Sleep Disorders in Chronic Fatigue Syndrome

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Doi: 10.5958/j.0973-340X.7.2.007

From the days when William Osler, published ‘The principles and Practice of Medicine’ printed by D Appleton and company in 1892, the description of chronic fatigue syndrome (CFS) as neuroasthenia, a condition of weakness or exhaustion of the nervous system, has been popularly known. He described that patients will have sleeplessness, mood changes and weariness on least exertion, the aching in the neck and local tenderness in the spine. This was the first description of CFS.

Most patients with CFS often complain about non-refreshing sleep. When sleep dysfunction disturbs their day-to-day activities, they need to attend a sleep clinic. Improvement in sleep quality in these patients will have positive effects on the sense of well-being.

Patients with CFS having a good night’s sleep have less complaints during the day. Disturbances of internal biological clock manifest as fatigue, poor concentration and sleep disturbances, and in CFS patients, a role of circadian pattern abnormality is detected. Daytime fatigue and sleepiness with rapid eye movement REM abnormalities are common in patients with CFS. In this group of patients, there is also increased physiological sleep. To know the prevalence of primary sleep disorders in CFS a study was done on 46 patients who underwent all night polysomnography and Multiple Sleep Latency TestMSLT. In all, 46% showed apnoea hypopnoea index AHI >5 and 5% showed evidence of periodic leg movement syndrome PMLS.

The diagnosis of CFS is not easy. The criteria for diagnosis are 1. Clinically unexplained persistent or relapsing fatigue of at least 6 months duration results in reduction in levels of occupational, educational, social or personal activities and concurrent occurrence of at least four accompanying symptoms: post-exertional malaise, unrefreshing sleep, significant impairment in memory, concentration, headache, muscle pain, joint pain, sore throat and tender lymph nodes. Unrefreshing sleep is common in all CFS patients. Physical examination must be documented by a physician on at least two occasions at least one month apart who should look for low-grade fever, non-exudative pharyngitis and for palpable or tender anterior cervical posterior cervical or axillary lymph nodes, which should be less than 2 cm in diameter.

The problem with CFS is whether it is a pathologically discrete entity as opposed to a debilitating, but nonspecific condition shared by many different entities. The association between restless leg syndrome (Ekbom syndrome) and CFS is well documented. One of the major complaints the CFS patients have is pain in legs.

The sleep apnoea and CFS co-exist together with mild psychological problems and can be considered as comorbidity. Drugs like sodium oxalate in neurology seems to produce good relief giving the researchers to postulate that good response to CFS suggests a disturbance of sleep similar to narcolepsy in people with CFS or fibromyalgia. Further studies are going on to know the precise cause of CFS.

Study by Spitzer and colleagues also indicate in their CFS sample a very high incidence (58%) of previously undiagnosed primary sleep disorder such as sleep apnoea/hypopnoea syndrome and restless legs/periodic limb movement disorder.

The circadian patterns of activity, sleep and cortisol secretion in patients with CFS show no circadian rhythm.
disturbances, but role of automatic activity in the experience of the unrefreshing sleep warrants more studies9. Autonomic disturbances during sleep may be one of the reasons for the daytime disturbances during sleep.

Other causes of poor sleep quality may be due to automatic hyper arousal, perceived stress and pain. Vagal induced cardiac changes in heart rate could explain the biological correlate of poor sleep in CFS patients10,11.

In some of the CFS patients, the truncated RNase-L fragments act as unregulated cellular components and cut cellular RNA, which increases immune cells suicide rate and opens the door to opportunistic infections. This will also cause dysregulation of ion channels in many cell types, which result in unexplained sweats, transient hypoglycemia, and reduction of pain sensitivity threshold, depression, visual problems, sleep disturbances and hypersensitivity to toxic chemicals. This may be one of the causes for unexplained signs and symptoms in CFS patients. The low-molecular-weight RNase-L will produce channelopathy with low body potassium, metabolic alkalosis and hyperventilation. These people may have polyuria, central fatigue and sleep disturbances.

Patients with CFS often report that excretion makes the symptoms worsen and people thought it may be due to the underlying sleep disorder. CFS patients, as a group, always had sleep disturbance; but after doing exercise12,13,14,15 they reported less sleepiness. Exercise helps CFS patients to reduce fatigue. It is now advisable to give physician charted exercise programmes for CFS patients in a clinical setting.

In most of the CFS cases, the sleep disturbances are in the following order: periodic movement disorder, excessive daytime sleepiness, apnoea and narcolepsy. The objective sleep disturbance is common in CFS16. It is proven beyond doubt that all patients with CFS should undergo polysomnography to rule out sleep disorders so that their treatment and activities of daily living can be scheduled better.

In sleep studies of patients with the ‘fibrositis syndrome’ and healthy subjects undergoing stage 4 sleep deprivation, it was observed in both groups the anomalous presence of alpha rhythms in the non-rapid eye movement sleep EEG. This phenomenon has been then termed as alpha-delta sleep18.

Cyclic alternating pattern (CAP) was found in 65% in fibromyalgia patients versus 45% in controls and hypothesised that CAP in CFS may be a result of chronic pain, reducing sleep efficiency, and causing more CAP and more arousals and also increases the occurrence of periodic breathing19. Upper airway resistance syndrome is now considered the same as CAP20. Repetitive increases to airflow within upper airway lead to brief arousals and daytime somnolence. The people do not meet the criteria of sleep apnoea. In this study, manometric and pneumotachographic measurements are the gold standard for the diagnosis of this syndrome. This is mainly seen in women.

Periodic leg movements are due to repetitive cramping or jerking of legs during sleep. It can range from a small movements in the ankles and toes to wild flailing of all limbs. This affects about 60% of CFS patients and is more common in females21. Clinicians should routinely query CFS patients regarding RLS symptoms and treatment of RLS can improve sleep and quality of life of these patients.

