have speculated that such changes may have been induced by one of the following: altered upper airway motor tone, increased airway compliance, or excessive inspiratory driving pressures caused by proximal airway narrowing.

The above study demonstrated different size and shape configuration of the airway in children with OSAS in both inspiration and expiration as compared with control subjects. Subjects with OSAS exhibited an airway shape narrowed across the A–P axis. This could be caused by anatomic features influencing the width of the lateral pharyngeal wall and/or by neuromotor factors affecting upper airway dilator muscle activity along this axis (i.e., genioglossal activation). These differences, together with the magnitude of area changes during tidal breathing, may contribute to a more collapsible airway in children with OSAS during sleep, as suggested by functional studies [46, 50, 60].

Soft Tissues

Adenoid and Tonsils In normal children without OSAS, the soft tissues, particularly the tonsils and adenoid, grow commensurate with age maintaining a constant proportionality with the pharyngeal airway [7, 15]. It has been speculated that disproportional overgrowth of the adenoid and tonsils in children with OSAS results from inflammation and/or infections but the mechanisms leading to this process have not been elucidated [15].

Arens et al. measured the size of the adenoid and tonsils in children with OSAS compared to controls [47]. They found that both were significantly larger in the OSAS group; 9.9 ± 3.9 cm^3 and 9.1 ± 2.9 cm^3 versus 6.4 ± 2.3 cm^3 and 5.8 ± 2.2 cm^3 ($p < 0.005$; $p < 0.0005$, respectively). In addition, the combined size of the adenoid and tonsils correlated significantly with the apnea/hypopnea index ($p = 0.03$, $r = 0.51$), suggesting that volumetric measurements of these

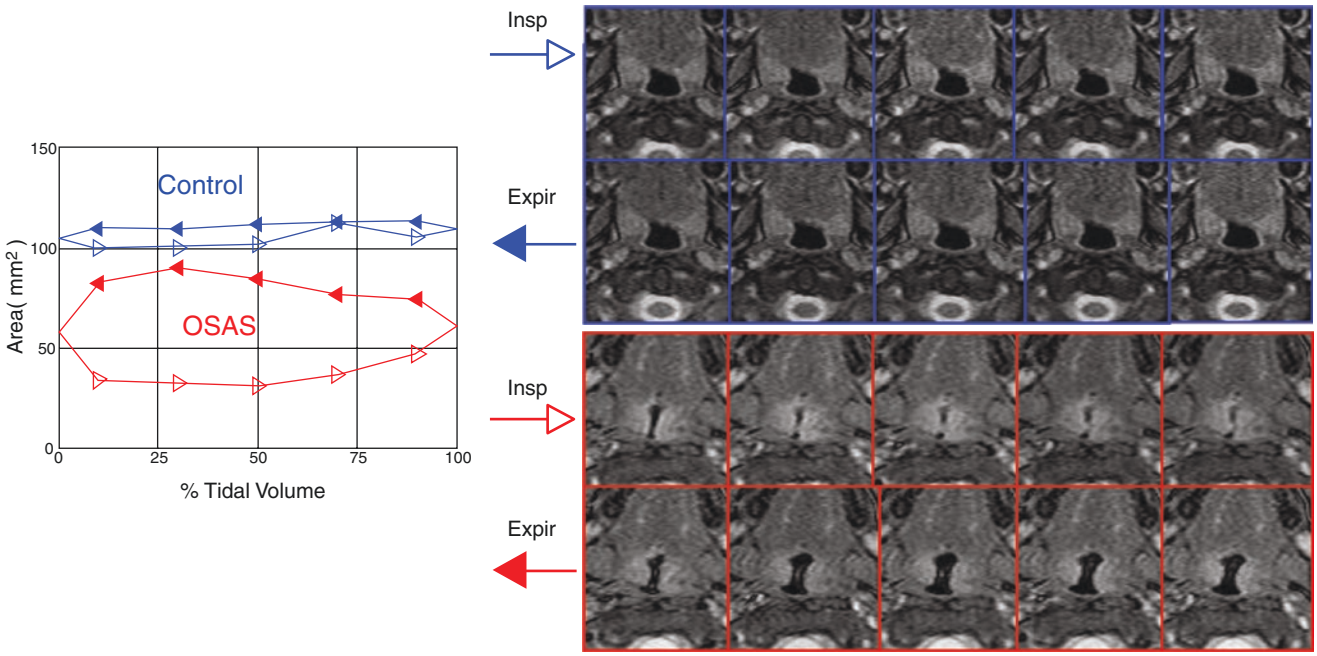

Fig. 35.4 Airway dynamics – cross-sectional area during tidal breathing in Control and OSAS. Dynamic changes in cross-sectional area at mid-tonsillar level during tidal breathing (TV), 5-vol increments of inspiration (Ins), 5-vol increments of expiration (Exp) in a control child (*top panels*) and a child with OSAS (*bottom panels*)

tissues may be useful in predicting the severity of obstructive sleep apnea in children.

In most cases, large tonsils and/or adenoid can explain the clinical symptoms of children with OSAS, and surgical removal of these tissues cures or ameliorates the disorder in the majority of cases [33, 61–63]. However, it is estimated that in 10–15% of otherwise normal children with OSAS, this disorder is not resolved by the simple removal of the tonsils and adenoid [64–66].

