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Pediatric Obstructive Sleep Apnea: Where Do We Stand?

Yu-Shu Huang[a, b] · Christian Guilleminault[c]

[a]Department of Child Psychiatry, Chang Gung Memorial Hospital and College of Medicine, and [b]Craniofacial Research Center and Sleep Center, Chang Gung Memorial Hospital and University, Taoyuan, Taiwan; [c]Stanford University Sleep Medicine Division, Redwood City, CA, USA

Abstract

Pediatric obstructive sleep apnea (OSA) was initially described in 1976. In 1981, Dr. Guilleminault emphasized that pediatric OSA was different from the clinical presentation reported in adults. It was characterized by more disturbed nocturnal sleep than excessive daytime sleepiness, and presented more behavioral problems, particularly school problems, hyperactivity, nocturnal enuresis, sleep terrors, depression, insomnia, and psychiatric problems. The underlying causes of pediatric OSA are complex. Such factors as adenotonsillar hypertrophy, obesity, anatomical and neuromuscular factors, and hypotonic neuromuscular disease are also involved. Adenotonsillectomy (T&A) has been the recommended treatment for pediatric OSA, but in the recent past this practice has been placed very much in question. Therefore, we will discuss the mechanism of pediatric OSA and investigate obese and nonobese pediatric sleep-disordered breathing. Moreover, the important concept that dysfunction leads to the dysmorphism that impacts on the size of the upper airway has been advanced recently. Finally, the treatments of pediatric OSA, such as T&A, medication, the orthodontic approaches (rapid maxillary expansion, or mandibular advancement with functional appliances), positive airway pressure, and noninvasive treatment, such as myofunctional therapy (MFT), will be investigated. A "passive MFT" has been tried recently, but very few results exist. In conclusion, we have made progress in our understanding of pediatric OSA, and we can even recognize factors leading to its development or worsening. However, pediatricians and pediatric subspecialists are often unaware of the advances and the remedies available.

Pediatric Sleep-Disordered Breathing

Pediatric obstructive sleep apnea (OSA) was initially described in 1976 [1]. In 1981, Guilleminault et al. [2] published a review of 50 pedi-

atric patients and emphasized that pediatric OSA was different from the clinical presentation reported in adults. The authors emphasized that these children had more disturbed nocturnal sleep than excessive daytime sleepiness, and presented more behavioral problems, particularly school problems related to attention deficit, poor school performance, hyperactivity, symptoms classified as "attention-deficit-hyperactivity syndrome," nocturnal enuresis, sleep terrors, sleepwalking and confusional arousals, symptoms classified as "NREM parasomnias," depression, insomnia, and psychiatric problems. Cardiology-related symptoms were infrequent, but tachybradycardia was regularly noted. Adenotonsillectomy (T&A) was performed and successful in some but not all children, as was clearly demonstrated on follow-up. A small group of children presented an abnormal weight increase after T&A. These children presented apnea and hypopneas closely following the current polysomnographic definition. However, a year later Guilleminault et al. [3] published a new report indicating that children may present the same chronic symptoms, yet polysomnographic investigations performed with these children using esophageal pressure manometry showed an absence of apnea and hypopnea, but the presence of abnormal upper airway (UA) resistance and more or less snoring. In 1982, many of the features presented today in reports on pediatric sleep-disordered breathing (SDB) were already clearly indicated and some of the issues still need further research. These include recurrence post-T&A, weight increase following T&A, and the issue of having SDB with similar complaints, symptoms, and clinical findings at evaluation associated with and without snoring, and with very different patterns of abnormal breathing at the polysomnography evaluation.

The obesity epidemic became relevant in the 1990s, adding a further level of complexity. Two different syndromes were observed in the same individual: obesity per se could lead to the same complaints and symptoms as OSA syndrome in a normal-weight child, and obesity could lead to the development of OSA as a comorbidity due to the deposit of fat in the tongue tissues and other UA muscles. This then could lead to a chest-bellow syndrome related to the abdominal fat deposit, and it could worsen the symptoms seen in a slim OSA child. Attributing the respective responsibilities to obesity and OSA in their clinical presentation was difficult, particularly due to the fact that often the child is not seen early, but only after several years of evolution.