In patients with CFS, polysomnography is indicated when a sleep-related breathing disorder or periodic limb movement disorder is suspected, initial diagnosis is uncertain treatments fail or precipitous arousals occur with violent or injurious behaviour. Polysomnography is not indicated for the routine evaluation of transient insomnia, chronic insomnia or insomnia associated with fibromyalgia or CFS22.

A night of poor sleep is followed by increased pain ratings the following day and the day of increased pain is followed by a night of poor sleep in most of CFS patients. By looking at the polysomnography, wrist actigraphy, sleep and pain diaries and diffuse noxious inhibitory controls, it was shown that CFS patients have dysfunctional sleep and pain23. Impaired sleep is associated with reduced activation of the inhibitory pathway and frequent sleep disruptions can cause a reduction in the descending inhibitory control of pain and this is why the CFS patients have high sensitivity to pain24. Sleep improvement reduces the pain in these patients.

Disturbances of the internal biological clock manifest as fatigue, poor concentration and sleep disturbance. It is seen that CFS patients do have circadian rhythm disturbances25. Daytime sleepiness and abnormal REM regulation are seen in most of the CFS patients. Despite the increased daytime sleepiness most of the CFS patients complain of severe fatigue26.

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How do we manage sleep issues in CFS patients? You have to explore sleep hygiene and behavioural issues and look for a primary sleep disorder like RLS/PLM, sleep apnoea or UARS, bruxism. Review the current medications for sleep side effects and review all previous treatments. We should assess for nocturnal pain generators and screen for depression and anxiety. You should encourage the patients to have regular sleep schedule and advise to sleep as long as possible (usually 7–8 h for adults). Adjust the room environment to decrease stimuli like sound, light, temperature. Try not to force sleep and resolve worries or concerns before sleep. Avoid caffeine, alcohol and tobacco in the late afternoon. Exercise regularly more than 4 h prior to bedtime and avoid daytime naps longer than 20–30 min. Low-dose or very low-dose cyclobenzaprine (1–4 mg) can be tried. Cognitive behavioural therapy for treatment can also be tried on young and middle-age patients rather than pharmacotherapy.

In conclusion, lot of work has to be done in CFS and sleep disturbances as the problem co-exist in majority of patients.

References


Upper Airway Sleep Disorders in Children: Orthodontist’s Role

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Abstract
Significant component of craniofacial development occurs within the first four years of life. A total of 90% of the craniofacial development is complete by the age of 12 years. Therefore, it can be concluded that morphometric features that puts an adult at risk of obstructive sleep apnoea (OSA) or sleep disordered breathing (SDB) were probably present at the age of 12 years. Class II malocclusions, narrow maxilla, mandibular deficiency, retrognathia, long face problems, inferiorly and posteriorly placed hyoid bone are all considered as craniofacial anomalies that predisposes a child to SDB. Craniofacial anatomy can influence the upper airway and environmental factors, like adenotonsillitis, nasal allergy, pemicious oral habits (prolonged pacifier use, thumb sucking, tongue thrusting and mouth breathing), and can also influence the growth and development of the craniofacial complex. It has been stated that mouth breathing as an ongoing pattern may be a sign of impending sleep apnoea. So it is of paramount importance for the healthcare professionals to keep a close eye on the risk factors and make appropriate referrals for requisite preventive, interceptive and corrective treatment. Promotion and propagation of breast feeding in infants, adeno-tonsillectomy, maxillary expansion and functional appliances aimed at posturing the mandible in forward position/optimal position, habit breaking appliances and maxilla-mandibular distraction osteogenesis are the preventive, interceptive and corrective treatment options at our disposal. This communication is aimed at providing an overview of orthodontist’s role in the management of upper airway sleep disorders in children in the back drop of craniofacial risk factors, environmental influences and appropriate orthodontic and dentofacial orthopaedic intervention strategies.

Introduction
Obstructive sleep apnoea and other upper airway sleep disorders, like snoring and upper airway resistance syndrome, not only affect adults but are also seen in children. OSA is estimated to occur in 1%–3% of children and snoring is believed to occur in 3%–12% of the population1,2. Management of SDB in children is by an interdisciplinary approach involving paediatrician, oto-rhino-laryngologist, pulmonologist, orthodontist, maxillofacial surgeon and speech therapist. SDB, particularly OSA, affects memory, school performance, growth and development, cardiorespiratory health in children3–6. Craniofacial development is almost 90% complete by the age of 12 years. Hence, all those craniofacial risk factors that are
responsible for SDB are present at a very young age\textsuperscript{7,8}, hence, there is a very strong case in hand to recognise these craniofacial risk factors and institute the appropriate preventive, interceptive and corrective treatment strategies so that breathing at night during sleep is optimised. Orthodontists are specialists who deal with the growth and development of the face and jaws in particular and prevention, interception and correction of malaligned teeth and jaws. So there is a need for the orthodontic profession to integrate management of upper airway sleep disorders into their practice, so that their expertise is leveraged optimally for the prevention and comprehensive management of SDB in children. The other specialties also need to have a basic understanding of the orthodontist's competence and role for better interactions and appropriate referrals.

This paper aimed at providing an overview of the orthodontist's role in the management of SDB with special emphasis on craniofacial risk factors, their recognition and appropriate intervention.

**Discussion**

Upper airway is like a collapsible tube supported by the craniofacial skeletal bones, which include maxilla, mandible, cervical vertebrae and hyoid bone. The patency of this passage is maintained by various muscle groups whose tonicity is crucial to overcome the collapsibility. Human beings being bipedal have a unique airway/air passage compared to other quadripedal mammals. Unlike the other quadripedal mammals where the larynx is approximating the soft palate to facilitate simultaneous eating and breathing, in humans the larynx descends inferiorly to facilitate phonation and speech. Unlike other mammals where the tongue is more forwardly placed, in human the tongue is posterior and contained within the oral cavity and is integral to maintenance of upper airway patency. This unique phenomenon necessitate human to possess an erect head posture and craniocervical extension to facilitate breathing. So the craniofacial risk factors can have severe cascading effects on various entities, predominantly airway.