Although the importance of adenoidal and tonsillar hypertrophy in the pathogenesis of childhood OSAS is unquestioned, much remains to be learned. It is possible that the three-dimensional orientation of these tissues, and how they overlap in the airway, is a more important factor, and may significantly affect flow resistance during sleep [47, 53, 59].

Tongue Size The tongue is one of the largest structures defining the oropharyngeal airway and bounds its anterior aspect. It is composed of extrinsic muscles (genioglossus, hyoglossus, and styloglossus), which alter its position; and intrinsic muscles, which alter its shape; both of which can affect airway size and shape. Arens et al. found that the overall volume of the tongue in nonsyndromic children with OSAS did not differ from controls [47].

Soft Palate There are few data on the dimensions of the soft palate in children with OSAS. Using direct measurements, Brodsky et al. [67] did not find a correlation between soft palate length and severity of tonsillar hypertrophy in children with OSAS. Using MRI, Arens et al. [47] noted a 30% increase in the volume of the soft palate of children with mild to moderate OSAS compared to controls. They speculated that the larger palatal volume might have been due to edema and inflammatory changes secondary to chronic snoring, as described in adults [68–70].

Craniofacial Structure

Several studies using cephalometrics support the idea that children without distinct craniofacial anomalies have subtle craniofacial morphometric features associated with OSAS [49, 71–74]. Kawashima et al. [75] reported that children with OSAS and more pronounced tonsillar hypertrophy had retrognathic mandibles and increased posterior facial height compared to children with OSAS and less pronounced tonsillar hypertrophy. Shintani et al. [71] noted that the relationship of the mandible with respect to the cranial base was retrognathic in children with OSAS compared to normal children. Zucconi et al. [76] noted that children with OSAS had increased craniomandibular, intermaxillary, goniac, and mandibular plane angles, indicating a hyperdivergent growth pattern (angle between nasion-sella line and mandibular line >38°).

In contrast to the above, other investigators suggested that the craniofacial changes found in children with OSAS are mild, and are reversible following adenotonsillectomy [74, 77, 78]. This is supported by a study evaluating upper airway structure using MRI, showing no significant differences in

the size of the mandible and maxilla of children with OSAS versus controls [47]. Furthermore, in a more comprehensive evaluation of the mandible after three-dimensional reconstruction, the above authors found no difference in eight dimensions of the mandible between children with OSAS and controls, suggesting that mandibular size and shape does not play a significant role in the causation of childhood OSAS in nonsyndromic children [79].

Childhood Obesity

Earlier descriptions of childhood OSAS characterized children as being of normal weight, and failure to thrive was a common complication [33 m 80]. However, the dramatic increase in pediatric obesity [81, 82] is not reflected in most of literature characterizing risk for OSAS from early infancy to late childhood [44, 82–88] although a large epidemiological study involving 399 children between 2 and 18 years of age found that obesity was the most significant risk factor for OSAS, with an odds ratio of 4.5 [44]. The prevalence of OSAS was reported to be 46% by Marcus et al. in unselected obese children undergoing polysomnography [86]; Silvestri et al. reported a prevalence of 59% in obese children referred for evaluation of sleep disordered breathing [85]; and Kalra et al. reported a prevalence of 55% in morbidly obese children undergoing bariatric surgery [89]. The reason for such a high prevalence of OSAS in obese children compared to the 2% reported in the general pediatric population [44] is unknown. However, it may be related to a different underlying pathophysiology of the disorder distinguishing it from OSAS in nonobese children, and/or an augmented effect on regular causative factors, resulting from their obesity accelerating growth of upper airway lymphoid tissues [54].

In nonobese children with OSAS the most common treatment is adenotonsillectomy [90]. Adenotonsillectomy cures or ameliorates the disorder in the majority of cases [33, 61–63]. However, as noted earlier, it is estimated that in 10–20% of otherwise normal children, significant residual symptoms exist after surgery [64–66, 91]. Similarly, several investigators emphasize the role of adenoid and tonsillar hypertrophy in obese children with OSAS [86, 92–94]. A recent study suggests that 45% of morbidly obese children and adolescents with OSAS have evidence of adenotonsillar hypertrophy [95]. However, after adenotonsillectomy in obese children with OSAS, residual OSAS is noted in up to 50% of children [96]. This finding suggests that other anatomical and/or functional factors play a significant role in the pathophysiology of OSAS in this group.

Obese children may have excess deposition of adipose tissue within the muscles and tissues surrounding the airway, limiting airway size and increasing airway resistance as observed in adults [97]. Additional factors that may predispose obese children to OSAS include altered chest wall mechanics and reduced lung volumes due to altered body composition [54, 98], resulting in decreased oxygen reserves and decreased central ventilatory drive [83, 99]. However, the exact effects of weight gain or weight loss on upper airway structure and function have not been studied in obese children. Moreover, as mentioned above, other mechanisms affecting upper airway neuromotor tone and increasing upper airway collapsibility could have a compound effect in these children with an anatomically compromised airway.

Adolescence

There are few data related to the epidemiology of OSAS in adolescence. Only one study assessed the prevalence of the disorder in this age group and estimated it at 1.9% [100]. It is not known whether OSAS appearing in adolescence is an extension of the clinical disorder of childhood, with adenotonsillar hypertrophy as a major risk factor, or whether it represents an early manifestation of the adult form of OSAS, with obesity as a major risk factor.

