Upper Airway Resistance Syndrome in Children: A Clinical Review

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Upper airway resistant syndrome (UARS) is more common in children than is obstructive sleep apnea syndrome (OSAS). Age will color the symptoms associated with the syndrome. UARS must be looked for in families with adult sleep-disordered breathing. Polygraphic recording during sleep will show flow limitation with usage of nasal cannula/pressure transducer system, but the abnormal breathing during sleep may be indicated also by burst of tachypnea without saturation drops. Esophageal pressure monitoring may be the only way to confirm a suspected diagnosis. A mild developmental anomaly of the craniofacial skeleton is often seen in these children even in the presence of enlarged tonsils and adenoids. Children with sleep-disordered breathing should have a maxillomandibular examination to assess the need for orthodontic treatment to expand the oral cavity.

HISTORICALLY, obstructive sleep apnea syndrome (OSAS) was the first sleep-disordered breathing syndrome described in children.[1] However, by 1982, it was reported that prepubescent children might present with similar symptoms as the one described for OSAS, but apneas and hypopneas were not noted and oxygen saturation drops were mostly absent.[2] In this initial report, it was emphasized that children presented increased respiratory effort as monitored by esophageal pressure or abnormal breathing frequency. The notion that apneas were much less frequent in children (particularly prepubescents) than in adults was progressively accepted, and in 1996[3] this finding was acknowledged in recommendations from the American Thoracic Society (ATS) on polygraphic recordings in children. The fact that abnormal breathing patterns during sleep may not be associated with an interruption of naso-oral flow for longer than two breaths has received less attention.

The initial report in 1982 did not give a name to this finding for some time. When a similar finding was made in adults based on the associated measurement of airway resistance, we coined the term "upper airway resistance syndrome" (UARS) to attract the attention of clinicians to this phenomenon.[4] The issue at stake is that apneas and hypopneas, defined in children as events lasting longer than two missed breaths, and most commonly associated with some change in oxygen measurement (and, for some, end tidal CO_2 increase),[5,6] are not the most common abnormal breathing patterns during sleep.

A difficult issue in children is that clinical symptoms and clinical presentations are very different during infancy (artificially defined as the first 12 months of life), during the "toddler age" (again artificially defined as 12 to 48 months), during prepubescent childhood, (from 48 months until the appearance of Tanner stage 2[7] signs), and teenagers (12 years and up). There are few, if any, differences between a teenager and a young adult when considering the subject presented here. However, presentations are notably different between the three other age-related subdivisions.

GROWTH OF THE CRANIOFACIAL COMPLEX

The craniofacial skeleton grows very quickly during early childhood. It is this skeleton that will support the upper airway. By 4 years of age, 60% of the adult face is built and by 12 years of age, just before the onset of puberty, about 90% will be developed.

Puberty is associated with large hormonal changes, particularly involving sexual and steroid hormones. Testosterone is secreted more in boys than in girls, but these drastic hormone changes have a significant effect on muscle mass and mucous. If one considers the muscle mass that constitutes the tongue and pharyngeal muscles, it is a huge mass for the skeleton-defined space in which it resides. Interestingly, this mass will abruptly grow with hormonal secretion after most of the adult craniofacial skeleton is already in place. One can easily see how a mismatch may have consequences on the posterior airway space (PAS), defined as the airway behind the base of the tongue,

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limited inferiorly by the superior part of the hyoid bone. To understand breathing during sleep, one must have some familiarity with upper airway development.

UPPER AIRWAY DEVELOPMENT

There is much we do not yet know. The upper airway evolves mostly from the second, third, and fourth branchial arches. During fetal life, many factors seem involved in its development. The idea that genetic factors are involved in craniofacial development was established by the late 1950s, but we still lack substantial information on the genes involved and their chains of interactions. The overall growth of the brain has an impact on the size of the folds that represent the branchial arches, and any brain insult that decreases brain size may lead to an abnormal development of the upper airway. This explains the many (over 150) congenital syndromes associated with some type of brain injury during fetal life and abnormal breathing during sleep (sometimes also while awake).

