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CLINICAL REVIEW

From oral facial dysfunction to dysmorphism and the onset of pediatric OSA

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SUMMARY

The upper airway is a collapsible tube, and its collapsibility increases during sleep. Extrinsic factors such as atypical craniofacial features may increase the risks of airway collapse. We review early development of oral-facial structures and the anatomical variants that may be present at birth and can impact nasal breathing. After birth, there is a continuous interaction between orofacial functions and growth of anatomic features. We review the dysfunctions identified to date that may impact orofacial development leading to sleep-disordered-breathing through changes in the orofacial growth. The identification of risk-factors, ultimately leading to full-blown obstructive sleep apnea, may allow early recognition of these factors and the development of treatments to eliminate early problems or at least decrease their impact.

Introduction

Obstructive sleep apnea (OSA) is related to the abnormal collapse of the upper airway during sleep. While we are able to recognize the presence of OSA when the symptoms are *full-blown*, diagnosis of the syndrome is much more difficult early in life because the recording of nasal airflow during sleep is not well understood and requires sophisticated analytical techniques [1,2]. Although new treatment avenues have been recently proposed, treatment approaches for children have continued to be particularly challenging.

The upper airway (UA) is a collapsible tube, and the muscles constituting its borders attach to bones that are part of the orofacial region. The muscles forming the limits of the UA are controlled by reflexes. Reflex-loops call upon sensory receptors, sensory nerve-fibers, brainstem neuron integrators, and a motor loop to activate these muscles. During sleep, it was shown that many of these reflexes are attenuated or even non-functional at times, particularly during rapid eye movement (REM) sleep. This leads to an increase in the risk of airway collapse during sleep as compared to wakefulness.

Studies looking at the laws of physics governing airflow in the UA have determined that fluid-dynamics can be applied to investigate changes in UA airflow [3]. One feature impacting the UA is its dynamic airway collapsibility. Abnormal collapsibility in both children and adults has been related to sleep and different sleep states causing fundamental modifications of pharyngeal muscle tone and reflex responses. Other factors have also been considered including one's body position during sleep. Both intrinsic and extrinsic factors affect this risk of collapsibility: the UA has an intrinsic collapsibility that is studied via the evaluation of *critical pressure* [4–7], while extrinsic factors may lead to increased overall collapsibility. Three external factors impacting the retropalatal and retroglossal space of the UA have been firmly established: 1) UA fat deposits, 2) non-fat related hypertrophy of UA tissues in which chronic inflammation is a contributor, and 3) craniofacial features impacting UA size.

However, infants are rarely born *obese*. Obesity is acquired over time. Arens, Schwab, and colleagues [8,9] have shown the highly negative effect of fat infiltration on UA muscles. This induces a narrowing of the upper-airway leading to sleep-disordered breathing (SDB), and we have previously shown the impact of orofacial anatomical build-up and the risk of UA collapsibility in overweight subjects [10]. Therefore, we will not consider this co-morbidity here.

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Abbreviations

AF	amniotic fluid
AHI	apnea hypopnea index
CPAP	continuous positive airway pressure
EDs	Ehlers Danlos syndrome
EMG	electromyogram
GA	gestational age
HOX	Homeobox
ICU	intense care unit
NICU	neonatal intense care unit
OSA	obstructive sleep apnea
PSG	polysomnogram
REM	rapid eye movement
RME	rapid maxillary expansion
SDB	sleep-disordered breathing
T&A	adenotonsillectomy
TST	total sleep time
UA	upper airway

Cranio-facial growth

The earliest form of the face appears in the fourth week of fetal development. Migration of cranial neural crest cells, developing into facial prominences, is an important step in fetal development, and the family of Homeobox or HOX genes play a major role in the development of the final tissues [11].

By the ninth week of fetal development, the initial cartilaginous facial skeleton is well established. By the twelfth week of fetal growth, areas of ossification appear and bone rapidly replaces the cartilaginous template forming the early cranial base. At the same time, the bones of the cranial vault, mandible, and maxilla develop through intramembranous ossification [12,13]. Post-natal development is also rapid. The head that represents nearly a quarter of the child's length at birth is about 12% of what it will be in adulthood. Sixty-percent of the adult-sized face is developed by 6 y of age, with maximum growth occurring between birth and 2 y of age.

During infancy and early childhood, the cranial base increases in length through endochondral ossification that occurs at important growth sites called synchondroses (growth centers). Two of these growth centers, the intermaxillary synchondrosis and alveolodental ligament, are active until near the end of puberty. The growth of the cranial base is the initial engine of facial growth through enchondral ossification. The maxilla and mandible are pulled down and forward by the soft tissues (i.e., muscles) to which they are attached.

However, the maxilla benefits from growth at the mid-palatal suture and the alveolar process that accompanies tooth eruption, but the mandible lacks an open suture and grows mostly through enchondral ossification at the temporomandibular condyles. The dental-alveolar structure develops with the eruption of teeth, and the maintenance of the occlusal contact is an important element for vertical ramus growth [14–19].

Fetal functions and development of the oral cavity

Fetal echography has brought a large amount of knowledge [20,21]. Development of the oral cavity begins near the 2nd month of pregnancy: Cells from neural crest build five *modules* that will create the face and the oral cavity. The internal area of the oral cavity is the same as the skin with presence of the same sensory receptors for pressure, pain, touch, temperature, etc.

The movement of the fetal tongue between the 6th and 10th weeks of gestational age (GA) allows the closing (i.e., vertical, horizontal, and transverse planes) of the primitive mouth (stomodeum). The tongue's new placement below the palate changes from a previous vertical orientation to a horizontal orientation. This organization is under the control of the 39 homeobox genes (HOX). At this time in gestation, mutations involving these genes will lead to congenital orofacial syndromes such as Pierre Robin sequence, as well as Digeorge, Caylar, Moebius, CHARGE, brachio-occulo-facial, Joubert, or Dandy Walker syndromes. These syndromes are not part of this review.

From the 3rd to the 5th months of GA, brain-stem neuronal networks aimed at sucking and swallowing are created, and an organization of normal oral functioning occurs. Such organization is critical for the development of the *sucking-swallowing* functions that will be needed at birth.

The two neuronal networks for sucking and swallowing are integrally related [22]. First of all, there is sucking and very closely related swallowing with the appearance of an esophageal reflex leading to the movement of the bolus to the esophagus with specific timing of the oro-pharyngeal and then esophageal reflexes. These sensory-motor reflexes are triggered by contacts between the tongue and palate and the lips and palate. There are additional contacts between the hand, foot, elbow, etc. and the lips that occur with progressive fetal growth in utero. There is also the appearance of the "Hooker reflex" [23] where lip stimulation (i.e., contact with lips) leads to the opening of the mouth with protrusion of tongue. These reflexes are closely related to those seen at birth (i.e., the cardinal reflexes) followed by a suck-swallow automatic activity.

This reflex activity is stereotypical with mouth opening, as well as lip, cheek, and tongue action with aspiration of fluid via propulsion of the fluid related to the backward motion of the tongue. This aspiration of fluid is associated with 1) mandibular movements and contraction of external pterygoid muscles acting on the growth centers of the mandibular condyle and activation of growth of the ramus of the mandible, 2) followed by swallowing with esophageal peristalsis. As shown by fetal echography [20,21], the fetus *sucks* amniotic fluid in greater and greater quantities with fetal aging. There is continuous formation of amniotic fluid (AF) during fetal life. The sucking-swallowing fetal reflex leads to absorption of 7 ml/AF/d at 16 wk GA and 500 ml/AF/d at birth. There is a continuous training of sucking swallowing functions that allows the normal development of the oral cavity during the third trimester of fetal development.

Postnatal development of swallowing reflex

The fetal oral reflexes function immediately at birth, but superimposed on these reflexes will be the development of *active* swallowing function between 6 and 12-mo post-natal age. The development of the cortico-geniculum pathway allows voluntary swallowing to become integrated with the initial fetal neuronal network. The primitive oral swallowing reflex is active throughout life. Active swallowing is a *"praxia"* (i.e., performance of movement) associated with mastication and is related to feeding training with the presence of an inhibitory circuit (to refine these oral functions). In summary, the fetal neuronal network for *suction/sucking* is unchanged but the neuronal network for *swallowing and mastication* adds a secondary network overlaid on and integrated with the primitive swallowing and phasic bite reflexes.

Nasal breathing

At birth, an infant is an obligatory nose breather. Beginning in the 1960s, important attention was drawn to the development of

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nasal breathing early in life. Planas [24] indicated normal airflow through the nose can be considered a "*praxia*" that develops very early in life. Nasal ventilation provides direct feedback to thoracic-ventilatory movements. The regulation of *nasal airflow thoracic ventilatory movements* involves a complex series of reflexes etched in the motor cortex [24–26]. Lack of normal nasal breathing, typically coupled with thoraco-abdominal ventilation, leads to deficiencies in the development of normal breathing. This occurs particularly during the respiratory coordination learning phase of the infant when the amplitude of the thoraco-abdominal ventilatory movements adjust to instantaneous nasal resistance. Therefore, too much nasal resistance can negatively impact the development of thoraco-abdominal ventilatory movements.