Obesity and Sleep-Disordered Breathing

Obesity is a complex disorder leading to worsening supine ventilation secondary to restrictive chest-bellows syndrome [4]. Obesity also leads to progressive fatty infiltration of the neck and UA. MRI studies have shown that a progressive fatty infiltration of the geniohyoid and genioglossus muscles occurs along with the dissociation of muscle fibers with fat cells [5]. Certain ethnicities, particularly African-American children, have a stronger association between obesity and SDB [6].

Obesity is associated with a progressive dysfunction of the adipocytes. Preadipocytes differentiate into mature adipocytes and form adipose tissue in response to a positive energy balance. Adipose tissue not only stores energy, but also acts as a dynamic endocrine organ, vital for hormone and cytokine (adipokine) secretion. White adipose tissue, located in abdominal and subcutaneous deposits in mammals, performs the majority of energy storage and adipokine secretion [6]. Brown adipose tissue mediates the nonshivering thermogenesis, well known to protect infants from cold exposure. Genetics play a role in the control and development of white adipose tissue and brown adipose tissue. Dysfunction of adipocytes leads to the stimulation of adipokines, particularly TNF-α and interleukins 6 and 1.

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These defects lead to pivotal inflammatory responses, both local and general, in addition to abnormal secretion of peptides found not only in the adipocyte, but also in the gut and brain. Peptides such as leptin, adiponectin, obesin, etc., are involved, and dysfunction of the adipocytes leads to leptin resistance and ghrelin dysfunction. These 2 peptides are crucial to food intake, insulin resistance, and the dysregulation of glucose and lipid control [7]. Overweight and obese individuals, with or without SDB, will develop these dysfunctions.

The consequences of these abnormalities affect the cardiovascular, respiratory, metabolic, and cerebral systems. Sleep fragmentation, which occurs with abnormal breathing, will cause changes in metabolic controls in part through the process of epigenetics, by which environmental events trigger a genetic cascade that would not have otherwise occurred. Obesity along with fatty infiltration of the UA will always lead to SDB from simple flow limitation to frank OSA.

Why Does the Upper Airway Collapse during Sleep in Nonoverweight Children?

Pharynx and Internal Factors

The pharynx is a collapsible tube: unlike the lower airways, there is no rigid support. The UA, consisting of skeletal muscles and soft tissues, supports nonrespiratory functions, such as sucking, swallowing, and vocalization/phonation, etc. Sleep causes fundamental modifications of pharyngeal muscle tone and reflex responses and can lead to narrowing and increased UA resistance in normal individuals.

The control of muscle tone during wakefulness and during sleep is different; this is true for the muscles constituting the walls of the UA in humans. There are 2 sleep states: rapid eye movement (REM) sleep and non-REM sleep; muscle control differs during the 3 states of alertness: wakefulness, and non-REM and REM sleep, respectively. In physiological terms, REM sleep is associated with the greatest amount of inhibition of volitional muscle tone. Sleep favors UA collapse, particularly due to the loss of tonic activation of UA muscles at the end expiration. Also, sleep usually occurs in a recumbent position and the degree of recumbence has an impact on the size of the UA, with lying flat on one's back being the position leading to the largest amount of change, compared to an erect position, due to the action of gravity and atmospheric pressure. The UA presents an intrinsic collapsibility that can be modelled as a "collapsible tube," with maximum flow (Vmax) determined by upstream nasal pressure (Pn) and resistance (Rn); the tube collapses and airflow stops at the critical pressure (Pcrit).

Pharynx and External Factors

External factors impact on the size of the UA, particularly when it is in a retropalatal or retroglossal position. Three of these factors are particularly prominent: fat deposits (related to the body mass index), craniofacial features (related to genetic and functional factors), and hypertrophied tissues, in part related to local inflammation. These external factors can be influenced by genetic and environmental factors.

Bone structure has an important role in the size of the UA. The development of the face is a very closely regulated event, with continuous interaction between the development of the entire brain, the skull, and the skull base. The growth of the transversal portion of the nasomaxillary complex is influenced by 3 factors: the development of the nasal fossae during fetal life, the growth of the ocular cavities related to ocular development during fetal life, and the activity of the intermaxillary suture that utilizes an endochondral mode of ossification and is active until about 16 years of age, and then undergoes complete synostosis by age 25 years. The face is located at the anterior-most point of the skull base and is therefore especially

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dependent on the processes involved in its growth, with the maxilla and mandible being "pushed forward" by the development of the skull base. The interaction between the developments of the nasomaxillary complex and the support of the head in an individual with vertical posture is a key adjustment.