Genetic factors[8] may explain the wide variety in the magnitude of ventilatory responses to hypoxia and hypercapnia in normal subjects. A recent study showed a high degree of heritability in peripheral chemoreceptor response to both gas challenges in monozygotic twins during infancy compared with dizygotic twins exposed to similar environmental stimuli. Recent epidemiologic studies have shown that sleep-related breathing disorders, such as OSAS, cluster within families. The presence of sleep-related upper airway obstruction syndromes is found not only in several generations but also in cousins and other descendents of siblings of index cases. Familial aggregation is shown to be dependent on age, gender, snoring, and body mass index (BMI).[8]

The craniofacial complex involves the maxilla, the mandible, and the mandibular growth. There are two extremes in the shape of the head: dolichocephalic and bradycephalic. The dolichocephalic extreme involves a higher anterior facial height in the lower third of the dentofacial skeleton, steep mandibular plane, and a higher than expected arched palate. In the former, there is a tendency towards a mandibular retrusion and retrograthic profile. There are normally compensatory mechanisms that change drift of maxilla and mandible to keep a normal airway. However, these mechanisms can be affected by environmental factors that have been well studied in the Rhesus monkey.

An induction of abnormal nasal resistance was obtained with nose occlusion with placement of silicon cones in each nostril, held back in the nose by a thread. This nasal resistance leads to immediate changes in the electromyogram recorded on genioglossal, geniohyoid, digastric, lip elevator, and other muscles. These muscles are part of the upper airway and involved in the act of breathing. They are also the muscles involved in the normal growth of the mandible (which is induced by the continued muscle contractions delivered on the bone). When present at birth, abnormal nasal resistance leads to abnormal mandibular growth, nasal disuse, and mouth breathing, particularly during sleep. The combination of abnormal mandibular growth due to abnormal EMG discharges and mouth breathing lead to morphometric changes with abnormal maxillomandibular development (increase in anterior face height, anterior cross bite, maxillary over-jet, decrease in maxillary arch length, narrowing of dental arch) and secondary abnormal upper airway size (see review by Gaultier and Guilleminault[8]).

The most common environmental factors leading to increased nasal resistance are allergy, infection, and abnormal size of lymphoid tissues located in the region (which may be influenced by allergies and airway and ear infections). Undoubtedly, individuals with genetic factors leading to small upper airways will have the greatest risk of being affected by environmental factors. These are the associations of the different risk factors for small upper airway.[8]

ABNORMAL BREATHING AND ABNORMAL UPPER AIRWAY RESISTANCE DURING INFANCY

Symptoms

There are no clear, consistent symptoms during the first 6 months of life. Most infants have been identified after experiencing an abnormal breathing event, often, but not always, seen while the infant is supposedly asleep. Initially the events were labeled "near miss SIDS" events[9]; they are now part of what has been defined as an "apparent life-threatening event" (ALTE).[10] Not all ALTE events are related to abnormal breathing during sleep, as shown in a recent study, but in the cited study they represented a bit more than 50% of the ALTEs.[10]

Often these ALTEs were reported at the time of a congested nose described as a "small cold" by the parents. The infant may have also presented "noisy breathing," and sometimes parents even mentioned "light snoring" before the event. Sweat during sleep was observed mostly around the neck but was sometimes more widespread. When the infant began to move, more agitated sleep is indicated, sometimes demonstrated by more awakenings during the night and being "more fussy" during sleep. This picture may be associated with more food regurgitation, which leads to the possibility of esophageal reflux.

Polysomnography

Polygraphic monitoring during nocturnal sleep was for years performed with nasal and oral thermisters, and sometimes with nasal cannula measuring end-tidal CO_2. These monitoring approaches have been shown to be less than adequate to investigate at-risk infants. Bu they have often shown presence of rare short obstructive events and an abnormal number of so-called "central apneas" lasting longer than two breaths and commonly leading to "sleep disturbance," or activation of brainstem reflexes with short live tachycardia.

Usage of esophageal pressure (Pes) measurement,[11,12] with usage of fluid-filled sensors the size of a feeding tube for a premature infant, and usage of pediatric nasal cannula/pressure transducer systems (Protech, Woodinville, WA), has shown that many of those infants presented more abnormal breathing patterns during sleep than thought to be present when using only thermisters. These patterns are seen more consistently than the less common obstructive apneas previously reported.