It was also found that normal nasal ventilation is critical for normal development of the sinuses. Investigations of children with deviated septa or enlarged adenoids near birth resulted in problems with nasal breathing and impacted skeletal orofacial development [27–31]. This is particularly important because, as previously mentioned, the face grows extensively between birth and 2 y of age.

Secondary skeletal changes involve the *anterior part of the nasal fossae*. In the anterior portion of the nasal fossae, a slight elevation in the floor of the nasal cavity was found to be related to normative bone resorption and abnormal narrowness in the transversal inferior part of the pyriform aperture [32,33]. This impacts development of the anterior portion of the maxilla. The impact on the maxilla, in turn, leads to malpositioning of the superior incisive teeth. Such malpositioning has a negative impact on the growth of the anterior portion of the maxilla and the nasal fossae. Abnormal nasal airflow also leads to a dysfunction in the development of the deciduous canine teeth that may lead to malpositioning of the permanent canines.

Skeletal changes also involve the *posterior part of the nasal fossae*. The impairment of nasal airflow impacts normal periosteum resorption, and this absence of resorption limits the normal lowering of the inferior portion of the nasal fossae.

Finally, abnormal nasal airflow leads to a narrowness of the *transversal section of the nasal fossae* and to abnormal sagittal growth of the maxilla (i.e., an inconstant impairment of the development and expansion of the maxillary sinuses). The narrowness of this transversal section may have an impact on the normal development of the 3rd molars later in life [19,31,34].

Abnormal nasal airflow also affects *the palate and its maxillary-alveolo-dental development* [19,24–31]. The development of the palate is impacted in three dimensions. First, there is *abnormal vertical development* with the appearance of a high, ogival/arched palatal vault. Secondly, a narrowness occurs whereby the *palate forms an extreme V-shape* and the narrowness involves both the area of the palate at the level of the nasal fossae and the section located under the sinus. It was noted that if nasal obstruction is predominant on one side of the nose, there is an asymmetry of the palatal vault with a deviation of the ogival arch toward the hypoplastic nasal fossa. Such changes have an impact on teeth orientation with an oblique teeth direction occurring on the side of the mouth with the least impairment and a vertical development on the other side [19]. Finally, there is a *sagittal impact* leading to development of a small maxilla.

Such changes interfere, as previously mentioned, with maxillary dental arch growth which will disturb mandibular dental arch development secondarily. In particular, the changes lead to the disappearance of the diastasis (or interspace) between the deciduous incisive teeth, which in turn interferes with the placement of the permanent teeth.

Nasal turbinates

At birth, the size of the nasal fossae is small, and comparatively, the nasal turbinates (i.e., structures that heat and humidify airflow) are large leaving only a relatively small passage para-median (medio-turbinal) [35,36]. The nasal turbinates normally decrease quickly in size, but at birth, they participate in the high nasal resistance observed in infants. The usual fast decrease in the size of the turbinates will not occur in the presence of local inflammation of the mucosae (as seen in the example of gastro-esophageal reflux) or uni-or-bilateral abnormal congenital enlargement of the turbinates. All of the studies reported here were performed during infants' wake time despite the fact that sleep represents between 70% and 75% of their 24-h cycle and the consequences of nasal narrowing are probably worse during sleep.

Other early-in-life functions involving the oral cavity

Nasal breathing is not the only function with a very important role in orofacial development. Coordination between nasal breathing and sucking must also develop very early in life. This is very apparent during breastfeeding and also necessary for bottle-feeding. Sucking and swallowing, as previously discussed, are very coordinated activities, and appropriate nasal breathing is crucial for these activities. Such coordinated actions (e.g., breathing and sucking) play a role in the stimulation of the structures involved in orofacial growth early in life. Mastication at close to 6 mo of age is an added stimulus for such growth. Anomalies in these functions increase the risk of abnormal development of bone structures supporting the UA leading to an increased risk of collapsibility in the UA during sleep [37].

Monkey experimental investigation

Orthodontists performed fundamental experimental studies in the 1980s. Harvold and colleagues at the University of California San Francisco Dental School investigated the role of abnormal nasal breathing on the orofacial and dental development of newborn Rhesus monkeys [38–40]. These experimenters placed a soft, hollow, silicon, cone-shaped plug into the nares of the baby monkeys. The plug filled the nares and was held in position by a silk ligature. The study emphasized orthodontic changes, and sleep was not monitored. This experiment leads to a great increase in nasal resistance with persistence of expiratory airflow. The significant increase in nasal resistance had a dramatic impact on the naso-maxillary and mandibular skeletons of the baby monkeys.

The abnormal nasal resistance halted oral growth and led to abnormal development of the maxilla and mandible. There were also secondary adaptive changes in soft tissues associated with deviations in jaw posture and tongue activity. Systematic recording of orofacial muscles, including the genio-glossus and genio-hyoid muscles, demonstrated that such abnormal nasal resistance led to abnormal electro-myographic (EMG) activity (i.e., there was induction of an abnormal rhythmic EMG discharge pattern which was not seen in control animals). This pattern was slowly reversible once the nasal resistance was eliminated.

These experiments indicated that in growing monkeys where nasal breathing was gradually impaired, an adverse effect on the naso-maxillary complex and the mandible was observed. These morphometric changes were associated with altered functioning of specific orofacial muscles triggered by abnormal nasal inspiratory resistance [38–40].

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In summary: To maintain a UA lumen that avoids the risk of collapsibility during sleep means appropriate orofacial development during childhood.

Investigations

We questioned whether specific risk factors exist for the occurrence of SDB during early postnatal development and if these risk factors can be identified in children developing OSA. Early recognition of these factors may potentially lead to early interventions aimed at preventing OSA from occurring.

This report is based on the investigation of 1150 children with SDB, including 450 children from a prospective Taiwan premature infant cohort and 150 typically developing children who acted as controls in our investigations. The prospective studies were collected with IRB approval from Chang Gung Medical Center and signed consent forms from legal guardians, while retrospective data were collected with Stanford IRB-approved protocols. These protocols were performed over a 25-y period and results from independent protocols have been published in the past as indicated by the specific references associated with the quoted studies.

Role of abnormal muscle tone and abnormal breathing during sleep

Investigation #1 abnormal muscle tone and prematurity

It is reported that up to 15% of deliveries occur before 37 wk GA in industrialized countries. And, the earlier the delivery, the less practice of sucking-swallowing functions the infant will have. Also, infants born prematurely often present generalized hypotonia which was well demonstrated in clinical studies.

The Taiwan prospective premature infant cohort between 2010 and 2012 consisted of infants born between 25 and 37 wk GA who were considered premature [41,42]. These infants were recruited before discharge from the neonatal intensive care unit (NICU), while full-term infants, with gestational ages ranging from 38–40 wk and birth body weight of more than 2500 g, were enrolled from the neonatal outpatient clinic.

To be eligible for the study, specific inclusion and exclusion criteria were used (e.g., absence of intubation during the NICU stay and absence of neurological syndromes). This was a cohort of convenience, and only infants whose parents signed informed consent forms were placed in the cohort. Out of 520 children with prematurity, 450 infants were followed over 4 y. However, results in this study involve only the first 350 children followed for 4 y.

Sixty full-term infants were also recruited, and 53 were seen until 4 y of age. The protocol included evaluations shortly after birth (within the first week) and then at 3 mo, 6 mo, 12 mo, 18 mo, 24 mo, 36 mo, and 48 mo post birth. The children were evaluated via developmental scales and neurological evaluation which included feeding evaluations, actigraphy, polysomnogram (PSG) at beginning of study and on an annual basis thereafter, as well as systematic photographs of the face (i.e., frontal and lateral) and of the oral regions. Fiber-optic illumination was used in the photographs of the oral regions to evaluate the size and clinical presentation of the hard palate. Photos were scored blindly by a specialist who was not involved in the clinical evaluations.

Of the children whose sleep and breathing were evaluated during sleep (n = 350) [41], all attended the 4-y post-birth evaluation, but not all had attended the intermediary evaluations. At birth, the full-term infants had a mean palatal width of 24 ± 2 mm, measured at the mid-palatal level, and an apnea-hypopnea-index (AHI) of 0.3 ± 0.3 events/h. However, the infants with prematurity (total group) had a mean palatal width of 16 ± 4 mm and a mean AHI of 25 ± 15 events/hours. As previously reported, the greater the degree of hypotonia found in the infants with prematurity, the greater the breathing dysfunction recorded. At 12, 24, 36 and 48 mo, mixed and obstructive breathing events were the predominant pattern of abnormal breathing found as opposed to the initial recording where *central events* (also called *apnea of prematurity*) were noted [41,42].

At the 4-y evaluation, children born before 36 wk GA (n = 270, 77%) were significantly different in AHI and oxygen saturation (mean AHI = 14 ± 11 y; average lowest oxygen saturation of 89 ± 1.5%; Non-parametric Kruskal–Wallis *H* test, p = 0001) than controls born full-term. Children born after 36-wk GA were statistically similar (n = 80, 23%; mean AHI of 0.6 ± 0.2 events/h, and mean lowest oxygen saturation of 96 ± 2%) to controls born full-term.