Significant component of craniofacial growth is complete by the age of 4 years and is 90\% complete by the age of 12 years. So all those recognised craniofacial risk factors that are associated with SDB are present since very young age. Some of the recognised risk factors are retrognathic maxilla and mandible, lower and inferiorly placed hyoid bone, narrow maxillary arch, deep palatal vault, macroglossia, excessive lower face height and long face problems\textsuperscript{7,8}. These features may be seen in both syndromic and non-syndromic cases. Some of the common syndromes include Treacher Collins syndrome, Crouzons syndrome, Apert’s syndrome, Pfeiffer’s syndrome, Pierre Robin syndrome and cleft lip and palate\textsuperscript{9}.

Post-natal craniofacial growth is supported by various theories and the most accepted as per contemporary literature is functional matrix theory proposed by Dr. Melvin Moss in early 1970s, which summarises that growth of the face occurs as a response to functional needs and is mediated through soft tissue in which jaws are embedded. The facial pattern is genetically programmed, however, the epigenetic and functional factors ultimately determines the craniofacial architecture\textsuperscript{10}.

The initial influence of environmental factors can be associated with use of pacifiers and dummies. Breast fed children have been reported to have better developed jaws as compared to bottle/pacifier fed children\textsuperscript{11}. The breast feeding facilitates suckling unlike sucking facilitated by pacifier use. The muscular thrust produced by tongue on the palate helps in the expansion of the palatal vault and also impacts the craniofacial sutures, which respond by sutural growth\textsuperscript{12}. This initial impetus is crucial for optimising tongue posture, which later influences the maturing to adult swallowing pattern and maintaining the balance of orofacial musculature. On the contrary, a pacifier does not create adequate posterior oral seal and the impetus for maxillary arch development is not adequate. So the first step therefore would be to promote breast feeding, hence, breast feeding needs not only to be highlighted in the wake of immunological and nutritional benefits but also for balanced craniofacial development and it is cascading benefits with respect to optimising the patency of upper airway\textsuperscript{11,12}. There is mounting evidence from anthropological studies that pre-historic skulls had wide palate and large posterior nasal aperture. The broad width between the pterygoid plates resulted in a wide entry to the soft tissue portion of the airway. In the studies conducted on skulls after 1940s, skulls on an average had high palate and narrow arch resulting in smaller posterior nasal aperture\textsuperscript{14}. This can be attributed to widespread use of bottle feeding, pacifier and digit sucking, which cause adverse effects on the craniofacial development.
Many environmental factors influence the craniofacial growth, which in turn has an impact on the airway. Most common environmental influences concerned with craniofacial growth are oral breathing and nasal blockage. This is attributed to enlarged adenoids, tonsils, deviated nasal septum, nasal allergies and chronic upper respiratory infections. These environmental factors, particularly adeno-tonsillitis, result in increased cranio-cervical extension and forward head posture, which in fact is a compensatory mechanism to facilitate breathing	extsuperscript{8,14}. This compensatory mechanism ceases to exist in sleep resulting in the upper respiratory collapsibility, a commonest feature of SDB. These environmental factors also impact the orofacial balance resulting in the oral breathing, lowered posture of tongue, narrowing of upper arch due to aberrant buccinator mechanism and clockwise growth rotation of mandible. This often leads to classical Class II malocclusion and anterior open bite. The first interventional step would be recognising these environmental predisposing factors and eliminating them.

Adeno-tosillectomy would be the first step	extsuperscript{15,16}. Gulleminault (16) and colleagues in their seminal study compared the therapeutic efficacy of adeno-tonsillectomy alone and combination of adeno-tonsillectomy and rapid maxillary expansion (RME). They reported almost 100% cure in the groups those underwent both adeno-tonsillectomy and RME. The benefits of RME also been ratified in other reported studies	extsuperscript{17,18}. Change in the head and tongue posture and accelerated growth and closure of mandibular plane angle has been observed post adeno-tonsillectomy. This has been attributed to normalisation of secretion of growth hormone and mediators attributed to quality delta sleep	extsuperscript{14}. Appropriate referral of children suffering from SDB undergoing adeno-tonsillectomy to orthodontist by paediatrician and otolaryngologist for RME merits serious consideration.

RME is a procedure commonly prescribed by orthodontist for expansion of maxillary arch. Different sizes of jackscrews are secured to the teeth by soldering on bands on teeth or by bonding acrylic plate (Figure 1).

In growing children, the jackscrew is opened at a rate of 1 mm per day, which aids in opening/distracting midpalatal suture and expansion of palatal arch, thus increasing the oral volume. Literature reports the procedure enlarges the posterior nasal aperture, decreases nasal resistance and thus improves nasal breathing	extsuperscript{17,18}. The procedure is also positively associated with management of nocturnal enuresis and conductive hearing loss in children	extsuperscript{19}.

Pernicious oral habits like digit sucking habits, abnormal tongue thrusting and mouth breathing are impending risk for abnormal craniofacial growth and SDB like the pacifier habits. Digit sucking in particular after the age of 5 years is to be viewed much more seriously by treating physicians, paediatricians and dentists. Thumb sucking during the late deciduous and mixed dentition stage result in protrusion of upper anterior teeth, deepening of palatal vault and deficient growth of mandible due to counter pressure on mandibular condyles. Orthodontic intervention for these habits includes counselling and prescription of removal and fixed habit breaking appliances (Figure 2). These appliances basically encompass palatal cribs, made up of wire framework that would defer the patient to indulge in the habit. If the habit is corrected at appropriate age, the growth and development can get normalised. Similarly, tongue thrusting and mouth breathing can also be treated with orthodontic appliances, like tongue guard or oral screen. These appliances will help not only discontinuing the habit but also improve the orofacial muscular balance.