These polygraphic patterns are as follows:

1. Presence of increased effort lasting more than four breaths as indicated by measurement of Pes. "Abnormal effort" was defined as an abnormal inspiratory effort demonstrated by a more negative end-inspiratory Pes pressure. "Abnormal breathing" occurred when the peak effort was more negative than the mean + 2 SD of the child nonobstructed breathing peak end-inspiratory Pes on the recording. The increased effort may be associated with a crescendo type pattern, that is, a more negative end-inspiratory Pes with each successive breath,[13] or it may be associated with a successive array of abnormal breaths with similar peak end-negative inspiratory breaths (this pattern has been called a "sustained abnormal effort"[14]). The abnormal patterns end with a visual EEG arousal, and if no arousal is seen, it is followed by an abrupt decrease of effort called a "Pes reversal." [13]
2. The second pattern is an abrupt increase of effort indicated by a more negative peak end-respiratory effort, immediately followed by an absence of diaphragmatic movement lasting two or more breaths.[5] This pattern was called "central apnea" before, as Pes was not measured, but the diaphragmatic event is in fact secondary to the abrupt increase of effort; the abnormality precedes the diaphragmatic response.
3. The last pattern, initially seen more in rapid eye movement (REM) sleep, but even more indicative of abnormal breathing when seen in non-REM (NREM) or Quiet sleep, is an abrupt increase in breath frequency without increase in effort.[2,15] There is always a slight decrease in tidal volume with REM sleep, particularly in association with phasic event of REM sleep. But this change may normally lead to an increase of breathing frequency of one to two breaths/minute compared with Quiet sleep. A clear tachypnea will be seen with increase in breath frequency of four or more breaths per minutes (in young children) and three or more breaths per minute in older subjects. As "breathing frequency $\times$ tidal volume = minute ventilation," one may understand why this pattern may be seen: The increase in breathing frequency will compensate for the decrease in tidal volume. These events are not associated with oxygen saturation (pulse oximeter) or oxygen tension (transcutaneous Po_2 electrode) drops of any validity. This mode of defense leaves these infants at risk for significant desaturation if infection or other breathing problems occur, as they have already increased their breathing frequency and cannot call on this defense mechanism further.

Usage of end tidal CO_2 nasal cannula has indicated that some of these above-mentioned categories of events may be associated with some slight increase in CO_2 during the recovery breath following the Pes reversal,[5,6] but a systematic study has shown that end tidal CO_2 missed many increased effort breaths.

Experience with the nasal cannula/pressure

transducer takes less time to accrue than with other techniques. The nasal cannula/pressure transducer system tracing may indicate nasal flow limitation and a switch to oral breathing, which is always abnormal in a child, but there are events where the nasal cannula tracing is not demonstrative and Pes measurement is the only appropriate diagnostic tool.

Issue of Tonsils

The only study where systematic clinical investigation of the craniofacial features and investigation of the upper airway were done was reported by our group.[10,16] It turned out that the older the infants the easier it was to recognize small airway and abnormal maxillomandibular growth.

One of the questions raised is as follows: are the palatine tonsils always enlarged? Often the response is that they are too large for the existing space: the issue is more one of relative size than absolute "enlargement." This is important, as lymphoid tissues in a small space will lead to displacement of the tongue muscles. This will induce a secondary displacement of the point of impact of the muscle contractions on the maxillomandibular complex, and this change will have an impact on the appropriate growth, and growth in the appropriate axis, of the mandible (and the maxilla to some degree). Finally, investigation of the nose may show turbinate enlargement.

Treatment

During very early infancy, the question is largely unresolved. As shown below, many of these infants will have worsening of their clinical symptoms and will have more craniofacial feature changes,[10] earaches, upper airway infections that may become more chronic, and tonsillitis, which may be obvious with aging.[17] Also, impact on their autonomic nervous system with a great increase of vagal tone, which we have documented in older children, (see below) is probable.

Aggressive treatment of allergies and UA infection is always done. Recommending that the child sleep on his or her side is also important, possibly using some type of harness. Nasal continuous positive airway pressure has been tried with success in the most severe cases.[18] However, there is a risk of impacting the growth of the maxilla with the apparatus,[19] and growth of the skeleton must be observed closely. Presence of enlarged turbinates may be an indication for radiofrequency treatment, which we have found to be successful in older infants without any negative consequences.