Several studies have addressed the relationship between childhood OSAS and OSAS during adolescence. In a retrospective study, Morton et al. [101] found that sleep-disordered breathing in adolescence was more common in those who had undergone adenotonsillectomy during early childhood. Tasker et al. [102] noted a significant increase in inspiratory effort and snoring during sleep in adolescents 12 years after adenotonsillectomy, compared to controls. The latter authors speculated that airway narrowing could have originated in childhood and predisposed to OSAS during adolescence. Guilleminault and colleagues noted alterations in craniofacial morphology in three adolescents with OSAS and a history of upper airway obstruction in childhood. They hypothesized that both genetic factors altering craniofacial growth, and secondary modification of craniofacial growth secondary to adenotonsillar hypertrophy, predisposed these patients to OSAS [103, 104].

Another possibility is that OSAS during adolescence represents an early manifestation of the adult form of OSAS, especially when associated with obesity. It is well established that the antecedents of adult obesity begin during childhood and adolescence [81]. Childhood obesity in all age groups is currently on the rise, and the highest prevalence (15.5%) is seen in adolescent children between 12 and 19 years of age [105] also having all components of the metabolic syndrome [106–109]. Studies investigating the pathophysiology of OSA in this population have shown that upper airway lymphoid hypertrophy restricting airway size continue to be an important contributor to OSAS [54, 110] (Fig. 35.2c, d) though functional factors impacting airway collapsibility may also play an important role [111].

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders associated with overweight

and obesity. It affects 5–10% of adolescent girls and women of reproductive age [112]. PCOS usually presents during adolescence with irregular menstruation and clinical signs of hyperandrogenism and is associated with obesity and cardiometabolic abnormalities [113]. In recent years it has been shown that adolescent girls [114] and adult women with the disorder have a significantly higher prevalence of OSAS compared to women without the disorder [115–117], screening for OSAS has therefore been recommended in these subjects [118].

Summary of Anatomic Considerations

Various anatomic mechanisms may lead to OSAS in children. However, a smaller upper airway is noted in all age groups and probably predisposes to airway narrowing and collapse during sleep. OSAS is uncommon in infancy. However, children born with craniofacial anomalies are at increased risk for the development of a severe form of the disorder.

The most common type of childhood OSAS occurs in children between 2 and 8 years of age and is associated with adenotonsillar hypertrophy in most cases. Surgical removal of the adenoid and tonsils ameliorates the disorder in most but not all children, suggesting that other mechanisms such as those leading to altered upper airway neuromotor tone during sleep may contribute to OSAS in these children.

Recent data suggest that obesity may be a leading cause for OSAS during adolescent years. This form of OSAS probably shares much with the adult form of OSAS and particularly with the metabolic consequences of the disorder. However, in contrast to the adult form of OSAS, adenotonsillar hypertrophy commonly observed in early childhood plays an important anatomical contributor in this age group as well.

Functional Considerations

There are several arguments that suggest that functional attributes have an important role in limiting and influencing OSAS in children. The first is that the upper airway in children is smaller compared to adults. Since the prevalence of OSAS is much lower in children, it is probable that children have nonanatomical attributes that enhance airway stability during sleep. The second is that airway obstruction occurs during sleep and not during wakefulness, suggesting that neuromotor activation keeps the airway open during wakefulness but not during sleep, when activation is diminished. The third is that subjects with OSAS survive each night. Therefore, there must be overriding mechanisms that prevent unremitting airway obstruction and anoxia from leading to death.

Central Ventilatory Drive

The role of ventilatory drive in the pathophysiology of OSAS in adults and children with OSAS is not fully understood. The central ventilatory drive changes with age from infancy to adulthood. Methodological limitations in measuring drive and mechanical and anatomical differences across the age spectrum do not allow precise comparisons of ventilatory drive throughout the life span. However, it appears that ventilatory drive gradually declines from childhood to old age, possibly because of declining basal metabolic rate with age.

Some adults with OSAS have been reported to have increased ventilatory responses to hypercapnia and hypoxia leading to a high-gain ventilatory control system that could predispose some individuals to irregular or periodic breathing, ventilatory instability, and apnea [119, 120]. This relationship is not firmly established; normal or even reduced ventilatory responses have also been reported in adults [121].

In comparison, nonobese children with OSAS were shown to have normal ventilatory responses to hypercapnia and hypoxia during wake and sleep [7, 122, 123], and other studies in obese children showed a blunted ventilatory response to hypercapnia in sleep. Such studies suggest that OSAS in children is unlikely to be initiated through ventilatory instability and high chemical loop gain [124, 125].

Ventilatory Response to Inspiratory Resistive Loading

During wakefulness, addition of an external resistive load leads to an immediate compensatory increase in ventilatory effort that maintains gas exchange. In sleep, this compensatory response is not normally seen unless there is a complete airway occlusion. With partial occlusion, a decrease in minute ventilation ensues and compensation of ventilation is delayed; this eventual correction is believed to be in response to gas exchange abnormalities. In normal children, this compensation can be limited and delayed by 3 minutes or more as compared to adults [126]. Young children with OSAS have reduced arousal responses to inspiratory resistive loads during sleep that together with the aforementioned inadequate compensation of ventilation may explain the prolonged periods of obstructive hypoventilation observed in childhood OSAS [126]. Similar abnormalities in upper airway reflexes and diminished response to resistive loading have been described in adolescents with OSAS and particularly if were obese and during REM sleep [127, 128].