The PSG showed that all children born prematurely with abnormal AHI were mouth breathers during sleep. The total sleep-time spent mouth-breathing was 88 ± 11% compared to 6 ± 3% in the control group of full-term children (Chi-square statistics: $p = .0001$). They all also presented with high and narrow palatal vaults. Their mean maxillary distance between the canines was significantly shorter at 4 y of age with a mean distance of 19 ± 3 mm versus 31 ± 1.8 mm in the full-term children with normal AHI. Systematic investigation of the UA revealed that tonsils were small in both groups of children and that abnormally elevated, mixed, and obstructive AHI was observed despite finding no abnormal growth of tonsils.

This ongoing longitudinal study demonstrated that a large number of infants born prematurely at 36 wk GA and younger had generalized hypotonia and presented with high apnea-hypopnea, initially with central and mixed apnea and then with mixed and obstructive events at follow-up. They also exhibited mouth breathing during sleep and the presence of a narrow palatal vault that persisted till 4 y of age. In contrast, full-term children and premature infants born 36 wk or older had no hypotonia at birth, no mouth breathing during sleep, normal PSG, and normal palatal growth. There is an association between abnormal muscle tone, presence of abnormal breathing during sleep, and abnormal development of oral facial structures (Figs. 1 and 2).

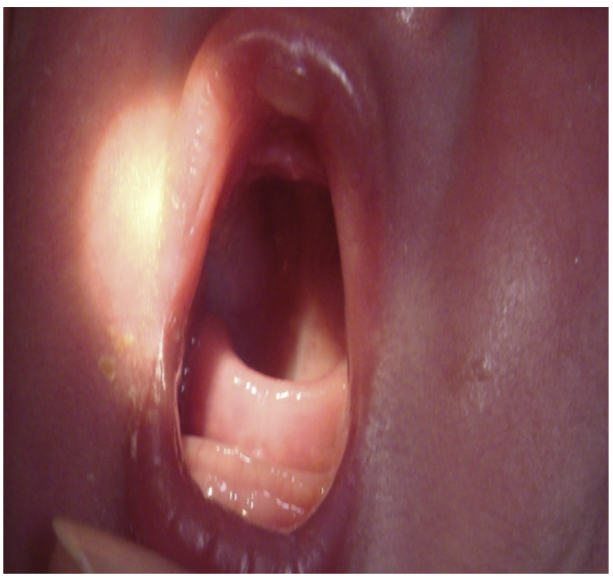

Fig. 1. Tongue of a 35 wk premature infant. The tongue is low placed in the mouth, and is hypotonic.

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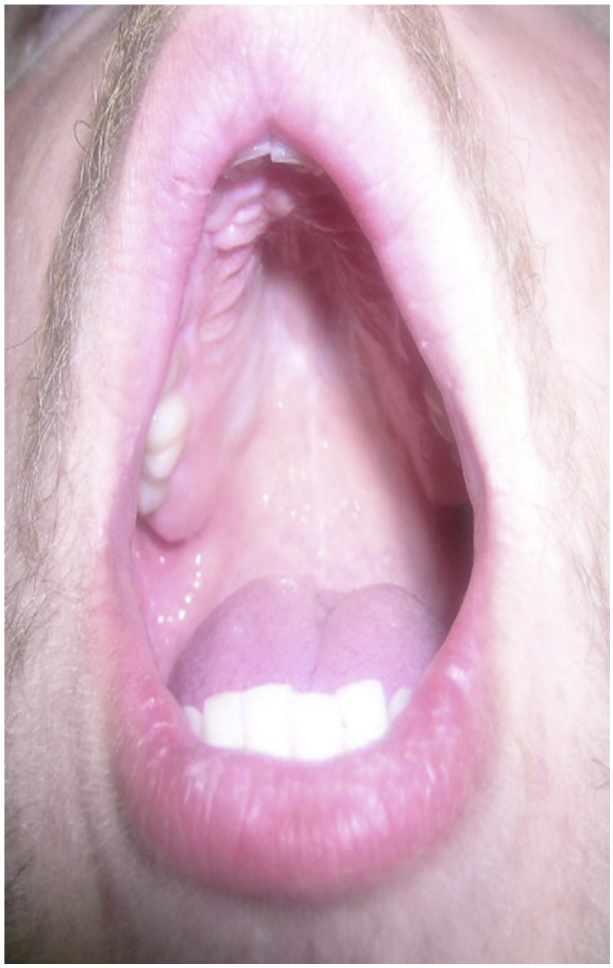

Fig. 2. Mouth of a young adult born prematurely at 33 wk GA. Note the high, narrow arched palatal vault and the very small oral cavity. During fetal life the concave horizontal part of the tongue is against the convex part of the palate, and sucking/swallowing reflex with swallowing of amniotic fluid and continuous movement of the tongue mold the palate. Such high tongue position and movement is present from birth-on with sucking/swallowing. During normal breastfeeding, ultra-sound studies and dynamic analyses showed that sub-atmospheric pressure in the range of −20 to −40 mmHg must be develop [87] with the tongue muscles that must exercise such a force to initiate normal sucking followed by swallowing that will involve movement of the mandible. Such force is applied on the palate and leads to widening of the vault. Absence of normal sucking/swallow will not induce such sub-atmospheric pressure and will not lead to application of such force to the palate.

Investigation #2 abnormal muscle tone and genetic disorder

Children with genetic muscle diseases were also studied for the presence of SDB and OSA, as well as given a clinical evaluation of orofacial development. Children and adults with myotonic dystrophy were recruited and monitored during their sleep to investigate the presence of SDB, sleep disturbances, and their daytime consequences [43,44]. Ten children were part of the research, with a mean age of 7.2 ± 3.2 y. All of the children reported daytime sleepiness and had abnormal PSG findings. They had sleep hypopneas more than apneas, an AHI at entry of 8 ± 3.6 events/h, and the lowest oxygen saturation of 89 ± 1.5%.

Five of the children studied under the above research protocol continued to have follow-ups with PSG for 5 y. They showed very poor compliance with any treatment aimed at their SDB. At their final research follow-up assessment, mean AHI was 11 ± 4 events/h and mean lowest oxygen saturation was 87 ± 3%. As all of the children grew older, they had poorer recordings. Clinical evaluation indicated all five children during long-term follow-up had a high (tongue-to-middle-of-palate) and narrow (measured between the maxillary canines) hard palate with initial mean width measurements of 22 ± 1 mm and follow-up mean measurements of 21 ± 1.5 mm, indicating the absence of growth. Two of them (age 14 and 16 y) had clearly developed over-crowding of the mandibular teeth when last seen.

Five other individuals were monitored again as late teenagers and young adults (mean age 21.5 ± 2.8 y). They had complaints of daytime sleepiness and high, narrow hard palates with a mean maxillary width between maxillary canines of 20 ± 1.8 mm during clinical evaluation, an AHI of 15.2 ± 2.4 events/h, as well as a lowest oxygen saturation of 88 ± 1.5% on PSG. None of them was compliant with prescribed nasal continuous positive airway pressure (CPAP).

The study of these individuals showed a progressive worsening over time of the AHI with a lack of normal oral cavity development. This included the presence of high, narrow hard palates and abnormal maxillary growth associated with a genetic disorder (i.e., myotonic dystrophy) affecting the muscles (e.g., orofacial muscles).

Investigation #3 adenotonsils and mouth breathing

OSA in children has been associated with enlarged tonsils and adenoids, and adenotonsillectomy (T&A) [T&A has been established as the recommended treatment for OSA for a long period of time]. Many studies, however, have shown that the percentage of children having normal AHI after T&A is variable and oscillates between 30 and 80% [45,46].

Two prospective and longitudinal studies were performed in two groups of children (aged 6–12 y and 4–6 y). These children were examined as well as given questionnaires and a PSG at the beginning of the study before their T&As and then again at 6, 12, 24, and 36 mo post-treatment. Sixty-five percent and 73% respectively for each age group were followed for the duration of the study. T&A was found to invariably improve the AHI at 6 mo post-surgery, but 68 and 59% of the children had a progressive worsening of their AHI at 3 y post-surgery with a mean AHI of 6.48 and 3.3 events per hour respectively [46].

A follow-up study was performed to understand factors associated with the progressive worsening over time of OSA post T&A. Sixty-four children aged 4–9 y with enlarged T&A and no other morbidity were monitored with special attention to mouth breathing. Sixty three were found to breathe through the mouth for more than 40% of sleep time with a mean AHI of 8.58 ± 3.15 events/h and mean lowest saturation of 89.97 ± 1.75. 54.7% (n = 35) of the group continued to breathe through the mouth after surgery (69 ± 11% of total sleep time (TST) versus 4 ± 3.9% for the *non mouth-breather group*). Children who were mouth-breathing had a significantly higher AHI than those who were not (mean 2.34 events/h for mouth-breathers versus 0.96 events/h for non mouth-breathing children $p = .0001$, paired t-test). After 12 mo, only 18 children came back for PSG, but again, mouth-breathing children had a significantly higher AHI than non mouth-breathing children ($p = .015$, paired t-test) [47]. The study showed that many children with enlarged adenotonsils who underwent T&A surgery, did not reach a normal AHI during sleep despite clear improvement [45,46,48]. Mouth breathing during sleep is very common among these children before surgery, and it tends to persist after isolated T&A, and then is often associated with residual abnormal AHI. Overall mouth breathing during sleep is considered abnormal, the cut-off point has been reported to be <10% of TST, with a calculation of normal mouth-breathing having a mean of 4% of TST [47,49,50].