Considering the issue of relative growth and interaction between normal breathing and normal skeletal development, we have taken tonsils out in infants 10 months and older. It is obvious that these infants will need follow-up to see how their skeleton is developing and if allergies or infections will lead to the recurrence of mucosal or lymphoid tissue growth.

THE TODDLER

Symptoms

Nocturnal symptoms are more obvious. The child may not sleep through the night, disrupting the parents' sleep by waking up crying, which leads to more behavioral problems related to parental response. Thumb sucking may be an important factor: the pressure exercise of the thumb may encourage some tongue repositioning and the combined maneuver of pressure and sucking can decrease the initial inspiratory resistance, particularly if mouth breathing is present (appropriate treatment of the breathing problem will help in stopping thumb sucking). Sleep terrors are a consequence of sleep disruption. To a lesser degree, sleep talking may occur. Agitated sleep is also frequent, associated with sweating, which will vary in severity depending on the fluctuation of nasal resistance. The head may be in hyperextension and sleeping position is more commonly on the abdomen, sometimes in the so-called "Mohammedan position," that is, knee under the belly with "butt" up, will be noted night after night. There is at least intermittent mouth breathing and intermittent snoring. Enuresis is variable in incidence but common.[2,5,20]

The family may report a positive history of recurrent earaches, UAR infections and respiratory allergies. It is difficult to assess sleepiness as napping is still occurring in controls, but the child is often hard to wake up in the morning and can fall asleep easily during quiet but interesting situations. The behavioral problems may be prominent: from rebellious attitude, unexplained aggressiveness towards peers, difficulty maintaining attention, and some degree of hyperactivity, to significant shyness, evidence of abnormal level of anxiety (anxiety is a well-known consequence of abnormal

nasal breathing), and hyperactivity. The behavioral problems impact the learning of social clues that began at this age. More uncommonly, the child may complain of intermittent headaches or may wake up during the night with regurgitation (rarely vomiting).[2,5,20]

Clinical evaluation may demonstrate the typical features of dolichocephaly. The child may be an intermittent mouth breather while awake. High and narrow hard palate, narrow dental arches, and abnormal development of mandible and maxilla may be recognized. Soft palate may be descending low with uvula behind base of tongue. Lymphoid tissues (tonsils and adenoids) and nasal turbinates may be clearly enlarged. Tonsillitis may be present. Sometimes lymphoid tissues are not very pathologically affected, but once again their size relative to the airway space may be too much.[2,5,8,20]

In summary, craniofacial skeleton and UA soft tissues are the two dominant parts of the clinical evaluation. Body growth retardation may occur but to a lesser degree than with OSAS.

Polysomnography

The polygraphic features outlined in infants will be seen here too. Once again, apnea is very uncommon, but tachypnea is frequently noted, not only during REM but also NREM seep. Increased effort is well documented with Pes, associated or not with flow limitation at nasal cannula/pressure transducer. Crescendos and abnormal "sustained effort" segments are easily recognized (Figs 1 through 3).

Treatment

The most common treatment is tonsillectomy, with or without adenoidectomy. The Ear, Nose, and Throat (ENT) specialist may have to be educated on the importance of a good airway, as tonsils may only impair breathing during sleep due to the overall smallness of the airway.

The most important element to remember is that if decrease in nasal and upper airway resistance improve air exchange and may help craniofacial