Arousals from Sleep

Arousals are a normal phenomenon of sleep and are defined as sudden shifts in EEG frequency lasting for 3 seconds. However, if arousals occur too often, they produce sleep disruption, and interfere with the restorative nature of sleep. It should also be pointed out that arousals may be considered protective to subjects with OSAS since they coincide with increased dilator muscle activity, reduced upper airway resistance, and restoration of normal ventilation.

Studies in children and adults have clearly shown that frequent arousals and sleep fragmentation often lead to decreased vigilance, sleepiness, and other neurocognitive impairments. Interestingly, children are much less prone to arousals due to respiratory events than adults and typically are less sleepy compared to adults with OSAS. The major stimuli for arousals from OSAS are thought to be mechanical stimulation of lung and chest wall stretch receptors due to increased respiratory effort. However, hypercapnia is also considered a potent arousal stimulus. Most obstructive events in adults are associated with arousals from non-REM sleep. In children most obstructive events occur during REM sleep, and associated arousals are less frequent than in adults. Normal children have a higher arousal threshold than adults; children with OSAS seem to have an even loftier threshold for arousal in response to inspiratory loading [126] and hypercapnia [123] compared to children without OSAS.

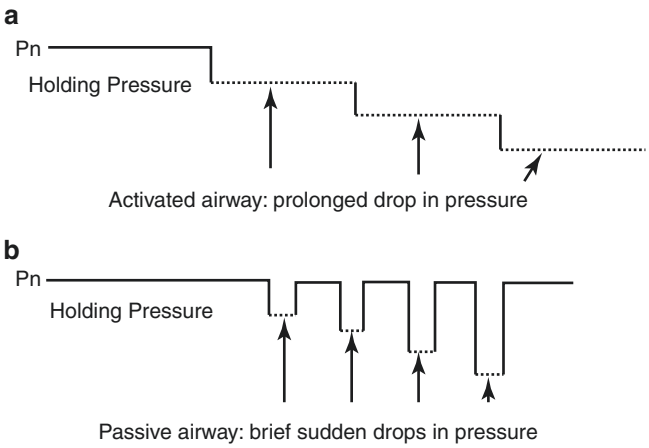

Fig. 35.5 Active and passive critical closing pressure protocols. Schematic of active and passive airway critical closing pressure protocols. Holding pressure (horizontal solid line) is maintained at levels just enough to abolish flow limitation. (**a**) Active protocol: To determine active critical airway closing pressure, nasal pressure (Pn) is reduced in 1–2 cm H_2O decrements (broken lines) and maintained for prolonged periods (1–10 min) to allow dynamic airway activation to occur and maximal inspiratory air flow is obtained at each pressure. Airway pressure is reduced until airflow approaches zero or arousal from sleep occurs. (**b**) Passive protocol: To determine passive airway critical pressure, pressure drops (broken lines) from holding pressure (horizontal sold line) are made for brief periods lasting five breaths, before dynamic responses are activated. Airway pressure is then raised to holding pressure rapidly for 1 or more minutes before dropping it further in increments of 1–2 cm H_2O pressure till zero flow is approximated or arousal occurs. Maximal inspiratory flow (Vi max) at each pressure setting is determined. Pressures employed span a range of positive to negative (sub atmospheric) values to estimate critical closing pressure

Upper Airway Neuromotor Tone

Flow through the upper airway depends not only on mechanical and anatomic factors but also the active dilation of the airway by neuromotor tone [8, 9]. Pressure–flow relationships based on the Starling model provide an understanding of airway stability in the "active" state with neuromotor activation and in the "passive state" before neuromotor responses are activated [7, 60, 129–131] (Fig. 35.5). Plotting a range of airway pressures against the resulting maximal inspiratory flows of breaths generates a pressure–flow line with the critical closing pressure (Pcrit) being represented by the intercept on the pressure axis (Fig. 35.6, adult). Airway pressure is applied by a nasal mask with the subject in a supine position and airflow is measured by a pneumotach; the pressures applied range from positive pressures to negative (subatmospheric) pressures. When pressure is maintained in a steady state, neuromotor activation occurs and the airway is in the active state; this active Pcrit is considered a measure of airway collapsibility. The nasal pressure at which the airway closes or is estimated to close by the pressure-flow line is typically lower for the active airway compared to the passive airway (Fig. 35.6). In children, the Pcrit tends to be very negative (i.e., motor tone is very high) such that extrapolation of the pressure flow line can become unreliable; the slope of the pressure–flow line is taken as the best estimate of upper airway collapsibility (Fig. 35.6, child). In addition, airflow in the first few breaths following a sudden drop in pressure, before neuromotor responses can occur, represents the "passive airway"; this passive Pcrit estimates mechanical and structural properties of the airway. A passive airway closing pressure can also be estimated by the pressure–cross-sectional area relationship endoscopically observed in anaesthetized subjects (in whom neuromotor activation is suppressed) analogous to the pressure–airflow relationship. Neuromotor activation can more directly be estimated by measuring the EMG activity of the genioglossus muscle, which is the major pharyngeal dilator.