Genetic factors are critical in this development. Most of the growth of the skull base is cartilaginous growth, and growth occurs in relation to "synchondroses" [8]. These serve as the sites of bone growth in the skull base and are located in the sutures between the bones forming the skull and skull base. Sphenoidal chondrosis is responsible for the vertical growth of the skull base. The skull base has an oblique direction and lowers the location of the occipital lobe, thereby affecting facial growth. The growth of the nasomaxillary complex is related not only to the sphenoido-occipital synchondroses, but also to the activity of the synchondroses of the skull base, and particularly the cleft at the following sutures: intermalar, intermaxillary, interpalatine, maxillomalar, and temporomalar.

Postnatal Activity

It is important to note that the intermaxillary suture is active postnatally, as mentioned above, and is influenced by specific functions, such as suction, mastication, swallowing, and nasal breathing. These functions mobilize the facial muscles that play a clear role in facial growth. The development of these functions is influenced by the quality of nasal respiratory roles, dental development, which involves the position and height of the alveoli and teeth position, and the activity and strength of the tongue and facial muscles. The vertical growth of the nasomaxillary complex is related to the activity of the posterior skull base, and also to that of the frontomalar, frontomaxillary, and maxillomalar sutures. It is also related to the position of the hard palate and alveolodental activity [8]. While the mandible is involved in the space controlling the size of the UA, it is independent of the base of the skull and is instead associated with the cervicothoracic-digestive axis. This structure involves many muscle and ligament attachments and dictates the head posture.

The Role of 2 Synchondroses Active Postnatally: The Intermaxillary and Alveolodental Synchondroses

Intermaxillary Synchondroses

The recognition of genetic impairments of endochondral growth leading to SDB is often delayed until after childhood. Ehlers-Danlos syndrome [9] is secondary to either an autosomal-dominant, autosomal-recessive, or X-linked mutation of genes located on proteins or enzymes, most commonly COL-1A1, COL 5A1, or 5A2. Clinical evaluation demonstrated the presence of an abnormally long face, narrow and high hard palate, and frequently associated crossbite. While initially only abnormalities of the nasomaxillary complex may be seen, as patients enter adulthood and develop worsening SDB, defects of the condyle may also be detected.

Alveolodental Synchondroses

When permanent teeth are absent or are extracted in early life during their growth period, this can lead to bone retraction and affect facial bone growth. There is an association between teeth agenesis and the presence of OSA in nonsyndromic children. Dental agenesis is linked to genetic mutations, with a dental homeo-code for the agenesis of canine, incisor, and molar teeth. The association between congenitally missing teeth and facial skeletal changes with "a straight to concave profile, pointed chin, reduced lower facial height and altered dental inclination" was noted by Ben-Bassat and Brin [10]. This was confirmed by more recent studies [11]. Dental research has shown that tooth agenesis is a common congenital disorder; it may be associated with syndromes, but it is also often seen in nonsyndromic children and its prevalence has varied, depending on the au-

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thor, with findings oscillating between 10 and 20% of the studied populations [12]. In 10% of agenetic cases, 2 teeth are involved, with the 2nd premolar and the lateral incisor being considered as more frequent cases of agenesis, and 1–2% having oligodontia. There is an important role for abnormal craniofacial growth in the development of pediatric SDB and involvement of synchondroses, particularly in those still active during childhood.

Craniofacial Muscle Activity, Genes, and Abnormal Orofacial Growth

There is an interaction between muscle activities, particularly those of the face, and the growth and normal development of the UA. Genetic abnormalities impairing the normal activity of the striatal muscles, including facial muscles, lead to SDB. The most studied genetic disorder involving mutations and generalized muscle impairment is myotonic dystrophy, both type I and type II [13].

The results of an environmental impairment of orofacial muscle activity experiment involving monkeys [14, 15] suggested that nongenetic postnatal impairment may have an impact similar to genetically induced muscle impairment. The experimental data showed the presence of a continuous interaction between abnormal nasal resistance and orofacial growth through the intermediary of abnormal muscle tone and mouth breathing (with a change in the mandibular condyle position). The abnormal growth leads to further worsening of the nasal resistance. The consequence is a small UA.