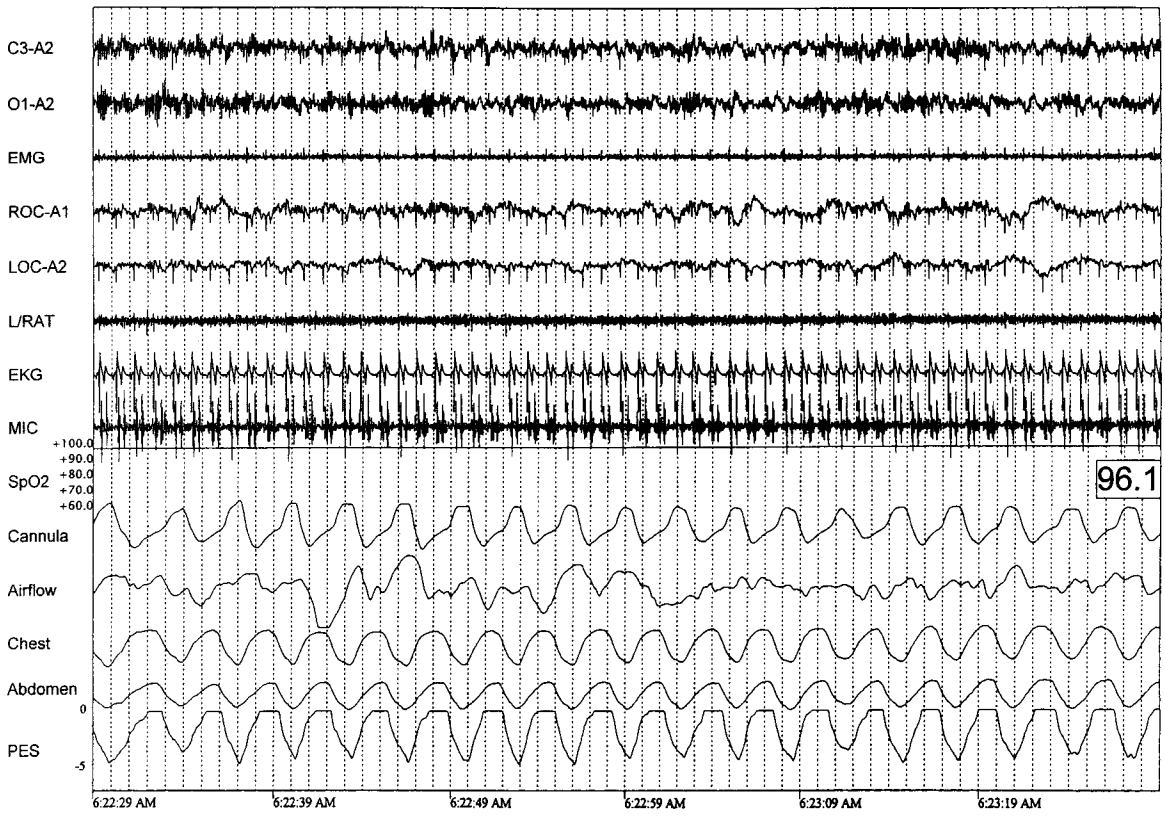

Fig 1. Normal breathing close to sleep onset in a 7-year-old boy. The respiratory rate is 19 breaths per minute, the peak end-inspiratory esophageal pressure is −4 cm H_2O. The duration of the tracing is 60 seconds.