The pediatric airway is very resistant to collapse compared to the adult airway, airway collapsibility increases with age during adolescence and is not a function of pubertal development [7, 129]. In children and adolescents with OSAS the critical closing pressure is much higher than non-OSAS children [7, 60, 128]. Childhood OSAS is most prominent in REM sleep which is associated with reduced pharyngeal tone and wide fluctuations of airflow, both of which probably contribute to OSAS. While closing pressure

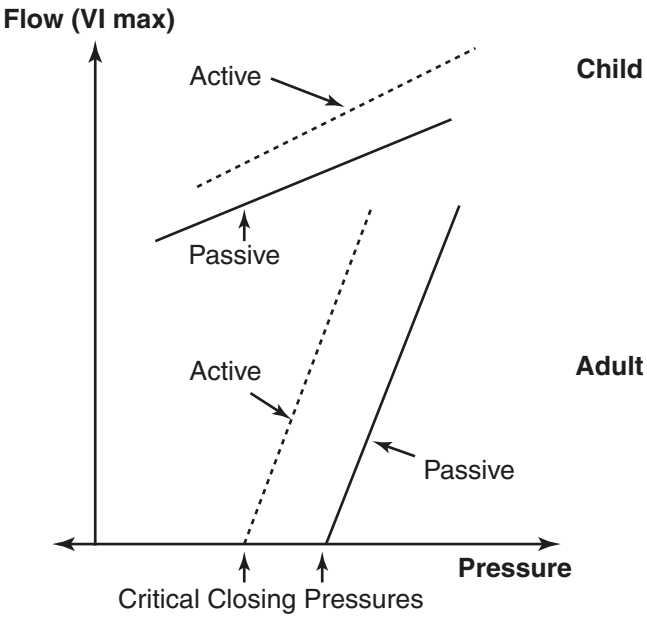

Fig. 35.6 Active and passive critical closing pressure (Pcrit) in a child and adult. Schematic representation of plots of nasal pressure (on *x*-axis) and maximum inspiratory air flow (Vi max) (on *y*-axis). Pressure flow lines calculated from flow at each pressure setting in the active or passive condition are used to obtain critical closing pressures; the intercept on the *x*-axis is the critical closing pressure. The activated pressure flow line (dashed line) has a lower airway closing pressure than the passive airway pressure flow line (solid line). Children tend to have very stable airways with a zero slope (dashed and solid line at top)

is difficult to measure in REM sleep for practical reasons, reduced airway tone can be demonstrated by EMG studies of the tongue muscles. Awake children with OSAS have higher baseline EMG tone than normal children, most probably to compensate for their narrower airways. With sleep onset these children have a rapid decline in EMG tone [132], with a further decline in REM sleep, predisposing them to airway obstruction during sleep [133].

Upper Airway Sensation

The afferent (sensory) loop of the upper airway negative pressure reflex also plays a role in promoting airway stability. During wakefulness, topical nasopharyngeal anesthesia results in increased upper airway collapsibility in both children [50] and adults [134]. Similarly, during sleep, the application of topical nasopharyngeal anesthesia in adults results in increased upper airway collapsibility, leading to obstructive apnea [135–138]. The resultant worsening of apnea appears to be due at least in part to changes in muscle tone [139], but also to blunting of the arousal response [135, 138]. These studies are supported by the study of Tapia et al. showing impaired sensation along of the tongue and hard palate and possible primary sensory function abnormality in children with OSAS during wakefulness. The latter authors speculated that this has been secondary to nerve damage and/or hypoxemia caused by OSAS [140].

Summary of Functional Consideration

The pediatric airway is very resistant to collapse compared to the adult airway, and airway collapsibility increases with age and during adolescence. This trend may explain the lower prevalence of OSAS in children compared to adults. Differences in ventilatory drive, arousal thresholds, airway reflexes during sleep, and active and passive properties of the upper airway also suggest different pathophysiological mechanisms in childhood OSAS compared to the adult form.

Active and passive techniques assessing airway collapsibility in sleep in children with OSAS show that the critical closing pressure is higher than in non-OSAS children. However, the overall ventilatory drive in response to hypoxia and hypercapnia is probably normal in OSAS children, although infants have a strong biphasic response to hypoxemia, and are more likely to develop central apnea when exposed to prolonged hypoxemia. The central ventilatory drive also plays a role in augmenting upper airway neuromotor reflexes and tone. Normal children have brisker upper airway reflexes during sleep than adults, perhaps due to their greater central ventilatory drive. These reflexes appear to be blunted in children with OSAS. Finally, children with OSAS are less likely to arouse in response to upper airway obstruction and do not compensate for prolonged increases in inspiratory resistive load. This may explain why patients in the pediatric age group often have obstructive hypoventilation rather than discrete, cyclic obstructive apneas.