Less systematic retrospective studies, but with longer follow-up times, have also shown similar findings: Groups of children were seen close to 6 y of age and initially treated by both T&A and rapid maxillary expansion (RME); at the end of treatment they underwent PSG demonstrating normal AHI and normal lowest oxygen

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saturation. Clinical evaluation revealed the presence of a normal palate and appropriate oral facial anatomy confirmed by cephalometric X-rays.

These children were recommended to pursue a myofunctional treatment program for 6 mo. In retrospective studies, subgroups of these children were found again at an age close to puberty: These limited investigations indicated that children who did not participate in an orofacial reeducation program at the time of their initial treatment presented again with signs and symptoms of OSA, as well as with abnormal AHI and lowest oxygen saturation on PSG. Additionally, they had re-occurrence of high and narrow hard palates and mandibular retrusion. These negative changes were not noted in children who had re-education of mouth-breathing and persistence of nasal breathing during sleep (i.e., orofacial myofunctional treatment) [51,52]. These studies were reported as only indicative of the value of orofacial reeducation programs due to the large number of missing children at follow-up. Despite their limitations, these studies suggested or indicated that regular mouth breathing during sleep can be detrimental to the normal development of the oral facial region, and may lead to or be related with recurrence of abnormal breathing during sleep in association with an abnormal oral-facial growth in pre-pubertal children.

Investigation #4 enlarged nasal turbinates and mouth breathing

Considering that mouth breathing during sleep may be detrimental to both normal oral and facial growth and may be associated with occurrence of pediatric sleep apnea, we performed a systematic search for factors that may lead to mouth breathing. Enlarged nasal inferior turbinates are commonly seen in association with respiratory allergies. We performed a systematic investigation of children with enlarged nasal inferior turbinates [53,54].

The study appreciated the contribution of untreated enlarged nasal turbinates to SDB and evaluated the impact of their treatments on SDB. A prospective, non-randomized study of 86 pediatric patients, mean age of 9.4 ± 4.4 y recognized with enlarged turbinates was performed. The diagnosis of nasal obstruction was made either by subjective complaint or caregiver observation, and SDB affirmed by PSG. Turbinate hypertrophy was confirmed on clinical examination. The examination consisted of anterior rhinoscopy with direct visual inspection of the anterior nasal cavity using a nasal speculum and fiberoptic headlight. The severity of nasal obstruction at the anterior end of the inferior turbinate was graded based on a five point scale per nostril: 0 (turbinates not visible), 1 (0–25% blockage), 2 (25–50% blockage), 3 (50–75% blockage), 4 (75–100% blockage) [53]. The mean score presented by the studied subjects was 5.7 ± 0.72 [compare to a score of 2.6 ± 0.58 post treatment with radiofrequency n = 79]. All subjects with 50% or more nasal blockade had, an abnormally high palatal vault and abnormal breathing during sleep with mouth breathing for more than 50% of total sleep time. The mean AHI at entry was 9 ± 6 events/h and the mean percentage of time spent mouth breathing was 61 ± 12% (Figs. 3 and 4).

Another investigation was performed in individuals referred from an allergic practice for clinical suspicion of SDB during a year. The retrospective investigation identified 14 teen-agers, mean age 14 ± 3.1 y, all subjects had been diagnosed with chronic allergic rhinitis and were referred by a single specialist for suspicion of SDB in association with their chronic allergic symptoms. Clinically, subjects reported of disrupted nocturnal sleep (100%), school difficulties with inattention (57%) or poor performance with difficulty learning (14%), and snoring during sleep (98.6%). All subjects had had T&A performed at least 6 y prior referral or

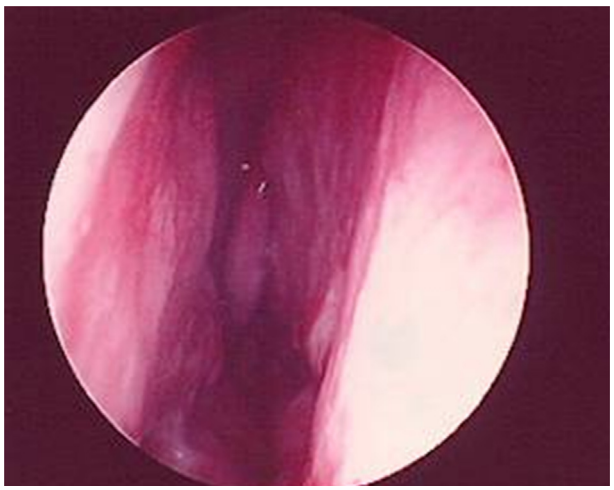

Fig. 3. Normal nasal passage in a prepubertal child. The nasal septum is on the right of the photo which is taken through a fiber-optic-scope.

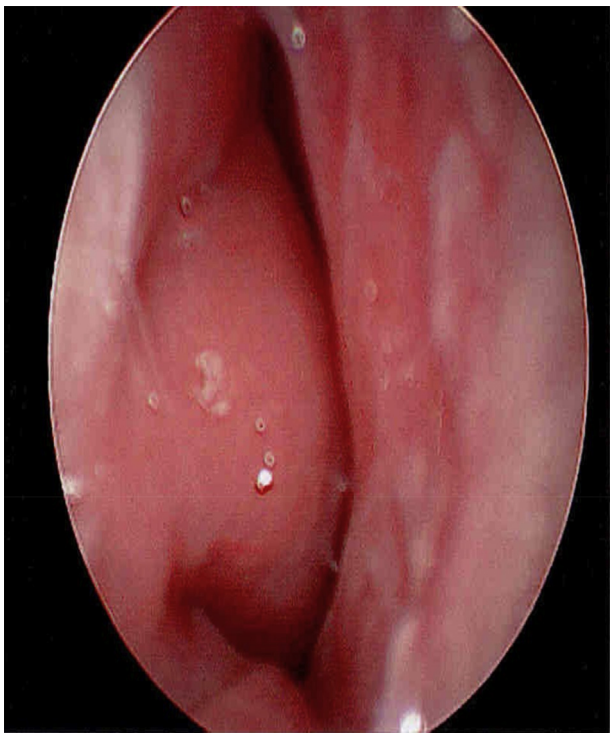

Fig. 4. Enlarged nasal inferior turbinate in a prepubertal child. The nasal septum is on the right of the photo taken through a fiber-optic scope. Compare to Fig. 3.

presented tonsils 2+ or less at Friedman et al. clinical scales [55,56]. They all had a high abnormal palatal vault. PSG demonstrated a mean AHI of 9 ± 6 events/h, abnormal presence of mouth breathing oscillating between 60 and 90% of nocturnal sleep-time. All children had also been referred to an orthodontic practice by the referring allergologist, and had cephalometric X-rays performed at the orthodontic office, showing abnormal maxillary growth.

These investigations showed the impact again of disrupted nasal breathing, this time related to chronic nasal allergies, on the association between abnormal maxillary development, and presence of mouth breathing during sleep, and SDB.

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Investigation #5 short nasal lingual frenulum, mouth breathing and abnormal oral facial growth

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. A short lingual frenulum has been associated with sucking and swallowing difficulties early in life leading to "clipping" of the frenulum in the newborn [57–61]. In older children, speech difficulties have also been related to untreated short frenulum [62–65]. A short lingual frenulum was also shown to lead to mouth breathing with modification to the position of the tongue and secondary orthodontic impacts resulting in an anterior and posterior crossbite, a disproportionate growth of the mandible, and an abnormal growth of the maxilla [58–62]. We systematically investigated the presence of a short frenulum in children born full-term and referred for suspicion of OSA, and performed a retrospective investigation of all pediatric cases, ages between 3 and 13 y old, seen during a 18 mo period. Syndromic children and children with neuro-psychiatric syndromes, chronic medical condition, and obesity were not included in the investigation. The position of the frenulum was examined and considered to be abnormal if: 1) it was attached underneath the tongue at any point between the mid-point and the apex 2) it inserted at its expected place under the tongue like in a normal subject, but was short and did not reach the apex. The tip of the tongue was also noted with indication of a heart, a V shape, or square [62,64] (Fig. 5). The length of the frenulum was measured twice between two points: measurements were done once when the short frenulum was recognized and once at the end of the clinical evaluation. Measurements were done as recommended by Kotlow [65], by determining the "free-tongue" (i.e., the part of the tongue above the frenulum top insertion, with measurements considered to be normal when equal to or longer than 20 mm) and by measuring the opening of the mouth with a caliper: The maximum opening was measured from the lower left incisive to the upper left incisive, and another measurement was taken with the mouth opened wide and the tip of the tongue touching the incisive papilla: If the difference between the two measurements was less than 50%, this measure was considered to be normal [66]; if the difference was more than 50% presence of a short lingual frenulum was scored. All children had diagnostic PSG using our standard protocol [67]. Out of 150 successively seen children diagnosed with OSA, 42% had a short frenulum. The presence of the short frenulum was associated with abnormal development of the oral cavity including the presence of a high and narrow palatal vault, abnormal maxillary growth, and scores of 4 or less on the Mallampati–Friedman scale [55]. A second study looked specifically at the association between the growth of the maxilla and the mandible in the presence of a short lingual frenulum. This study involved 1000 individuals (both adults and children) who were seen in an orthodontic practice, and its results similarly demonstrated an association between a short frenulum and the development of maxillary deficiency [66]. Also a small group of 27 children aged 2–17 y, with a short frenulum and demonstrated presence of OSA, underwent frenulectomy and follow-up [68]. All children had an abnormal oral cavity at the beginning of the study, with high and narrow palatal vault. These children underwent orthodontic palatal expansion using tooth-anchored expansion. They were also recommended to undergo myofunctional therapy [37,69,70] to re-educate oral facial muscles and nasal breathing. But only a subgroup of these children underwent such re-education: At post-treatment PSG individuals submitted only to orthodontic treatment showed improvements, but children continued to present higher than normal AHI and an abnormal amount of mouth-breathing during sleep. Those who underwent complete treatment, including myofunctional therapy for mouth-breathing during sleep, had normal palatal vault and no mouth-breathing during sleep.