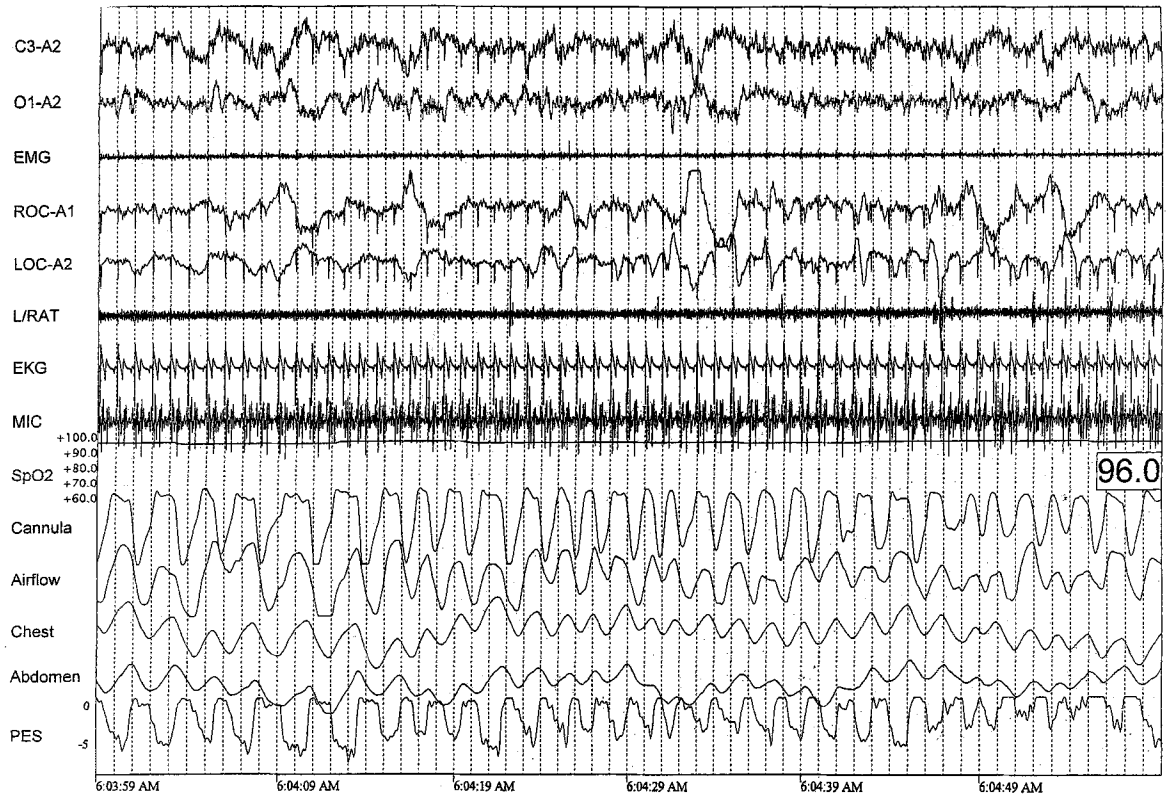

Fig 2. Breathing during REM sleep in the same boy as in Fig 1. The duration of the tracing is 60 seconds again. Note the tachypnea, the respiratory rate is 33 breaths per minute, the saturation does not change, there is no significant increase in respiratory effort as indicated by esophageal pressure monitoring. The tachypnea indicates the abnormality of breathing.

skeletal growth, the morphologic changes that may have occurred may not spontaneously regress. Systematic orthodontic evaluation by an orthodontist educated on sleep-disordered breathing will be needed.

THE PREPUBESCENT CHILD

Referrals at this age come from two dominant sources: school and orthodontists educated on sleep disorders.

Symptoms

The most common symptoms are hyperactivity, difficulty maintaining attention, difficulty performing in school, reports of daytime tiredness and, more rarely, sleepiness. There may also be difficulty with peers and abnormal social interaction due to aggressiveness. Teachers will sometimes describe the child as "being absent," suspect drug use, and recommend medical help be sought.[2,5,20]

A positive history of loud snoring, agitated sleep with continuous movements, difficulty getting up in the morning, abnormal nocturnal sweating, intermittent morning headaches, persistent or reappearing enuresis, sleep talking, sleep walking, sometimes associated with "nightmares" or sleep terrors, and presence of bruxism are the most common nocturnal symptoms. The interviews indicate quite a variable association of daytime and nighttime complaints.[2,5,20]

Orthodontists will refer patients to a sleep center if a history or signs of bruxism or presence of abnormally small maxilla or mandible associated with enlarged tonsils are seen, particularly if parents report positive history of snoring.

Clinical Evaluation

The clinical evaluation will show findings of similar to those seen in toddlers: impact on body growth is variable from very prominent to absent. Often one may see identification on the side of the tongue or cheek mucous due to accidental biting,