Biomechanical Considerations

In recent years, biomechanical modeling of the upper airway has been developed to characterize the anatomical and functional mechanisms that play a role in the pathophysiology of OSAS in children. This approach, called image-based modeling, uses imaging modalities such as magnetic resonance imaging (MRI) with engineering tools such as computational fluid dynamics (CFD) to analyze individual subjects. Dynamic imaging and image-based flow models create a rich data set that may help to explain how anatomy, tissue properties, and muscle function contribute to flow limitation, hypopneas, and apneas. Upper airway pressure fields modeled by CFD have been validated in vivo [141] and in vitro [142, 143]. The pharynx in OSAS is often restricted where the adenoid, soft palate, and tonsils overlap [53], and CFD models can identify the location and quantify severity of anatomical restrictions. CFD model outcomes based on the drop

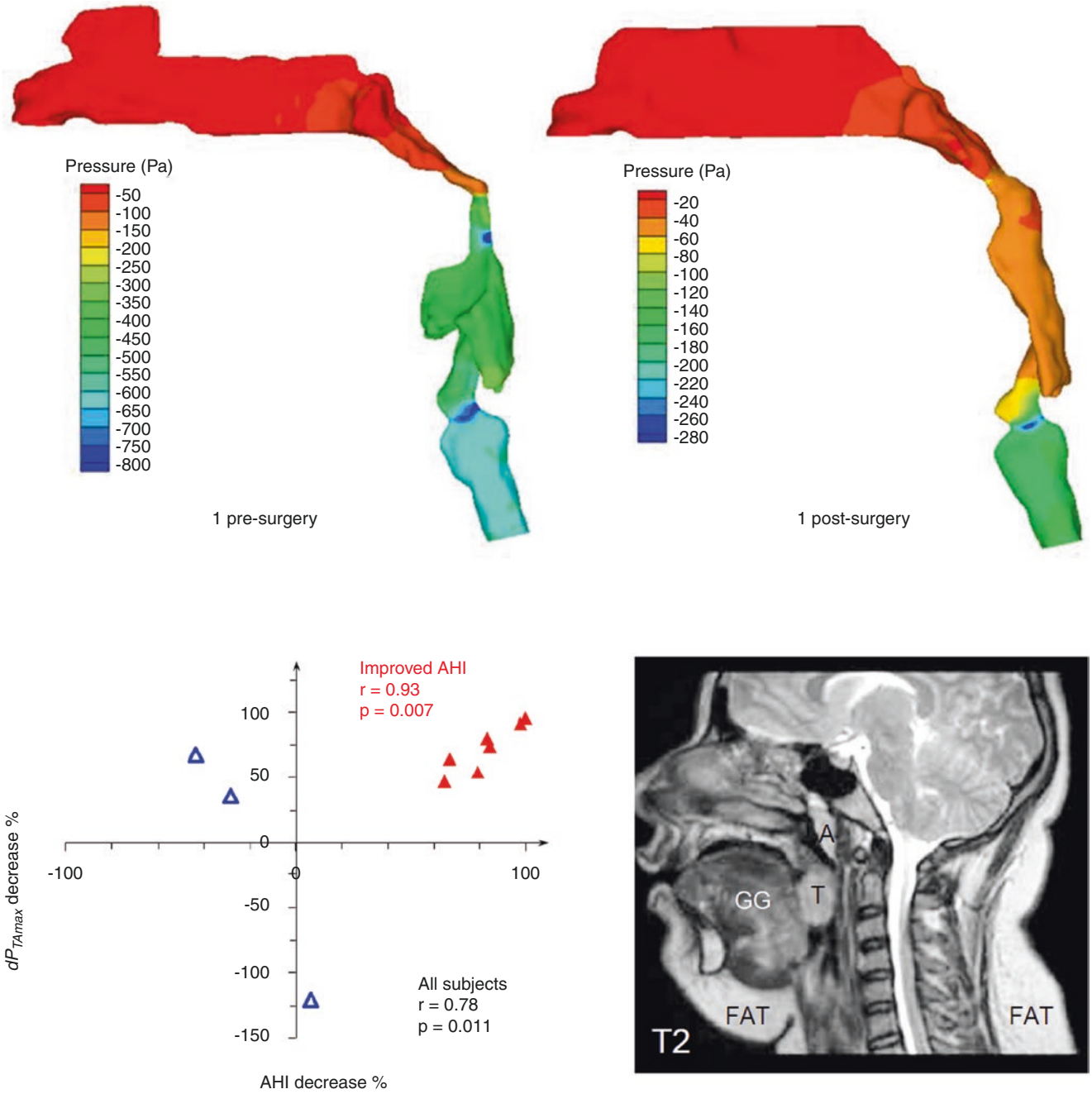

Fig. 35.7 Image-based CFD as a tool to assess surgical outcomes in children with OSAS. Top: CFD pressure fields at peak inspiratory flow, before (left) and after (right) adenotonsillectomy surgery, in a subject with 100% improved AHI postsurgery. Maximum pressure drop from choanae through the "overlap region" where tonsils and adenoids overlap (T and A on lower right image), dP_{TAmax}, was reduced by 96% after surgery. Bottom left: reduction in dP_{TAmax} after surgery correlates strongly with improvement in AHI, especially in patients with significant postsurgery improvement. Bottom right: sagittal centerline MR image before surgery showing enlarged tonsil (T) and adenoid (A) also overlapping with the soft palate

in pressure between the choanae and location of maximum restriction have been correlated to OSAS severity in obese children [141, 142, 144]. Such studies identified the drop in airway pressure between the choanae and the point of maximal narrowing at maximum inspiratory flow, dP_{TAmax}, as the CFD measurement that most consistently correlated with OSAS severity [141, 145]. Changes in CFD pressure drop correlate strongly to improvements in OSAS after AT surgery [145] (Fig. 35.7) or oral appliance placement [146, 147]. Compared to CFD biomarkers, correlation to strictly

anatomical biomarkers such as cross-section area or airway volume is often weaker or not significant [141, 148]. The above works show that CFD has matured as a robust and accurate method to compute the effect of anatomical restriction over the upper airway air pressure field.