Mandibular deficiency is one of the most common risk factor associated with SDB	extsuperscript{20}. As early as in 1902, monoblock was prescribed in a child with Pierre Robin syndrome to prevent asphyxia	extsuperscript{21}. Various mandibular advancement appliances were designed and developed during the last century by orthodontists to promote and redirect mandibular growth (Figure 3). These appliances help in holding or posturing the mandible forward by harnessing myotonic and myodynamic properties of facial muscles. These are together labelled as functional appliances. Although orthodontist historically has been prescribing these appliances to harness growth, the merits of improving breathing during sleep have not been highlighted adequately and are under reported. The commonly prescribed appliances for this purpose are activator, bionator, twin block and frankel’s functional regulators. Clark	extsuperscript{22} designed a simple removable twin block appliance for correction of Class II malocclusion due to mandibular deficiency. He has highlighted the merits of these appliances in the light of improvement of airway	extsuperscript{22}.

David Page, Mohony, Dave Singh and William Hang are strong advocates of use of functional jaw orthopaedics
for improvement of airway\textsuperscript{23,24}. They have aptly interrelated airway, mode of breathing and craniofacial formation during growth and development and have pointed out the philosophy of form following function and function following form. According to them it is imperative to normalise form and function as early as possible, so that function is optimised for life.

The facial features that indicate the risk for SDB in children are summarised vide Table 1.

**Table 1:** Facial features that indicate the risk for SDB in children

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Clinical feature</th>
<th>Presentation</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Adenoid facies</td>
<td>This is a condition with long face. The face is rounded and offers a blank stare.</td>
</tr>
<tr>
<td>2</td>
<td>Allergic shiners</td>
<td>These are dark circles that are often found under the eyes. They are related to reduced or absent nasal breathing with increased amount of mouth breathing.</td>
</tr>
<tr>
<td>3</td>
<td>Poor or inadequate lip seal</td>
<td>The lips are found to be apart with difficulty to maintain lip seal.</td>
</tr>
<tr>
<td>4</td>
<td>Small nares</td>
<td>The opening of nasal airway is small and appears constricted.</td>
</tr>
<tr>
<td>5</td>
<td>Nasal crease</td>
<td>Horizontal line that goes across the nose above the tip of the nose. Clinical feature may be associated with allergy.</td>
</tr>
<tr>
<td>6</td>
<td>Intra-oral features</td>
<td>Bruxism or worned teeth cross bite, high arched palate, scalloped tongue, enlarged or swollen uvula, enlarged tonsil, deep or collapsed bite.</td>
</tr>
<tr>
<td>7</td>
<td>Facial profile</td>
<td>Convex facial profile retruded chin</td>
</tr>
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Maxillary deficiency is often associated with decreased velo-pharyngeal airway space because of posteriorly placed velum. Maxillary deficiency is most commonly observed in operated cleft lip and palate CLP cases. SDB is reported higher in CLP cases due to severe maxillary growth disturbance\textsuperscript{25,26}. The anterio-posterior discrepancy is often associated with narrowing of maxillary arch or transverse discrepancy, which also impacts the tongue posture. So early intervention by expansion of maxillary arch and protraction with the maxillary face mask will not only facilitate growth but also improve the velo-pharyngeal airway space.

Cephalometrics is the most common investigation resorted by orthodontist for diagnosis and treatment planning. Although a two-dimensional image it gives adequate information regarding jaw relationship, soft tissue relationship and airway (Figure 4). It is economical and easily available. Orthodontist should leverage this modality not only for routine treatment planning procedure but also to screen patients for airway compromise. Most of the common airway measurements that can be easily done on lateral cephalogram are nasopharyngeal airway space, posterior airway space, velopharyngeal airway space and hyoid distance.

Various craniofacial syndromes with severe mandibular deficiency can be life threatening. Mandibular advancement by distraction osteogenesis can be a life saving measure in these cases. The technique involves incremental traction to regenerate to harness elongation of mandibular corpus. The procedure often carried out by maxillofacial surgeons in collaboration with the orthodontists using various paediatric introral distraction devices. Large amount of mandibular advancement is possible by this technique. Significant improvement in airway parameters and breathing has been reported in literature\textsuperscript{27,28,29}. Similarly, severe maxillary deficiency particularly as in case of operated CLP can be addressed at very early age by mid-face distraction. This is done by Lefort I osteotomy of maxilla using RED or modular internal distracter. Literature recommends maxilla-mandibular distraction as most successful approach in management of severe OSA other than tracheostomy in craniofacial syndromes and success rate approaches 100%\textsuperscript{27,28}.

![Image: Rapid maxillary expansion with HYREX appliance](image-url)

Dentofacial esthetics should never be achieved at the cost of compromising the airway. Airway parameters must therefore be made integral to orthodontic practice. There are reports of bicuspid extraction at younger age, which have attributed to development of OSA in adult life. Reasons cited are reduced airway volume and tongue space. So extraction orthodontics must be weighed against airway compromise and long-term health benefits.

Conclusion

Orthodontist needs to be more involved in airway management and craniofacial development in growing children. Current literature shows that early orthodontic and orthopaedic intervention impact the airway and breathing. Orthodontic and orthopaedic intervention can lead to normal and healthier life. Orthodontic specialist has the competence to recognise craniofacial risk factors for SDB and practice appropriate prevention, interception and corrective treatment. As interdisciplinary approach is the only way forward in management of SDB in children. Regular interaction and understanding of the role of various specialities is the need of the hour for evidence based practice of sleep medicine.

References


The phenomenon of sleep exists across the animal kingdom. Sleep is an important and critical behavioural state essential for maintaining health and survival. Sleep is defined behaviourally as a physiological state of rapidly reversible period of immobility associated with characteristic posture, reduced motor activity and increased response threshold for external sensory stimulation. During sleep, we do not interact with the external environment and often enters into dream state. Sleep is essential for the adaptation of organism to its environment and thereby important for the growth and survival. Cetaceans such as dolphins execute many functions such as locomotion, thermoregulation and so on while one hemisphere is engaged in sleep like activity. Sleep is thus necessary for proper functioning of the brain and is necessary for the survival of the organism. During the process of evolution, sleep also has undergone evolutionary changes may be to sub-serve specific functions. Birds and mammals are endowed with both non rapid eye movement (NREM) and rapid eye movement (REM) sleep states, whereas lower vertebrates exhibit only NREM sleep. Thus, REM sleep is introduced late in the phylogeny may be to meet the challenges associated with development of brain complexities and associated cognition.