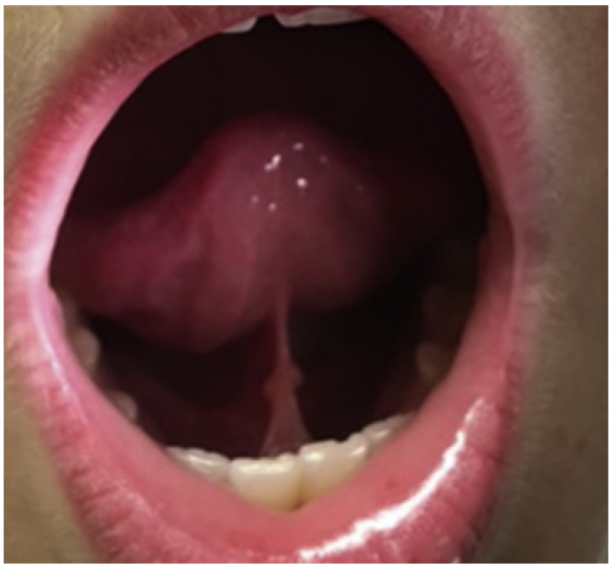

Fig. 5. Lingual abnormal frenulum. The tongue is kept low-placed in the oral cavity and its movements are restricted due to the short vestigial fibrous element. The tongue cannot mold the palatal vault and stimulate normal orofacial growth when sucking, swallowing, chewing, speaking and nasal breathing.

These different studies showed that the presence of an untreated abnormal lingual frenulum at birth led to development of an abnormal oral cavity, a maxillary deficiency, the presence of a small UA favoring its collapse during sleep, and the occurrence of OSA. Treatment of the small cavity during early childhood using orthodontic techniques improved breathing during sleep and normalized the size of the oral cavity [66]. However, the lack of muscle re-education of the oral-facial region using myofunctional therapy techniques and the absence of nasal breathing re-education is associated with the persistence of mouth-breathing and abnormal breathing during sleep [69,70].

Investigation #6 connective tissues diseases and OSA

Abnormal growth and development of the bone structures supporting the UA is associated with OSA. The absence of normal orofacial muscle activity leads to the persistence of mouth-breathing and abnormal breathing during sleep. Two areas are involved in post-birth growth of the orofacial cavity and facial structures (i.e., the maxillary synchondrosis or intermaxillary cartilage and the alveolo-dental ligament). Both structures are very much involved in orofacial growth until about 13–15 y of age. Impairment of these orofacial *growth centers* may lead to pediatric OSA.

Connective tissue diseases including Marfan and Ehlers Danlos syndrome (EDs) are related to genetic mutations that present with an impairment in the development of normal connective tissues. We performed a systematic investigation of individuals with the hyperlax/hypermobile form of EDs. The study involved both teenagers and adults [71].

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Thirty-four successively seen patients, with EDs and complaints of poor sleep, fatigue, or excessive daytime-sleepiness, were investigated using our clinical protocol and PSG. Two of them had a vascular form with a history of arterial dissection. All of the patients presented with high and narrow palatal vaults, and 17.6% of them had a cross-bite. All had abnormal maxillary deficiency, but mandibular impairment was also noted in 24 of them. Anterior rhinomanometry [72] was performed in seven of these patients who demonstrated an abnormal level of nasal resistance compared to normal controls.

After the completion of the initial study, offspring of adult EDs patients were evaluated, and 11 children aged 3–17-y were diagnosed with this genetic familial syndrome. These 11 children underwent the same clinical evaluation and PSG. They demonstrated high and narrow palatal vaults, maxillary deficiency, and OSA similar to their parents. There was a progressive increase in AHI with age. Younger subjects presented with a lower AHI (amount of flow limitation) than older subjects who always presented with a higher AHI and more problematic orofacial findings during evaluation (Figs. 6 and 7).

This hereditary collagen-vascular disease is inherited in an autosomal dominant, autosomal-recessive, or X-linked fashion. It involves variable genetic mutations located on proteins (COL1A1, 1A2, 3A1, 5A1, 5A2, TNXB) or enzymes (ADAMTS2, PLOD1, BUGALT7). The most common types 1 and 2 involve COL1A1, COL5A1, and COL5A2. These genetic mutations present in the intermaxillary cartilage and the nasal septum early in life. This leads to abnormal orofacial growth, initial development of nasal flow limitation, progression of anatomic orofacial abnormalities, and occurrence of more severe SDB with higher AHI over time [71].

Investigation #7 oligodontia and the alveolo-dental growth center

The dento-alveolar growth center remains very active until about 15 y of age and plays a role in the vertical expansion of the oral cavity and its widening. A study of children with congenital oligodontia (i.e., congenital absence of permanent teeth roots that can be noted very early in life on X-rays) and at least two missing permanent teeth demonstrated an impact on maxilla-mandibular growth and progressively developing OSA [73].

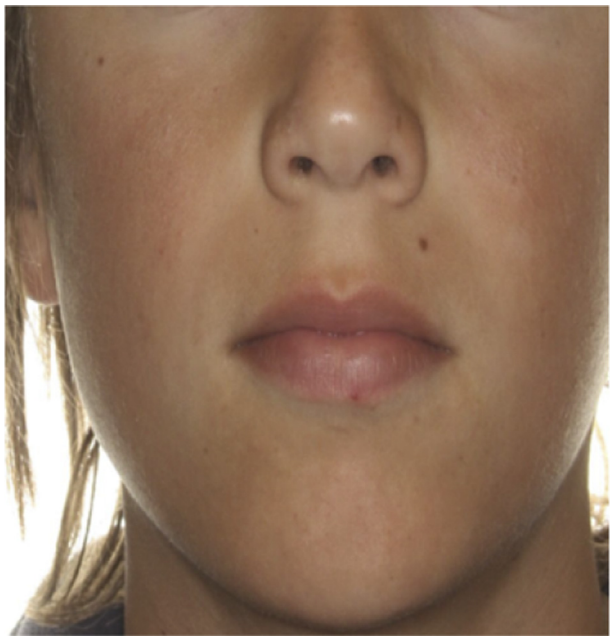

Fig. 6. Long and narrow face of a child with Ehlers-Danlos syndrome.

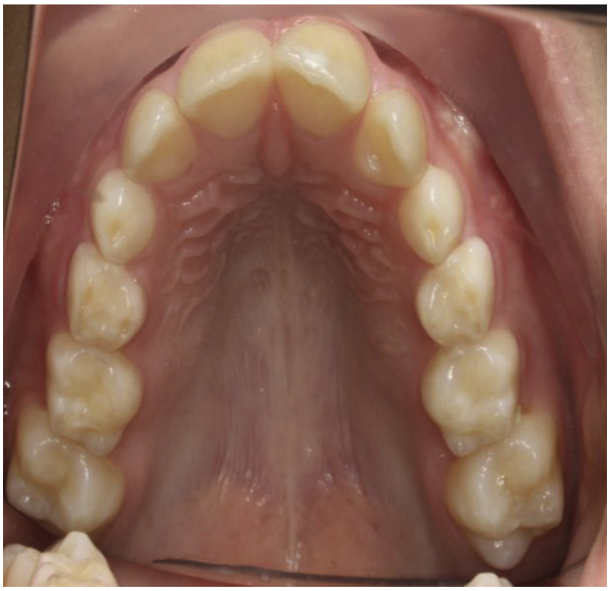

Fig. 7. High, narrow and arch palatal vault of the child with Ehlers Danlos syndrome. This is the abnormally small oral cavity of the child presented in Fig. 6.

A systematic investigation of 31 children with oligodontia revealed frequent positive family history of oligodontia, and OSA was found in several of the affected family members. However, family genetic studies were only performed in two families indicating mutations previously reported with oligodontia. Genetic studies can be demanding given that a minimum of 70 different genes have been implicated in teeth development.

Children missing at least two teeth had abnormal orofacial presentations with long and narrow faces, narrow and high palatal vaults, abnormal length of the lower 1/3 of the face, and abnormal clockwise rotation of the mandible [73–77]. PSG demonstrated the presence of OSA. Compared to age-matched children with OSA seen at the same time, the PSG findings were not as severe particularly at an early age as the results noted with aging (Figs. 8 and 9).