There is a syndrome, known to be familial (although its genetic origin has not been demonstrated to date), which is clearly associated with the development of a small UA and SDB: the short lingual frenulum syndrome (ankyloglossia) [16, 17]. A short lingual frenulum has been associated with difficulties in sucking, swallowing, and speech. However, the oral dysfunction induced by a short lingual frenulum can lead to oral-facial dysmorphism, which decreases the size of UA support. The lingual frenulum is a vestigial embryological element that is mostly fibrous in its consistency as a result of adhesion between the tongue and the floor of the mouth during embryogenesis. Apoptosis controlled by genes separates the tongue from the primitive pharynx during embryogenesis [16–19]. "Clipping" of the short lingual frenulum is still proposed when difficulties are recognized early in life, but long-term results are reported as unpredictable when "clipping" is performed after the first few months of life. A short lingual frenulum modifies the position of the tongue. The orthodontic impact of this abnormal position may result in an anterior and posterior crossbite, a disproportionate growth of the mandible, and an abnormal growth of the maxilla [20, 21]. The tongue is normally placed high in the palate, and the continuous activity related to sucking, swallowing, and masticating induces stimulation of intermaxillary synchondrosis, as already mentioned. The interaction between abnormal bone growth stimulation and an absence of nasal breathing with secondary development of mouth breathing is responsible for the abnormal development of the oral-facial bone structures supporting the UA, thus increasing the risk of UA collapse during sleep. The abnormal oral-facial growth leading to a reduction in the ideal size of the UA occurs at a variable speed depending on the individual, and abnormal breathing during sleep occurs over time, with initial flow limitation, then progressive worsening toward full-blown OSA syndrome.

Nongenetic Impairment of Muscles and Abnormal Oral-Facial Growth

In children, prematurity is often associated with generalized muscle hypotonia. Its severity is dependent on the degree of prematurity, in spite of the disappearance of the diaphragmatic apneas of prematurity [22]. The development of OSA is observed. This atypical breathing pattern is associated with the development of mouth breathing

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and a high and narrow hard palate. Early premature infants often have abnormalities involving feeding functions, such as suction, mastication, and swallowing, with weakness of orofacial muscles that negatively alter craniofacial growth and lead to a small UA.

Functional Dysfunctions

These different studies demonstrate that impairment of the growth of the oral cavity and oralfacial structures early in life leads to the development of an abnormal anatomy of the bone support of the UA, increasing the risk of UA collapse during sleep. Some specific dysfunctions involving muscle tone lead to abnormal functions that impact on bone development of the structures supporting the UA; these functions include sucking, masticating, swallowing, and nasal breathing. Abnormal nasal breathing leads to mouth breathing, which is another dysfunction.

The concept that dysfunction leads to the dysmorphism that impacts on the size of the UA has recently been advanced. This concept has led to different treatment initiatives with the goal of: (a) demonstrating the negative effect of not addressing the dysfunction when treating OSA, and (b) trying to address the dysfunction directly and as early as possible.

Treatments and Outcomes

Negative Effect of Not Addressing the Dysfunction

For years, T&A has been the recommended treatment for pediatric OSA, but in the recent past this practice has been placed very much in question. First, many studies have shown that the use of T&A in pediatric OSA patients may have variable results, reaching an AHI of 1 or less in about 50% of cases (and as low as 32% in obese children) [23–27]. However, a long-term follow-up study [28] performed first in 6- to 12-year-old children with OSA and repeated in 4- to 6-year-old children with OSA who underwent T&A showed progressive recurrence and worsening in both "apparently cured" and "significantly improved" children, and in 68% of the children after 36 months of follow-up in the first study. Recurrence was also noted in the second study, except that progressive worsening was slower in the younger children (4- to 6-year-old group). The issue of the role of T&A has been raised by others. The CHAT study looking at children with low but abnormal AHI showed that a delay in performing T&A may not show the same polysomnography results as in the initial investigation. Recent studies of children post-T&A have shown that despite T&A removal, children may still present mouth breathing [11]. This mouth breathing may be related to the fact that children who have been mouth breathers for a certain time due to obstruction of the nose and UA have a "disuse" of their nose when breathing, and removal of obstructive UA tissues does not mean a systematic return to normal nasal breathing during sleep [11]. This mouth breathing may also be related to the progressive occurrence of dysmorphism secondary to the presence of mouth breathing that impacts on maxillary and mandibular growth, as shown in the experiment preformed on Rhesus monkeys [14, 15], or to dysmorphism related to congenital dental agenesis [29, 30] or other secondary dysfunctions (such as a short lingual frenulum or prematurity, etc.).