Sleep is essential for energy conservation. Waking enhances brain plasticity events, increases protein synthesis and so on, but extended wakefulness lead to pronounced brain glycogen depletion causing energetic challenges to the brain. Sleep on the other hand protects the brain from oxidative stress and helps repair mechanisms. A constant daily quota of sleep is maintained through the mechanism of sleep homoeostasis. Recent studies provide convincing evidences on the role of adenosine and other sleep regulatory substances in establishing the homoeostatic drive for sleep. In addition, other cellular energetic pathways like glycogen, electron transport, astrocyte to neuron lactate shuttle and clock transcription proteins get modulated during sleep–wake cycle. It is proposed...
that these metabolic pathways help brain to transit from an energy-attenuated catabolic wake state to sleep state where energy gets replenished\textsuperscript{34,35}. Sleep deprivation on the other hand reduce glycogen store and ATP, affect cerebral protein synthesis, cell proliferation and neurogenesis\textsuperscript{34}. Studies have emphasised the harmful consequences of sleep deprivation right from \textit{Drosophila} to mammals. Sleep loss, sleep restriction or sleep deprivation brings about cognitive impairment, reduced vigilance, increased sleepiness, fatigue and disturbed mood\textsuperscript{6,7}. The neurobehavioural effect of sleep loss has been demonstrated among shift workers, nursing professionals and frequent international travellers, medical residents on duty for long hours and among patients with chronic pain\textsuperscript{8,9}. Sleep deprivation in humans interferes with routine normal life and impairs alertness, memory, cause disorientation and confusion even in situations that demand high levels of alertness and vigilance. Sleep deprivation affects neurogenesis, brain plasticity events and thus impede cognitive functions\textsuperscript{6,7}, alter immune system, increases the risk of cardiovascular disorders and metabolic disorders\textsuperscript{10}. When the organism is sleep deprived, the body tries to recover the lost sleep by sleep rebound. The existence of sleep rebound after sleep deprivation reveals that sleep is essential for health and fitness. The recovery of sleep following sleep deprivation is characterised by enhanced slow wave sleep and slow wave activity. Thus, it is considered that the depleted energy during waking state gets replenished during sleep, especially, during slow wave sleep. Increased slow wave sleep after hibernation or torpor is attributed not as a part of sleep rebound but as means to neural repair and regeneration and synaptic homeostasis. Extremely low temperatures are known to limit synaptic repair and regeneration and synaptic homoeostasis. Extremely low temperatures are known to limit synaptic transmission, and thereby reducing the synaptic efficiency. Therefore, sleep is important for adaptive neuronal plasticity, which plays an important role for survival along with energy conservation\textsuperscript{1}.

The tight regulation of brain plasticity mechanisms determines the functioning and energy dynamics of the brain. It has been hypothesised that the total synaptic strength of the brain changes as function of wakefulness and sleep\textsuperscript{11}. Synaptic strength increases during wake and reaches maximum before sleep is being induced. When sleep ensues synaptic strength decreases and reaches baseline by sleep end. Thereby, synaptic homeostasis is maintained and is correlated with sleep. During wakeful state, learning and interaction with environment brings about increase in the strength of the synapses. This waking plasticity mechanism is associated with increased energy demands and space requirements saturating the learning capabilities. Whereas, sleep helps to prune the weak synapses and strengthen the relevant ones. It is suggested that average synaptic strength peaks at the end of wake hours, therefore, demanding enhanced slow wave activity and downscales the synaptic strength. As the synaptic strength reduces, the slow wave activity also reduces during later sleep period. This sleep dependent down scaling of synapses play an important role in learning and memory, neuronal development and growth\textsuperscript{12}.

Sleep is known to have its functional role related to memory, learning and brain plasticity. Sleep enhances the ability to recall spoken language, spatial memories, auditory patterns and motor skills. Jenkins and Dallenbach in 1924\textsuperscript{13} for the first provided the special role of sleep in enhancement of learning. Since then many studies have provided valid information on the role of sleep in memory consolidation. What magic does sleep do for memory consolidation? It is suggested that memory traces are being reactivated in the hippocampus and are being sent to cortex during slow wave sleep for long-term consolidation\textsuperscript{14,15}. Such reactivation process helps in the integration of memory representations in the network of pre-existing long-term memories. The memory representations are further subjected for synaptic consolidations during REM sleep\textsuperscript{15,16}. Therefore, both NREM and REM sleep states complement each other for consolidation of memories as well as their transformation to long-term memory. Sleep thus provides an ideal state for consolidating and integrating memories.

In humans, sleep architecture undergoes prominent maturational process in sleep timing, duration and their regulatory mechanism to establish a definite adult sleep morphology\textsuperscript{17}. Sleep plays a major role in neural maturation and proper synaptic connections during development\textsuperscript{18,19}. Altered sleep architecture in conditions of schizophrenia, depression and anxiety disorders have been attributed to the developmental disturbances of sleep maturation process\textsuperscript{19}. In general, sleep is important for CNS maturation, strengthens the synaptic connections, prune the unwanted connections and thus fine-tune neuronal connections to generate appropriate behaviours.

Presently, our understanding of sleep is undergoing a great paradigm shift. The classical electroencephalograph (EEG) changes that aid in defining various sleep stages represent the dynamic interaction between thalamo-cortical oscillations and the special
electrophysiological properties of thalamic neurons. There are now emerging evidences that SWA can be use dependent local network phenomenon of cortical columns. EEG studies following learning of spatial task using left hand showed higher SWA in the right parietal region associated with coordination of spatial task. The local sleep activity induced by learning task brings about plastic changes, which aids in enhancing the performance. Further, the down scaling events globally or locally play an important role in increasing the signal-to-noise ratio in neuronal circuits. These energy-efficient events during sleep brings about great beneficial effect on brain per se so the cognition and performance.