While congenitally missing teeth suggested the possibility of genetic mutation behind the deficit, a small group of children with two or more permanent teeth extracted early in life were also studied approximately 5 y post-extraction [73]. These children presented with orofacial findings similar to the teenagers with congenitally missing teeth. This supports the hypothesis that environmental manipulation of elements involved in orofacial growth during childhood (e.g., early permanent tooth removal) may lead to subtle changes in bone support of the UA and to increased risk of collapsibility during sleep. As with several of the previous investigations, the sleep and breathing abnormalities were more marked with affected subjects getting older.

This succession of studies led to the theory that abnormal breathing during sleep is associated with factors leading to subtle derailment in the development of the maxilla and mandible, impacting the bone supports of the collapsible UA. Impairment of

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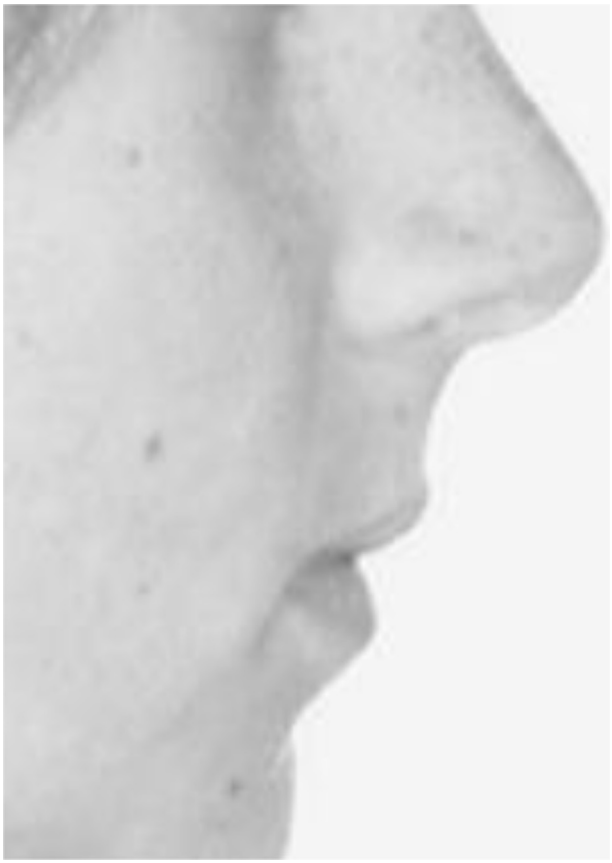

Fig. 8. Profile of a child with oligodontia. Note the clear retro-position of the mandible.

the UA muscles had a similar impact, but the subtle imbalance of bone positions also affected the activity of the UA muscles. The functional changes in nasal breathing and other orofacial activities appear to lead to changes in normal UA contraction particularly during sleep. These functional changes seem to lead to mouth breathing and to absence of abnormal UA muscle contractions and to secondary growth derailments with further worsening of abnormal breathing and the orofacial growth dysfunction [i.e., series of negative feed-back loops].

Given that normal orofacial functions have such an impact on growth and possibly on the development of dysfunction, re-education of normal orofacial function may affect the subtle dysmorphia noted in developing individuals. This concept has been advancing in the field of the orthodontics-stomatology and the corresponding field of *orofacial myofunctional therapy* with beneficial results [37,78]. Orofacial myofunctional therapy is aimed at obtaining appropriate head, neck, and torso posture; appropriate tongue resting position with the tongue lightly suctioned against the palate; appropriate swallowing; appropriate mastication using both back molar areas (i.e., posterior chewing); appropriate nose breathing while maintaining a closed mouth continuously while awake and asleep; as well as appropriate speech and articulation. Such behavioral modifications can be obtained through daily re-education exercises [37,79,80].

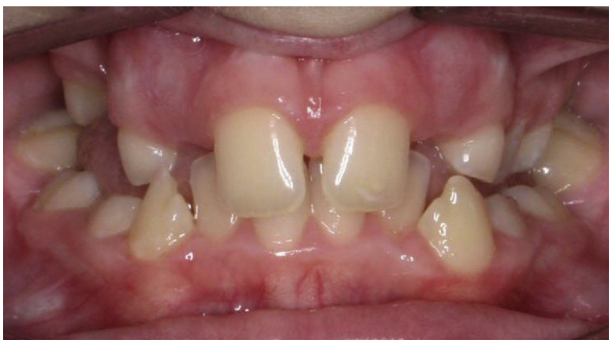

Fig. 9. Oligodontia. Note the missing teeth and the very narrow maxilla with a cross-bite clear on right of figure, compared narrowness of maxilla with the one noted in Fig. 7.

Investigation #8 myofunctional therapy

Orofacial myofunctional therapy was only recently applied in the field of OSA. Guimarães et al. [69] were the first to report successful application of this technique to adults with OSA. They demonstrated significant improvements in function after 3-mo of daily orofacial myofunctional exercises. In children, retrospective studies revealed that those who received functional orofacial re-education had long-term remission of OSA with no re-appearance of subtle orofacial dysfunction compared to children treated with adenotonsillectomy and/or RME without orofacial myofunctional re-education training [52,79,80].

Investigations of children with incomplete treatment and recurrence of SDB was shown to be associated with persistence of mouth-breathing during sleep as a primary finding [51,52]. The persistence of mouth-breathing during sleep resulted in ongoing breathing dysfunction for the many hours the children slept. Unfortunately, current forms of orofacial myofunctional re-education are difficult for children younger than 4-y of age who do not have sufficient attention spans, cannot perform the sophisticated exercises found in typical orofacial myofunctional treatment, and/or do not want to perform the requested exercises with consistency. Efforts have been made to find both active and passive re-education approaches for these young children, and this continues to be an area of research and study [81].

Current conclusion

OSA is related to the increased collapsibility of the UA during sleep. These series of investigations demonstrated that abnormal changes of anatomical supports in the upper airway increases the risk of collapse, which in turn leads to sleep apnea syndrome.

Beginning at birth, nasal breathing is not the only function with a very important role in orofacial development. Very early in life, the coordination between nasal breathing and sucking develops (sometimes referred to as suck-swallow-breathe synchrony). Sucking and swallowing are two significantly synchronized activities which also play an important role in the stimulation of structures involved in maxillary growth early in life. Near 6 mo of age, mastication is an added stimulus with development of an "active" swallowing function associated with the development of a cortico-geniculum pathway, and development of "praxia" involving tongue and swallowing [21,22]. Anomalies of these functions increase the risk of abnormal development in the bone structures supporting the UA. Dysfunctions lead to or worsen subtle changes in orofacial growth early in life. Such abnormalities have a greater impact during early childhood than later in life, since important development of the human face occurs particularly between birth and six years of age with a second peak during puberty.

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Abnormal orofacial growth, induced by dysfunction, leads to development of a smaller than typical upper airway with increased risk of collapse during sleep. There is a progressive worsening of dysmorphia and a slow worsening of sleep disordered breathing over time. While sleep apnea requires a sleep test with a significant amount of time for proper monitoring, sleep-related flow limitation may be the first indication of dysfunction. Therefore, abnormal breathing patterns should be looked for when performing PSGs in at-risk children.

The speed at which dysmorphism occurs is variable, and symptoms of SDB may be unrecognized for years. Apnea or hypopnea, with oxygen saturation drops, may be slow to show up in a PSG depending of the type and importance of the initial dysfunction. Dysmorphism has a negative impact on neurological development, and functions worsen overtime due to the slow impact on local receptors (i.e., the part of reflexology involved in maintaining the UA sufficiently open during sleep).

Factors such as local inflammation [82] induced by the dysfunctions and mouth breathing will add their negative effects leading to vicious cycles, and a progressive neurological impairment of the normal functioning of the reflexes active during the different sleep states may occur [83–85]. Mouth breathing is associated with progressive enlargement of tonsils [i.e., a secondary reaction] as shown in the premature longitudinal study. Histologic studies of enlarged tonsils have demonstrated an abnormal amount of inflammatory cytokines in situ, and a local inflammation is present. Investigation of blood inflammatory factors, not only TNF-alpha and high-sensitive CRP but also inerleukins 1,6,17 and 23 showed presence of abnormal elevation of these factors in the circulating blood [82]. Following T&A, preliminary data [86] indicate a significant decrease in these factors, with persistence of mild but abnormal elevation of some, such as Il-23, in children with residual low amount of apnea-hypopneas and persistence of mouth breathing during sleep.

In sum, the abnormal orofacial growth may have different genetically or environmentally induced etiologies; but recognition of the factors leading to orofacial dysfunctions and their treatments early in life may decrease the frequency of OSA – a syndrome that affect at least 7% of the pediatric population and spill over into adulthood.

Practice points

- There is a continuous interaction during childhood between oral-nasal functions and oral-facial growth. Impairment of orofacial growth always leads to increase risk of upper-airway collapsibility during sleep.
- Early in life identification of factors impairing the normal oral-nasal functions allow treating risk factors preventing secondary negative impacts on the oral-facial growth.
- Knowledge of mechanisms responsible for, and consequences of, oral-nasal dysfunctions allows early clinical recognition of children with potential risks and the appropriate treatment of these risks.
- Creation of units teaching mothers how to deal with the already existing dysfunctions (such as in prematurity) or how to avoid their development should be an important effort of neo-natal and early infant development services.