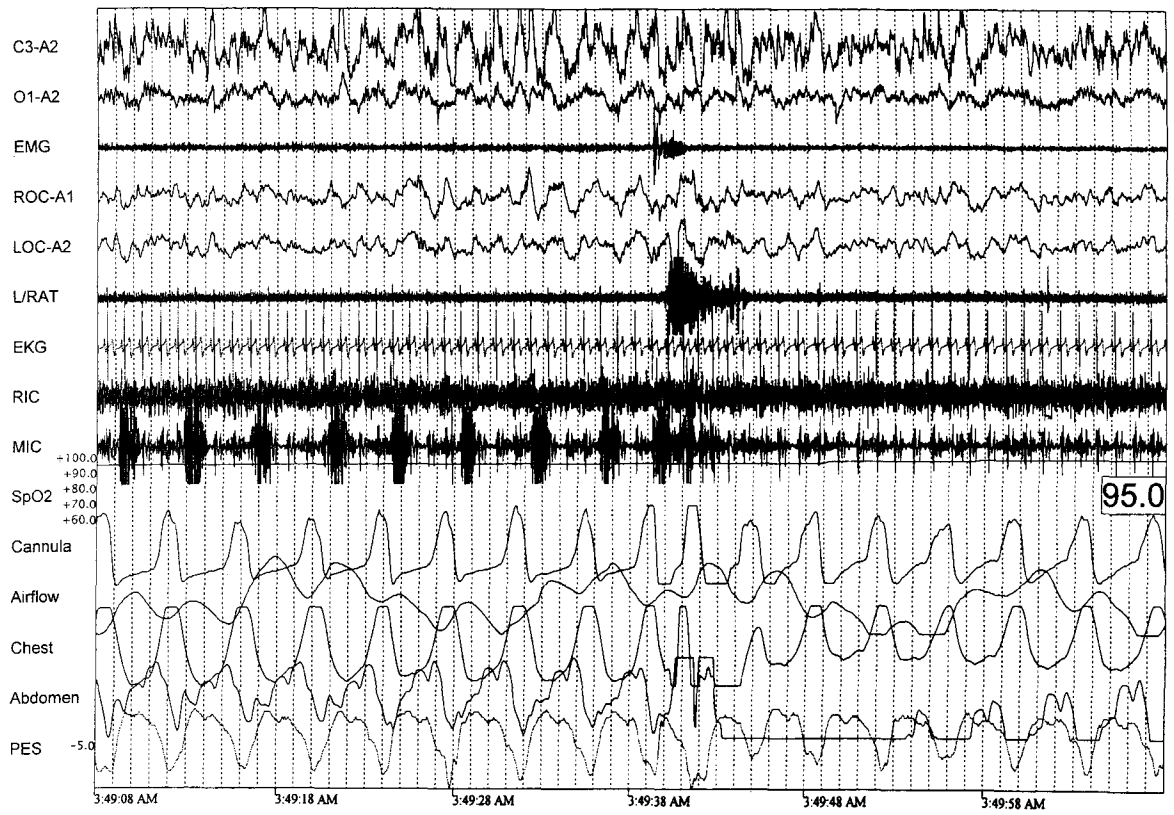

Fig 3. Example of increased respiratory effort during sleep in the same 7-year-old boy during stage 2 NREM sleep. Note the progressively more negative esophageal pressure (Pes) at peak end inspiration (Pes channel). Pes reaches −15 cm H_2O. There is no oxygen saturation drop. An EEG arousal can be seen at the end of the abnormal breathing pattern, with a drop in respiratory effort, indicated by a less negative esophageal pressure at peak end inspiration: this is called a "Pes reversal" (right side of tracing). Snoring is present before the arousal ("mic" for "microphone" channel). The child presents continuous snoring during NREM sleep, complains of fatigue in the late afternoon, and the kindergarten teacher has mentioned to the parents that their son is falling asleep around 1:00 PM and needs a nap, otherwise he becomes very aggressive and irritable. Obstructive sleep apneas are never observed in the recording. The duration of the tracing is 90 seconds.

particularly with bruxism. Pectus of the thorax may be seen, related to the degree of inspiratory effort during sleep. Polygraphic recordings show findings similar to those seen on toddlers.

Autonomic Nervous System Dysfunction

In children with familial history of sleep-disordered breathing, reports of signs of mild autonomic dysfunction can be obtained in 8- to 12-year-olds with probing. It consists of cold hands, cold feet, and reports of light-headedness (and sometimes dizziness) when abruptly bending and standing up. None of the children have reported fainting when abruptly standing up from awakening as opposed to teenagers.

Blood pressure (BP) measurements during quiet wakefulness reveal presence of a small subgroup of subjects with much lower diastolic pressure than the others. The most common group has BP of 105/90//70/60, but a small subgroup—mean age: 9 years 10 months—presents diastolic BP, seated at rest for 15 minutes, oscillating between 55/42 mm Hg. The eight identified individuals (four boys) were small for their age (between 30^{th} and 55^{th} percentile for height and between 30^{th} and 45^{th} percentile for weight) but were not the only subjects in these height and weight ranges with UAR during sleep. As the low diastolic pressure may have been related to their body habitus, these eight children with low BP at rest were submitted to a tilt test. They were compared with an age and body mass index (BMI) matched UARS subjects without low BP and a group of age- and sex- but not BMI-matched normal subjects. The tilt test was