Addressing the Dysfunction as Early as Possible

The introduction of orthodontic treatment (rapid maxillary expansion or bimaxillary expansion) [31, 32] has also shown that some children may not need T&A. The orthodontic treatment of dysmorphism that leads to a small UA (again with rapid maxillary expansion or other orthodontic approaches) may be sufficient to avoid T&A and restore nasal breathing during sleep [31, 32]. However, both orthodontics and T&A may be needed.

The use of myofunctional therapy (MFT) alone when dealing with pediatric SDB has not

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been widely investigated. Results of studies performed on children with orthodontic problems have shown that isolated extensive and well-controlled MFT can lead to a return to a normal oral-facial anatomy [31], but the effect on SDB is unknown. The absence of MFT in association with T&A or other treatments to address dysmorphism induced by dysfunctions has been clearly shown to lead to the persistence or recurrence of pediatric SDB.

MFT and proper tongue positioning in the oral cavity have been described since 1918 as leading to an improvement in mandibular growth, nasal breathing, and facial appearance. MFT is comprised of isotonic and isometric exercises that target oral (lip, tongue) and oropharyngeal structures (soft palate, lateral pharyngeal wall). Breathing, particularly nasal breathing, swallowing, mastication, and suction are some of the daily functions that help the oral cavity gain growth during early childhood and participate in the normal development of the oral-facial structures. Normal development of oral-facial structures is important for air exchange, particularly during sleep. During childhood sleep, the tongue will be positioned against the palate and help widen the palate (the adult width is between 40 and 50 mm). The continuous interaction of the tongue with active intermaxillary synchondrosis and the alveolodental growth region are factors in the normal development of oral-facial structures [32]. MFT [32, 33] aims to obtain appropriate head posture, appropriate positioning of the tongue on the palate against the upper teeth, appropriate swallowing, appropriate mastication using both sides and posterior chewing, appropriate breathing through the nose and keeping the mouth closed, appropriate "cleaning" of the nose, and appropriate speech and articulation. Active parental involvement is required to obtain valid results. Specialized educators exist in many countries, but educational programs vary widely in depth. A meta-analysis [33] showed that MFT, in association with other therapeutic approaches, may lead to complete remission of OSA in about 60% of children with whom it is used. The major problem is compliance with daily exercises and continuous parental involvement with the training exercises of the child; this treatment approach is called "active MFT" [33].

A "passive MFT" [34] has been tried recently but results are only available in an abstract form; however, such an approach would be very useful: it calls upon mandibular devices that would lead to sensory stimulation of the tongue, leading to tongue muscle activity. More work in this area is needed.

Positive Airway Pressure

When all of the above fails, or when a syndromic presentation or hypoventilation during sleep is present, positive airway pressure is considered. However, long-term follow-up of children treated with masks that are placed on a developing face reveals a negative effect: the impairment of facial growth, already well documented in children, may occur within 1 year. Furthermore, use of a chin strap that "pushes back the chin due to its anchorage" increases this very negative effect. Specialists have used a mask with pressure on the forehead to decrease this important and ignored negative effect, and have associated positive airway pressure usage with daytime MFT, but currently this negative effect is often poorly addressed.

Conclusion

We have made progress in our understanding of pediatric OSA, and we can even recognize factors leading to its development or worsening. However, pediatricians and pediatric subspecialists are often unaware of the advances and the remedies available. The frequency of pediatric OSA can be significantly decreased if "fundamental functions" (nasal breathing, sucking, swallowing, masticating, and phonation) are regularly evaluated for appropriate development, and if any ex-

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isting defect is properly addressed. Treatments allowing normal development exist, and educational material and training for parents is available; the education of specialists and diffusion of existing knowledge, including to parents, is needed [35].

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Prof. Christian Guilleminault, MD, Biol D
Stanford University Sleep Medicine Division
450 Broadway Street, Pavilion B, 2nd Floor, MC 5730
Redwood City, CA 94063 (USA)
E-Mail cguil@stanford.edu

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