Research agenda

- Oral-nasal dysfunctions lead to changes in orofacial growth with creation of negative feedback loops. But such interaction leads also to development of stimulation of local inflammatory factors that are part of the negative feed-back loops: knowledge on the role of local inflammation of such interaction is currently limited. Also breakage of the identified negative feedback loops is a treatment goal; but currently treatment approaches are limited, and long term follow-up of most of the proposed treatments are lacking. The factors behind the variability of the speed at which the identified loops lead to the full blown syndrome are unknown; and their role in the severity of the adult form of the syndrome has to be determined.
- Investigation of normal fetal movements particularly during the last trimester of pregnancy coupled with fetal echography evaluating systematically the normal functioning of suction-swallow reflexes and absence of abnormal blockade of the lower face (including mandible) in the pelvis should be performed particularly initially in "at risk pregnancy".
- Creation of neo-natal units aimed at recognition and treatments of dysfunctions should be done. It should aim at education of mothers in collaboration with professionals to address the dysfunctions at birth or at time of recognition, with start of myofunctional therapy and usage of special feeding techniques calling upon usage of orthopedic nipples. Systematic evaluation of short and long term results of such efforts should be obtained.

Conflict of interest

The authors do not have any conflicts of interest to disclose.

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References

[1] Stoohs R, Guilleminault C. Snoring during NREM sleep: respiratory timing, esophageal pressure and EEG arousal. Resp Physiol 1991;85:151–67.
*[2] Arora N, Meskill G, Guilleminault C. The role of flow limitation as an important diagnostic tool, and clinical findings in mild sleep-disordered-breathing. Sleep Sci 2015;8:134–42.
[3] Powell NB, Mihaescu M, Mylavarapu G, Weaver EM, Guilleminault C, Gutmark E. Patterns in pharyngeal airflow associated with sleep-disordered breathing. Sleep Med 2011;12:966–74.
[4] Patil SP, Punjabi NM, Schneider H, O'Donnell CP, Smith PL, Schwartz AR. A simplified method for measuring critical pressures during sleep in the clinical setting. Am J Respir Crit Care Med 2004;170:86–93.
[5] Smith PL, Wise RA, Permutt S. Upper airway pressure-flow relationships in patients with obstructive sleep apnea. J Appl Physiol 1988;64:789–95.
[6] Marcus CL, McColley SA, Carroll JL, Loughlin GM, Smith PL, Schwartz AR. Upper airway collapsibility in children with obstructive sleep apnea syndrome. J Appl Physiol 1994;77:918–24.
[7] Marcus CL, Katz ES, Lutz J, Black CA, Galster P, Carson KA. Upper airway dynamic responses in children with the obstructive-sleep-apnea syndrome. Pediatr Res 2005;57:99–107.
[8] Arens R, McDonough JM, Corbin AM, Rubin NK, Carroll ME, Pack AI, et al. Upper airway size analysis by magnetic resonance imaging of children with

* The most important references are denoted by an asterisk.