On the whole, sleep is an autoregulatory global phenomenon called sleep. Local sleep activity induced by learning task brings about plastic changes, which aids in enhancing the performance. Further, the down scaling events globally or locally play an important role in increasing the signal-to-noise ratio in neuronal circuits. These energy-efficient events during sleep brings about great beneficial effect on brain per se so the cognition and performance. Practices like exercise and meditation exerts beneficial effect on sleep and help to maintain proper sleep organisation even in old age. To conclude, nature has provided the phenomenon called sleep as a mean to sub-serve the functions that are essential to maintain health and survival.

References

Subjects with Type 2 Diabetes may have Obstructive Sleep Apnoea even at Lower BMI Values

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Abstract

Aim was to evaluate subjects with type 2 diabetes at risk of obstructive sleep apnoea (OSA) using Epworth Sleepiness Scale (ESS). A total of 436 subjects (M/F=273:163) were evaluated and categorised as those unlikely to have significant OSA (ESS score <10; absence of snoring) and likely to have significant OSA (ESS score >10; presence of snoring). Body mass index (BMI), HbA1c and micro- and macrovascular complications were recorded. Among 436 subjects, 242 were unlikely to have significant OSA, of which 20% were randomly selected (n=58; Group 1) and compared with subjects (8.3%) likely to have OSA (n=36; Group 2). In all, 50% in Group 2 and 36% in Group 1 had hypertension (P=0.27). In Group 2, 2.8% had BMI (kg/m²) <23, 5.6% had 23–23.9, 19.4% had 24–24.9, 25% were between 25 and 26.9, and 47.2% had e”27. Diabetic subjects even with normal BMI were at risk of OSA and more likely to have macrovascular comorbidity.

Keywords: Epworth Sleepiness Scale, Obstructive sleep apnoea, type 2 diabetes, BMI

Introduction

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by frequent episodes of upper airway collapse during sleep. OSA has been recognised as a major contributor to morbidity and mortality in developed countries1-2. The prevalence estimates in Asia suggests that this is common not only in developed countries but also in developing countries. Epidemiological studies from North India have reported varying prevalence rates of OSA, ranging from 9% to 13% among the general population3. Excess body weight is a well-recognised risk factor for OSA4,5. OSA is also associated with poor glucose metabolism in individuals without diabetes and is a highly prevalent comorbidity as well as a risk factor for type 2 diabetes6. There are population, clinic-based and laboratory studies as well suggesting that both type 2 diabetes and OSA may be associated independently of the degree of adiposity7.

The gold standard diagnostic test for OSA is overnight polysomnogram, which involves simultaneous recordings of multiple physiologic signals during sleep. Identification of OSA using this test is expensive and may not be
accessible in all clinical settings, so a practical approach might be to screen first using questionnaire for OSA. Questionnaire may identify people with an increased likelihood of having OSA. Those at high risk should undergo polysomnography to confirm the diagnosis.

The aim of this study was to evaluate subjects with type 2 diabetes who are at risk of OSA through history of snoring and assessment of daytime sleepiness and also to assess the associated risk factors.

**Materials and Methods**

A total of 436 subjects (273 males and 163 females) with type 2 diabetes attending a diabetes specialty centre from September 2009 to March 2010 were evaluated using the Epworth Sleepiness Scale (ESS), which is a short questionnaire used to assess daytime sleepiness. Height and weight measurements were taken and body mass index (BMI; kg/m²) was calculated. HbA1c values and details on other micro- and macrovascular complications were recorded. Presence or absence of snoring was also recorded. Institutional Ethical Committee approved the study and written consent was obtained from each study subject. Subjects were identified as those who were less likely to have significant OSA (ESS score <10 and absence of snoring) or more likely to have significant OSA (ESS score >10 and presence of snoring).

**Statistical analysis**

Means and proportions were reported for continuous and categorical variables, respectively. Pearson chi-square and Student’s independent sample ‘t’-test were used appropriately to test the associations using SPSS version 16.0. P-value of <0.05 was considered to be significant.

**Results**

Of the 436 subjects evaluated, 242 (55.5%; M/F=145:97) subjects were identified as those who were unlikely to have significant OSA (score <10 and absence of snoring). Out of 242 subjects, 20% were randomly selected (n=58; M/F=34:24; Group 1) and were compared with subjects who were likely to have significant OSA with score ≥10 and with positive history of snoring. (n=36; M/F=24:12; 8.3%; Group 2). There was no gender difference observed among those at risk of OSA (men versus women: 16.5% versus 12.3%; P=0.477). The remaining study subjects with the absence of snoring and score ≥10; (n=15; 3.4%) and the presence of snoring but with score <10; n=143 (32.6%) were considered to be at low risk and excluded for comparison.

Table 1 shows the characteristics of the study subjects with and without risk for OSA. The mean age was similar between the groups (Group 1 versus Group 2; 55.2±9.8 versus 53.5±10;P=0.419). Group 2 subjects had higher mean BMI values in comparison with Group 1 subjects (27.2±3.1 versus 25.9±3.8 kg/m²; P=0.08). Majority of the study subjects (~80%) belonged to the middle-income category. Mean HbA1c values were above 9.0% and the mean duration of diabetes was more than 10 years in both the groups.