An early study of pressure drops and flow resistance in the pharynx of individual children with OSAS [142] showed significantly higher airflow resistance in the upper airway of mildly sedated young children with OSAS. The same trend was observed in wakeful older obese children imaged during relaxed tidal breathing [141]. In a minority of OSAS cases, airflow resistance was lower [149], suggesting that in these children OSAS does not result from anatomical restriction, but rather from altered *functional* factors related to tissue compliance and neuromuscular tone during sleep. Deficits in these factors can be suggested by the Pcrit which measures collapsibility of the upper airway, but Pcrit cannot identify the location of collapse or the anatomical or mechanical causes of collapse. Thus, image-based CFD may help to identify different patient phenotypes (Fig. 35.8) if it is combined with a functional assessment.

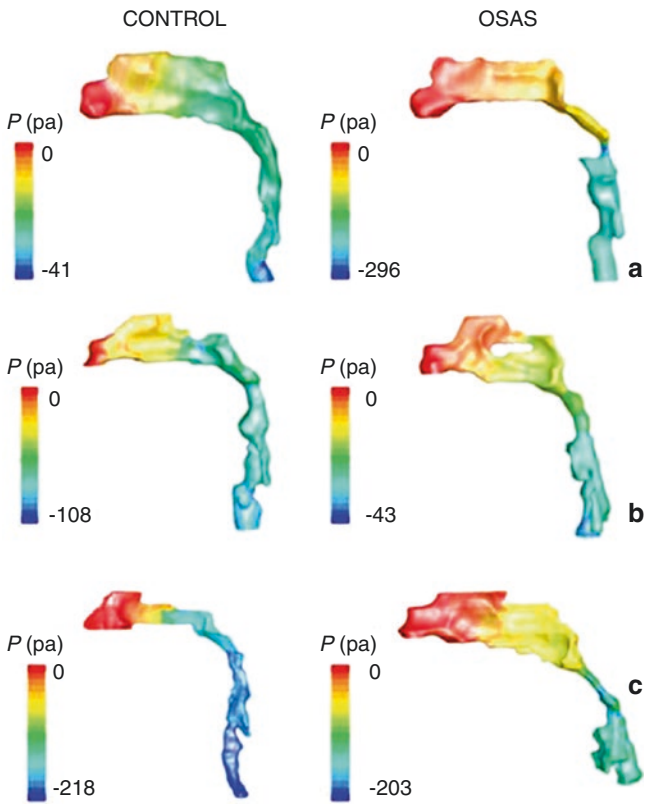

Fig. 35.8 OSAS phenotypes by computational fluid dynamics. (**a**) Anatomically driven OSAS: significant anatomical restriction in the "overlap region" leads to high pressure drop between choanae and minimum area of the pharynx in OSAS compared to controls. (**b**) Functional factor driven OSAS: OSAS with area restriction and CFD pharyngeal pressure drop similar to controls suggests loss of airway function during sleep. (**c**) Functional protection in control subject with anatomical restriction and high CFD pharyngeal pressure drop compared to OSAS. (From Wootton et al. [141]. ©American Physiological Society)

CFD analysis based on dynamic imaging may be used to characterize both anatomical and functional factors, using a novel noninvasive method to compute the effective regional mechanical airway compliance [150]. The effective compliance is the slope of a plot of cross-sectional area versus the local airway pressure, computed from image-based CFD. Effective compliance measures the combined effects of passive tissue properties and active airway muscle tone similar to Pcrit, but with the advantage of providing this data at any location along the airway in reference to the phase of the breathing cycle.

In a study of obese adolescent girls that combined dynamic MRI, CFD, and Pcrit, the effective compliance in the nasopharynx correlated significantly and negatively with both AHI and Pcrit [151], suggesting strong phasic airway dilator activation while awake, compensates for a collapsible airway, and loss of muscle tone during sleep leads to obstructions. An early study of sedated sleeping subjects showed positive effective compliance in subjects with OSAS, consistent with a passive, compliant pharynx susceptible to collapse [150]. CFD based on dynamic MRI of subjects before and after the onset of sleep has the potential to reveal both anatomical and functional factors to better identify OSAS phenotypes.

Airflow resistance of the nasal passages from nares to choanae is another important biomechanical factor that often determines the majority of the air pressure force in the pharyngeal airway prior to airway collapse. Nasal resistance measured using anterior rhinomanometry is significantly higher in children with OSAS than controls [152], and may be an important tool for screening and diagnosing OSAS.

Additional Considerations

Edema

Although increased soft tissue size surrounding the airway as a cause for OSAS is primarily related to obesity, chronic edema, and inflammation of the upper airway soft tissues may further restrict the dimensions of the upper airway. The mechanism for this effect is speculated to be the effect of chronic vibratory effects of snoring, and of upper airway soft tissue being tugged caudally during fluctuation in intrathoracic pressure, resulting in trauma to the upper airway soft tissues [69, 70]. Indeed, the therapeutic effect of CPAP is thought to be partially mediated through a reduction in upper airway soft tissue edema, and the use of CPAP has been shown to reduce soft palate volume [153].