performed just after morning awakening after a night spent in the laboratory with polygraphic monitoring and before standing up. In six of the eight low BP subjects, results indicated, using Finapress (Ohmeda, Boulder, CO) to measure BP, a much more important systolic BP drop than in both the matched UARS with normal BP and the normal controls. The mean systolic BP readings obtained supine before the test were respectively 91 ± 4 mm Hg (normal controls), 89 ± 3 mm Hg (normal UARS), and 87 ± 5 mm Hg (low BP UARS). At the end of the tilt test, performed in 3 seconds, with head up, no feet support, and loose belt to maintain body position at 80 degrees up, systolic BP presented a mean drop of 5 ± 2 mm Hg for normals, 6 ± 3 mm Hg for normal UARS, and of 13 ± 3 mm Hg for low BP group. This finding was significantly different (ANOVA P = .001). Simultaneous measurement of heart rate showed that there was a normal biphasic heart response with the tilt test, with an initial tachycardia peaking near beat 15 followed by a bradycardia near beat 30 following end of tilt test. This finding eliminated presence of autonomic neuropathy.

The other clinical difference between the two UARS subject groups was the severity of the maxillomandibular involvement. In the normal BP UARS group, the airway was narrow. This was clearly due to enlarged tonsils with or without adenoids, but the skeleton was mildly affected if at all. The low BP subjects presented important skeletal participation in the occurrence on the small upper airway with clear retroposition of mandible, high and narrow hard palate, long face, cross bite. Photographs from younger ages indicated presence of abnormal craniofacial features: long face and small chin, since a young age.[10] Medical history suggested symptoms of abnormal breathing during sleep having occurred very early on. Investigation of family history demonstrated presence of sleep-disordered breathing associated with craniofacial skeletal involvement in at least one of the parents.

Treatment

Treatment involved tonsillectomy with or without adenoidectomy and systematic orthodontic evaluation. If needed, slow maxillary distraction, maxillary and or mandibular expansion, dental appliance (ie, Delaire mask) were used. It was important to have direct contact with the orthodontist to emphasize that goals were skeletal expansion and that retrusive treatment was absolutely counter indicated.

THE TEENAGER

Symptoms

Sleep-related symptoms are the most common cause of consultation in our clinic. Teenagers are difficult to wake in the morning, which leads to missed morning classes, phase-delay symptoms, daytime tiredness, and fatigue at the end of the day. Daytime sleepiness particularly in quiet situations, mid-afternoon difficulty concentrating, and a decrease in school performance are the most common cause of referral. Daytime anxiety is much more common here than any other psychiatric symptom. Enuresis is rare, but somnambulism more frequent. Postnasal drip and nasal congestion in the morning are also commonly reported. Dentists may have reported evidence of bruxism, and it is often at that age that wisdom teeth are mentioned to be a problem and bilateral extraction recommended due to "small jaw."

Other Evaluations

Clinical evaluation and polygraphic recordings bring findings already outlined just above, including a history of autonomic dysfunction.

Medical history may reveal that tonsillectomy and adenoidectomy may have been performed in early childhood, but without appropriate follow-up and absence of associated orthodontic treatment. And sometimes there is a history of orthodontic treatment during teenage years, but without any understanding of airway problems and with realignment of upper teeth with retrusion techniques.

As craniofacial growth has largely occurred, it is in these individuals that surgical approaches may be most frequently considered. The appropriate investigation of the local anatomic features is needed as turbinate, soft palate, and skeletal treatments (from ostetomy to distraction osteogenesis) are available.[21,22]

CONCLUSION

UARS may lead to significant clinical symptoms related to the sleep disruption induced by repetitive breathing efforts. It may be difficult clinically to distinguish UARS from OSAS and appropriate-polysomnography will be needed. One of the most

interesting features is the autonomic nervous system dysfunction seen in some of these young subjects. UARS patients are mostly normal weight, even sometimes underweight. They often present craniofacial skeletal anomalies, they may be seen in families with anatomic risk factors, and will not present the repetative small Sao_2 drops seen with OSAS. Their abnormal efforts do not lead to sympathetic activation, but, as studied experimentally by St. Croix et al[23] and Seals et al[24] and as suggested by investigation in adults,[25] to a sympathetic deactivation and enhancement of vagal tone in subjects with longstanding abnormal breathing efforts during sleep during childhood. It is important to recognize the problem early in life to stop its evolution.

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