**Table 1:** Comparison of characteristics of study subjects with and without risk for OSA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (absence of snoring and score &lt;10) n=58</th>
<th>Group 2 (presence of snoring and score ≥10) n=36</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.2±9.8</td>
<td>53.5±10</td>
<td>0.419</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9±3.8</td>
<td>27.2±3.1</td>
<td>0.088</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.6±2.4</td>
<td>9.2</td>
<td>0.213</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>11.7±7</td>
<td>10.9±6.7</td>
<td>0.585</td>
</tr>
<tr>
<td>Income group (n %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8 (13.8)</td>
<td>7 (19.4)</td>
<td>0.575</td>
</tr>
<tr>
<td>Middle</td>
<td>49 (84.5)</td>
<td>29 (80.6)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ESS score</td>
<td>3.7±2.6</td>
<td>12.6±2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complications (n %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (36.2)</td>
<td>18 (50%)</td>
<td>0.270</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>18 (31)</td>
<td>14 (38.9%)</td>
<td>0.577</td>
</tr>
<tr>
<td>Cardiovascular disorder</td>
<td>19 (32.8)</td>
<td>5 (13.9%)</td>
<td>0.072</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>15 (22.4)</td>
<td>3 (22.2%)</td>
<td>0.816</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>16 (27.6)</td>
<td>8 (22.2%)</td>
<td>0.775</td>
</tr>
</tbody>
</table>

The mean ESS score was significantly higher in Group 2 in comparison with Group 1 (12.6±2.5 versus 3.7±2.6; P<0.001).

Hypertension was present in 50% in Group 2, whereas it was 36% in Group 1 (P=0.27). Dyslipidaemia (Group 1 versus Group 2; 31% versus 38.9%), cardiovascular disorders (12.1% versus 13.9%) and neuropathy (32.8% versus 13.9%) and the presence of other microvascular complications such as nephropathy and retinopathy were similar between the groups. In Group 2, the proportion of subjects in age (years) categories were 0% (<30), 16.7% (30–40), 16.7% (40–50) and 66.7% (>50) and in BMI (kg/m²) categories were 2.8% (<23), 5.6% (23–23.9), 19.4% (24–24.9), 25% (25–26.9) and 47.2% (≥27).
Discussion

The current study showed that 8.3% of the subjects with type 2 diabetes were at high risk of OSA based on simple history and questionnaire format, which would help identify and treat these patients early. Similarly, overall prevalence of individuals who had high risk for sleep apnoeas was observed between 10 and 12.4% in Pakistan based on Berlin questionnaire. In another study, Robert et al. reported that 16.3% were at high risk of OSA and 9.9% were at low risk based on Berlin questionnaire and the same subjects when subjected to polysomnography revealed that the prevalence of OSA among Indian subjects with diabetes was 24.3%. So there is a possibility of under estimation of the presence of OSA if the evaluation was based on questionnaire and an overnight polysomnography only can reveal the exact prevalence of OSA. Moreover, screening questionnaires for OSA have poor sensitivity and specificity and have not been validated in diabetes populations. A higher mean BMI in high-risk group observed in our study was similar to the BMI reported in the above study by Robert et al. The present study showed a higher proportion of subjects with hypertension in at risk group of OSA compared to control group (50% versus 36.2%). Another hospital-based study conducted in Hyderabad also reported that 80% of subjects with confirmed OSA by polysomnography had hypertension.

The present study highlights that subjects with type 2 diabetes of Indian origin even with lower BMI values were likely to have OSA. Nearly, 28% of high-risk group fall under BMI category <25 kg/m² and 67% of high-risk group were aged above 50 years. In addition, a trend towards increased macrovascular comorbidity was also observed in our study. However, larger studies have to be planned to further define the association of these factors with OSA among people with type 2 diabetes using polysomnography. Polysomnography may not be feasible in some settings due to limited resources, especially, in developing countries. So it is ideal to screen the subjects first using questionnaire and those who are highly susceptible should undergo polysomnography testing.

In conclusion, 8.3% of the subjects with type 2 diabetes were at risk of OSA based on questionnaire. Subjects with diabetes from Indian origin may have OSA even at lower BMI values.

References

Abstract
Background: The morphometric model (MM) provides a rapid, accurate and reproducible method for predicting whether patients in an ambulatory setting are at risk for obstructive sleep apnoea (OSA).

Introduction: The aim of this study was to estimate mean MM scores in a mixed Indian population and to investigate its correlation with the severity of OSA as determined by apnoea/hypopnoea index (AHI).

Materials and Methods: A total of 60 subjects were included in the study and were divided into two groups of 30 subjects each; Group 1: Patient group; Group 2: Control group. A comparative cross-sectional study design was employed and MM value as suggested by Kushida et al. was estimated by applying their clinical rule. To determine the correlation between OSA severity as indicated by AHI and MM values, linear and multiple regression models were applied.

Results: The comparison of MM values between OSA and non-OSA groups showed an extremely statistically significant difference. There was no significant correlation between the severity of OSA and MM values in this sample of Indian OSA patients.

Conclusions: The results of this study could facilitate the early recognition of OSA and support the available diagnostic setup.

Keywords: Obstructive sleep apnoea, morphometric model, apnoea/hypopnoea index, polysomnography, clinical rule, predictors

Predictive Morphometric Model Value Estimation and its Correlation with Severity of Obstructive Sleep Apnoea in a Mixed Indian Population: A Pilot Study

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Doi : 10.5958/j.0973-340X.7.2.011

Indian J Sleep Med 2012; 7.2, 48-54

Introduction
Even though obstructive sleep apnoea (OSA) is fairly common, it often remains undiagnosed in primary care practice. The failure to recognise the syndrome is in part due to limited availability of diagnostic facilities, which make the patients with OSA heavy users of health care resources, not only at the time of diagnosis, but also for years prior to diagnosis. While overnight polysomnography (PSG) is considered the ‘gold standard’ for the diagnosis of OSA, the need for accurate, quantitative diagnostic criteria is further supported by the significant cost incurred with routine PSG. However, the lack of a simple, non-invasive, repeatable method has been an obstacle for the early recognition of OSA patients.