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obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2003;167:65–70.
[9] Schwab RL, Pasirtein M, Pierson R, Mackley A, Hachadoorian R, Arens R, et al. Identification of anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med 2003;168:522–30.
[10] Jamieson A, Guilleminault C, Partinen M, Quera-Salva MA. Obstructive sleep apneic patients have cranio-mandibular abnormalities. Sleep 1986;9:469–77.
[11] Gaultier C, Guilleminault C. Genetics, control of breathing, and sleep-disordered breathing: a review. Sleep Med 2001;2:297–308.
[12] Aknin JJ, editor. La croissance cranio-faciale. Paris: SID Publ; 2007. p. 159–78.
[13] Som PM, Naidich TP. Illustrated review of the embryology and development of the facial region, part 1: early face and lateral nasal cavities. Am J Neuroradiol 2013;34:2233–40.
[14] Enlow Donald H. Facial growth. 3rd ed. Philadelphia: Saunders; 1990.
[15] Moss ML, Young RW. A functional approach to craniology. Am J Phys Anthropol 1960;18:281–92.
[16] Aknin JJ, editor. La croissance cranio-faciale. Paris: SID Publ; 2007. p. 1–254.
[17] Songu M, Adibelli ZH, Tuncyurek O, Adibelli H. Age-specific size of the upper airway structures in children during development. Ann Otol Rhinol Laryngol 2010;119:541–6.
[18] Mankarious LA, Goudy SL. Craniofacial and upper airway development. Paediatr Respir Rev 2010;11:193–8.
[19] De Coster PJ, Marks LA, Martens LC, Huysseune A. Dental agenesis: genetic and clinical perspectives. J Oral Pathol Med 2009;38:1–17.
[20] Levaillant JM, Bault JP, Benoit B, Couly G. La face fœtale normale et pathologique, aspects échographiques. France: Sauramps Medical Montpellier; 2013. p. 1–120.
*[21] Couly G, Levaillant JM, Bault JP, Benoit B, Kverneland B, Gitz L. Oralité du fetus. France: Sauramps Medical Montpellier; 2015. p. 1–138.
[22] Jean A. Brainstem control of swallowing neuronal network and cellular mechanisms. Physiol Rev 2001;81:929–69.
[23] Hooker D. The prenatal origin of behavior. New York: Hafner; 1952.
[24] Planas P. Rehabilitacion neuro-occlusal. Madrid (Spain): Salvat Editores SA; 1987. p. 1–287.
[25] Svensson P, Romaniello A, Wang K, Arendt-Nielsen L, Sessle BL. One hour of tongue-task training is associated with plasticity in corticomotor control of the human tongue musculature. Exp Brain Res 2006;173:165–73.
*[26] Komoda Y, Iida T, Kothari M, Komiyama O, Baad-Hansen L, Kawara M, et al. Repeated tongue lift movement induces neuroplasticity in corticomotor control of tongue and jaw muscles in humans. Brain Res 2015;1627:70–9.
[27] Doumenge R. Configuration de la voute palatine dans ses rapports avec les deviations de la cloison nasale. Ann Mal Oreille Larynx Nez Pharynx 1923;42:1057–68.
[28] Handelman CS, Osborne G. Growth of the nasopharynx and adenoid development from one to eighteen years. Angle Orthod 1976;46:24–36.
[29] Wolf G, Andernuber W, Kuhn F. Development of the paranasal sinuses in children: implication for paranasal sinus surgery. Ann Otol Rhinol Laryngol 1993;102:705–11.
[30] Schlenker WL, Jennings BD, Jeiroudi MT, Caruso JM. The effects of chronic absence of active nasal respiration on the growth of the skull: a pilot study. Am J Orthod Dentofacial Orthop 2000;117:706–13.
*[31] Cheng MC, Enlow DH, Papsidero M, Broadbent Jr BH, Oyen O, Sabat M. Developmental effects of impaired breathing in the face of the growing child. Angle Orthod 1988;58:309–20.
[32] Sitapara JB, Mahida JB, Mc Eroy TP, Elmaraghy CA, Deans KJ, Minneci PC, et al. Using the maxillary nasal angle to evaluate congenital nasal pyriform aperture stenosis. JAMA Otolaryngol Head Neck Surg 2015;141:539–42.
[33] Wormald R, Hinton-Bayre A, Bumbak P, Vijayasekaran S. Congenital nasal pyriform aperture stenosis is associated with surgical intervention, a pooled case series. Int J Pediatr Otolaryngol 2015;79:1802–5.
[34] Pirila-Parkkinen K, Pirttiniemi P, Nieminen P, Tolonen U, Pelttari U, Lopponen H. Dental arch morphology in children with sleep-disordered breathing. Eur J Orthod 2009;31:160–7.
[35] Gola R. Consequences de l'obstruction nasale chez l'enfant. Orthod Fr 2000;71:219–31.
[36] Neskey D, Eloy JA, Casiano RR. Nasal, septal, and turbinate anatomy and embryology. Otolaryngol Clin North Am 2009;42:193–205.
[37] Chauvois A, Fournier M, Girardin F. Reeducation des fonctions dans la therapeutique orthodontiques. Paris: S.I.D; 1991. p. 1–190.
[38] Harvold EP, Tomer BS, Vargervik K, Chierici G. Primate experiments on oral respiration. Am J Orthod 1981;79:359–72.
*[39] Miller AJ, Vargervik K, Chierici G. Experimentally induced neuromuscular changes during and after nasal airway obstruction. Am J Orthod 1984;85:385–92.
[40] Vargervik K, Miller AJ, Chierici G, Harvold E, Tomer BS. Morphologic response to changes in neuromuscular patterns experimentally induced by altered modes of respiration. Am J Orthod 1984;85:115–24.
*[41] Huang YS, Guilleminault C. Pediatric sleep apnea and the critical role of oral facial growth: evidences. Front Neurol 2013;3:184. http://dx.doi.org/10.3389/Fneuro.2012.00.184.
[42] Huang YS, Paiva T, Hsu JF, Kuo MC, Guilleminault C. Sleep and breathing in premature infants at 6 months of age. BMC Pediatrics 2014:14–303. http://dx.doi.org/10.1186/s12887-014-0303-6.
[43] Guilleminault C, Cummiskey J, Motta J, Lynne-Davies P. Respiratory and hemodynamic study during wakefulness and sleep in myotonic dystrophy. Sleep 1978;1:19–31.
[44] Cummiskey J, Lynne-Davis P, Guilleminault C. Sleep study and respiratory functions in myotonic dystrophy. In: Guilleminault C, Dement WD, editors. Sleep-apnea-syndrome. New York: AR Liss (Publ); 1978. p. 295–308.
[45] Guilleminault C, Huang YS, Glamann C, Li K, Chan A. Adenotonsillectomy and obstructive sleep apnea in children: a prospective survey. Otolaryngol Head Neck Surg 2007;136:169–75.
[46] Huang YS, Guilleminault C, Lee LA, Lin CH, Hwang FM. Treatment outcomes of adenotonsillectomy for children with obstructive sleep apnea: a prospective longitudinal study. Sleep 2014;37:71–6.
[47] Lee SY, Guilleminault C, Chiu HY, Sullivan SS. Mouth breathing, nasal disuse and pediatric sleep-disordered breathing. Sleep Breath 2015;19:1257–64.
[48] Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Mitchell RB, Promchiarak J, Simakajornboon N, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. Am J Respir Crit Care Med 2010;182:676–83.
*[49] Fitzpatrick MF, McLean H, Urton AM, Tan A, O'Donnell D. Effect of nasal or oral breathing route on upper airway resistance during sleep. Eur Respir J 2003;22:827–32.
[50] Fitzpatrick M, Driver H, Chata N, Vodu N, Girard A. Partitioning of inhale ventilation during sleep in normal subjects. J Appl Physiol 2003;91:883–90.
[51] Guilleminault C, Huang YS, Quo S, Monteyrol PJ, Lin CH. Teenage sleep disordered breathing: recurrence of syndrome. Sleep Med 2013;14:37–44.
[52] Guilleminault C, Huang YS, Monteyrol PJ, Sato R, Quo S, Lin CH. Critical role of myofascial reeducation in sleep-disordered breathing. Sleep Med 2013;14:518–25.
[53] Sullivan S, Li K, Guilleminault C. Nasal obstruction in children with sleep disordered breathing. Ann Acad Med Singapore 2008;37:645–8.
*[54] Lee SH, Choi JH, Shin C, Lee HM, Kwon SY, Lee SH. How does open-mouth breathing influence upper airway anatomy? Laryngoscope 2007;117:1102–6.
[55] Friedman M, Tanyeri H, La Rosa M, Landsberg R, Vaidyanathan K, Pieri S, et al. Clinical predictors of obstructive sleep apnea. Laryngoscope 1999;109:1901–7.
[56] Friedman M, Ibrahim H, Bass L. Clinical staging for sleep-disordered breathing. Otolaryngol Head Neck Surg 2002;127:13–21.
[57] Messner AH, Lalakea ML, Aby J, Macmahon J, Bair E. Ankyloglossia: incidence and associated feeding difficulties. Arch Otolaryngol Head Neck Surg 2000;126(1):36–9.
[58] Ricke LA, Baker NJ, Madlon-Kay DJ, DeFor TA. Newborn tongue tie: prevalence and effect on breast-feeding. J Am Board Fam Pract 2005;18:1–7.
[59] Hogan M, Westcott C, Griffiths M. Randomized, controlled trial of division of tongue tie in infants with feeding problems. J Paediatr Child Health 2005;41:246–50.
[60] García Pola MJ, González García M, García Martín JM, Gallas M, Seoane Lestón J. A study of pathology associated with short lingual frenulum ASSDC. J Dent Child 2002;69:59–62.
[61] Lalakea L, Messner AH. Ankyloglossia: the adolescent and adult perspective. Otolaryngol Head Neck Surg 2003;128:746–52.
[62] Marchesan QI. Lingual frenulum: classification and speech interference. Int J Orofacial Myol 2004;30:31–8.
[63] Defabianis P. Ankyloglossia and its influence on maxillary and mandibular development. (A seven year follow-up case report). Funct Orthod 2000;17:25–33.
*[64] Martinelli CR, Marchesan QI, Berretin Felix G. Longitudinal study of the anatomical characteristics of the lingual frenulum and comparison to literature. Rev CEFAC 2014;16:1202–7.
[65] Kotlow LA. Ankyloglossia (tongue-tie): a diagnostic and treatment quandary. Quintessence Int 1999;30:259–62.
[66] Yoon A, Zaghi S, Weitzman R, Ha S, Law CS, Guilleminault C, et al. Towards a functional definition of ankyloglossia: validating current grading scales for lingual frenulum length and tongue mobility in 1052 subjects. Sleep Breath 2017. http://dx.doi.org/10.1007/s11325-016-1452-7.
*[67] Guilleminault C, Huseni S, Lo LA. Frequent phenotype for paediatrics obstructive sleep apnea: short lingual frenulum. ERJ Open Res 2016;2:43–7. http://dx.doi.org/10.1183/23120541.00043-2016.
[68] Huang YS, Quo S, Berkoski JA, Guilleminault C. Short Lingual frenulum and obstructive sleep apnea in pre-pubertal children. Int J Pediatr Res 2015;1:1–5.
[69] Guimarães KC, Drager LF, Genta PR, Marcondes BF, Lorenzi-Filho G. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2009;179(10):962–6.
*[70] Camacho C, Certal V, Abdullatif J, Zaghi S, Ruoff CM, Capasso R, et al. Myofunctional therapy to treat obstructive sleep apnea: a systematic review and meta-analysis. Sleep 2015;38:669–75.
[71] Guilleminault C, Primeau M, Yuen K, Leger D, Metlaine A. Sleep-disordered breathing in Ehlers Danlos syndrome (a genetic model of OSA). Chest 2013;144:1503–11.
[72] Vogt K, Jalowayski AA, Althaus W. 4-phase-rhinomanometry (4PR)—basics and practice 2010. Rhinol Suppl 2010;21:1–50.
[73] Guilleminault C, Abad VC, Chiu HY, Peters BR, Quo S. Missing teeth and pediatric obstructive sleep apnea. Sleep Breath 2016;20(2):561–8. http://dx.doi.org/10.1007/s11325-015-1238-3.

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[74] Ben-Bassat Y, Brin I. Skeletodental patterns in patients with multiple congenitally missing teeth. Am J Orthod Dentofacial Orthop 2003;124:521–5.
[75] Shimizu T, Maeda T. Prevalence and genetic basis of tooth agenesis. J Dent Sci Rev 2009;45:52–8.
[76] Tavajohi-Kermani H, Kapur R, Sciote JJ. Tooth agenesis and craniofacial morphology. Am J Orthod Dentofacial Orthop 2002;122:39–47.
[77] Lisson JA, Scholtes S. Investigation of craniofacial morphology in patients with hypo and oligodontia. J Orofac Orthop 2005;66:1197–207.
[78] Solow B, Sandham A. Cranio-cervical posture: a factor in the development and function of the dentofacial structures. Eur J Orthod 2002;24:447–56.
[79] Moeller J, Paskay LC, Gelb ML. Myofunctional therapy: a novel treatment of pediatric sleep-disordered breathing. Sleep Med Clin 2014;9:235–9.
[80] Villa MP, Brasili L, Ferretti A, Vitelli O, Rabasco J, Mazzotta AR, et al. Oropharyngeal exercises to reduce symptoms of OSA after AT. Sleep Breath 2015;19:281–9.
[81] Chuang LC, Lian YC, Hervy-Auboiron M, Guilleminault C, Huang YS. Passive myofunctional therapy applied on children with obstructive sleep apnea: a 6-month follow-up. J Formos Med Ass 2016. http://dx.doi.org/10.1016/j.jfma.2016.08.002.
[82] Huang YS, Guilleminault C, Hwang FM, Cheng C, Lin CH, Lee LA. Inflammatory cytokines in pediatric obstructive sleep apnea. Medicine 2016;95:40–8.
[83] Friberg D, Ansved T, Borg K, Carlsson-Nordlander B, Larsson H, Svanborg E. Histological indications of a progressive snorers' disease in an upper airway muscle. Ann J Respir Crit Care Med 1998;157:586–93.
[84] Kimoff RJ, Sforza E, Champagne V, Ofiara L, Gendron D. Upper airway sensation in snoring and obstructive sleep apnea. Am J Respir Crit Care Med 2001;164:250–5.
[85] Guilleminault C, Huang Y, Kirisoglu C, Chan A. Is obstructive sleep apnea syndrome a neurological disorder? A continuous positive airway pressure follow-up study. Ann Neurol 2005;58:880–7.
[86] Huang SH, Guilleminault C. Inflammatory factors pre and post adeno-tonsillectomy in pediatric OSA sleep-apena. Sleep 2017;(Suppl.) [in press].
[87] Elad D, Kozlovsky P, Blum O, Laine AF, Po MJ, Botzer E, et al. Biomechanics of milk extraction during breath-feeding. PNAS 2014;111:5230–5. http://dx.doi.org/10.1073/pnas.1319798111.

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