Myopathy

It has been suggested that patients with OSAS have a primary myopathy. Several studies have demonstrated an

increase in type II fast twitch fibers in the genioglossus of patients with OSAS [154–156]. Type II fibers are less resistant to fatigue than type I fibers. It is possible that the increased number of type II fibers is secondary to chronic muscle injury which, in turn, may alter the size, length, and configuration of the affected muscles.

Gender

In adults, OSAS is far more common in males than females [157]. Considerable effort has been expended in trying to determine the mechanisms underlying this male predominance, but no clear explanation has emerged. Studies have not shown differences in pharyngeal anatomy resulting in a smaller pharyngeal lumen in males. On the contrary, females were found to have a smaller pharynx [158, 159], despite the presence of larger soft tissues in males [160]. It is therefore possible that the reduced occurrence of OSAS in females is due to a stiffer and less collapsible upper airway despite its smaller size [161–163]. Speculated mechanisms mediating differences in airway collapsibility include hormonal differences, differences in chemosensitivity, and differences in tissue properties [161, 162, 164].

In contrast, no gender differences have been noted in children with OSAS. Pillar et al. evaluated the upper airway length in pre- and post-pubertal non-OSAS children using CT images. They noted that airway length after normalization was significantly greater in males in post-pubertal years and speculated that such changes in length after puberty may predispose males to OSAS later in life [165].

As mentioned above, PCOS is one of the most common endocrine disorders associated with overweight and obesity and affects 5–10% of adolescent girls and women of reproductive age [112]. Screening for OSAS has therefore been recommended in these subjects [118].

Genetics

Genetic factors most probably play an important role in both the pathophysiology and health outcomes of OSAS in children and adults. However, genetic studies in the field of OSAS particularly in children lag behind other common medical disorders.

Evidence to suggest that OSAS is genetically mediated in children includes the following: (1) the strong association of OSAS with discrete craniofacial skeletal disorders restricting the upper airway such as Down syndrome, Treacher Collins, and Apert syndrome; (2) distinct genetic disorders associated with obesity that present with an extremely high prevalence of OSAS and sleep disordered breathing such as PWS, PCOS, and melanocortin-4 receptor deficiency. The above examples suggest that distinct genes regulating upper airway morphology, body composition, or ventilatory control also contribute to the pathophysiology of OSAS in such groups. However, so far, such genes have not been identified and it is unclear if such putative genes share similarities to genes responsible for OSAS on otherwise healthy children.

In adults, evidence to support that OSAS is a heritable disorder include the marked gender difference in disease prevalence and progression [157], familial aggregations of the disorder [166], and twin studies [167].

Genetic approaches to study OSAS have been utilized only in adults. Research in this area has been limited by the relatively small number of studies, small number of participants and the small number of replication studies. Standard genetic approaches include heritability studies to discover candidate genes using single nucleotide polymorphisms (SNPs) and OSAS phenotypes in case–control or cohort studies, or genome-wide linkage studies and genome wide association studies (GWAS) to identify causal genes without having a priori knowledge of functionality [168].

Nevertheless, several genetic association studies have identified candidate polymorphisms in genes linked to OSAS: the tumor necrosis factor alpha (TNF-α) gene (−308G/A) [169], the rs1409986 SNP in the prostaglandin E2 receptor (PTGER3) gene [170], and the rs7030789 SNP in the lysophosphatidic acid receptor 1 (LPAR1) gene [170].

Large-scale GWAS have identified loci for traits associated with OSAS such as: (1) polymorphism in the G-protein receptor gene (GPR83) [171] which is expressed in several areas of the brain including the hypoglossal nucleus, the dorsal motor nucleus of the vagus, and the nucleus of the solitary tract; (2) variants in the β-arrestin 1 (ARRB1) gene, which is an important regulator of hypoxia inducible factor 1 alpha (HIF-1α) [171]; (3) genes regulating obesity and body composition and insulin resistance [172]; and (4) genes regulating craniofacial structures [173]. It still remains to examine if these genes are applicable to risk for OSAS in children.

Research Questions

There are many pressing unanswered questions regarding the developmental pathophysiology of OSAS. In particular:

- What is the pathophysiology of the “idiopathic” OSAS often seen in infants?
- What is the natural history of childhood OSAS? Is childhood OSAS a precursor of adult OSAS, or a separate disease process? If the former, what is the recurrence rate during later life, and what are the risk factors for recurrence?

- What is the effect of childhood OSAS on craniofacial growth and structure? Does adenotonsillar hypertrophy per se result in craniofacial changes that could result in obstructive apnea later in life, or is the apparent adenotonsillar hypertrophy a result of overcrowding from a narrower upper airway? What is the potential role of treatments such as intraoral appliances and rapid maxillary expansion in changing craniofacial growth in children?
- When does the childhood pattern of OSAS transition into the adult pattern? What are the effects of puberty on upper airway function and structure?
- What roles do genetic, ethnic, and anthropometric factors play in the pathophysiology of OSAS?
- How can biomechanical studies using novel imaging modalities such as MRI improve diagnosis and treatment for children with OSAS?

Addressing these questions may improve diagnosis and provide optimal treatment outcomes for various phenotype of childhood OSAS in the upcoming years.

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