Although sleep laboratories have been set up in various centres in India, the availability of this service is...
very limited. The limited number of facilities available restricts the proper identification of OSA and may lead to underestimation of the magnitude of the problem and under-treatment, with undesirable public and personal health consequences. Common symptoms of the condition have limited predictive value in identifying patients with OSA. The morphometric model (MM) is a useful screening test to investigate the possibility of OSA in patients during initial office visits. The most commonly used predictive model is the MM given by Kushida et al. of the Stanford Sleep Disorders Clinic and Research Centre, California (hereafter referred to as the Stanford Morphometric Model: SMM), which provides a rapid, accurate and reproducible method for predicting whether patients in an ambulatory setting are at risk for OSA. This clinical MM was tested on Caucasian patients, where it was found that patients with values equal to or more than 70 typically had OSA. There is no data available on the applicability of the predictive model to Indian subjects.

We carried out a pilot study with the aim of estimating mean SMM scores in a mixed Indian population and its correlation with the severity of OSA as determined by apnoea/hypopnoea index (AHI). The results of this study could facilitate the early recognition of OSA and support the available diagnostic setup. Based on the intraoral findings, orthodontists may request a polysomnographic evaluation when OSA is suspected and the final diagnosis of sleep disorder; its severity and the evaluation of comorbidities are made by a physician according to polysomnographic findings.

Materials and Methods

This multi-disciplinary study was undertaken at the Division of Orthodontics and Dentofacial Orthopedics, Armed Forces Medical College, Pune, Maharashtra, India. The research protocols were reviewed and approved by the Institutional Ethical Committee of the Hospital. Informed consent under witness was obtained from each participant at enrolment after each subject was explained the nature and purpose of the study. To detect a clinically significant difference with 80% power, \( \alpha = 0.05 \) and a ratio between two groups of 1:1, 60 adult Indians aged 18 years and above were recruited for this study. A comparative cross-sectional study design was employed. The total of 60 subjects included in the study was divided into two groups of 30 subjects each; Group 1: Patient (test) group; Group 2: Control group.

The patient sample (test group) consisted of 30 randomly selected PSG-diagnosed OSA patients referred by the Department of Respiratory Medicine, Military Hospital, Cardio-Thoracic Centre, Pune, India, for the analysis of craniofacial morphology. PSG performed was level I, using a 16-channel polygraph (SleepScan Analysis VISION, Bio-logic Systems Corp, USA). For the purpose of this study, only one variable, the number of apnoeas and hypopnoeas, was utilised. There was no prior knowledge of the patient to be seen and there was no regular pattern of days to examine the patients. For the test group, the patients who satisfied the following criterion were included in the study: aged 18 years and above; polysomnographic evidence of OSA (defined as an AHI of \( \geq 5 \) /h of sleep); and the presence of at least 10 teeth in each arch.

The control group consisted of 30 randomly selected adults attending the dental outpatient department, with an Angle’s Class I molar relation and no history of sleep obstructed breathing. The control group was matched with the patient sample to the best extent possible for age, gender, height and weight. For the control group, the subjects who satisfied the following criterion were included in the study: aged 18 years and above; subjects with Angle’s Class I occlusion, Epworth Sleepiness Scale (ESS) score <9 (to exclude daytime sleepiness); no reported snoring by family members and the presence of at least 10 teeth in each arch. Snoring frequency, snoring intensity and ESS were used as a questionnaire for selection of subjects in the control group.

The exclusion criteria for both groups were as follows: edentulous subjects; subjects with hypothyroidism; subjects with history of orthodontic treatment; subjects with history of reconstructive/orthognathic surgery; subjects with craniofacial deformity, such as cleft lip and D or palate; subjects with history of pharyngeal surgery and subjects with patient-specific disorders (such as neuromuscular disorders).

Each of the groups consisted of 19 men and 11 women. Data collection was divided into three sections as follows:

a. Medical and sleep history including an ESS.

b. Clinical examination with anthropomorphic recordings of the subject’s height, weight and neck circumference (NC). NC in centimetres was measured with a tape measure, at the level of the cricothyroid cartilage in upright awake subjects. For
each subject, obesity was expressed as body mass index (BMI)\(^4\).

c. **Study model analysis:** Measurements were taken from the maxillary and mandibular study models using a pair of digital calipers (Workzone, Global tronics GmbH & Co, Germany), with a resolution of 0.01 mm.

Upper and lower dental arch study models were obtained with alginate impression material and dental stone. The following measurements were recorded on the study models\(^2\),\(^3\). All the measurements were carried out by the principal investigator.

1. **Maxillary intermolar width (Mx):** Distance between the mesiobuccal cusp tips of the crowns of the maxillary right and left permanent first molars (Figure 1).

2. **Mandibular intermolar width (Mn):** Distance between the mesiobuccal cusp tips of the crowns of the mandibular right and left permanent first molars (Figure 2).

3. **Overjet (OJ):** Horizontal overlap of the crowns of the maxillary and mandibular central incisors, in millimetres.

4. **Palatal height (P):** To standardise measurement of palatal depth/height, models were trimmed until the distal contact point of the upper first molars showed up on the edge. Distance from the mid-deepest part of the palate to the line connecting the left and right distolingual cusp tips of the upper first molars was taken as palatal depth (Figure 3).

**Figure 1:** Measurement of maxillary intermolar width on study model.

**Figure 2:** Measurement on mandibular intermolar width on study model.

**Figure 3:** Measurement of palatal height/depth

**SMM score was calculated by applying the clinical rule as follows:**

\[
P_+ (Mx-Mn)+3xOJ+3x(BMI-25.0)x(NC/BMI)
\]

Where \(P\) is palatal height in millimeters, NC is neck circumference in centimetres, measured at the level of cricothyroid membrane, Mx is distance between the mesial surfaces of the crowns of the maxillary molars in millimeters, Mn is distance between the mesial surfaces of the crowns of the mandibular molars in millimeters, OJ is overjet, horizontal overlap of the crowns of the maxillary and mandibular central incisors in millimeters, BMI is body mass index (kg/m\(^2\)).

**Data compilation and statistical analysis**

The readings were tabulated separately for the OSA (test) group and control group. The measurement of 20 randomly selected casts was repeated on separate occasions with a 2-week interval, for evaluation of intra-operator error. The difference between the first and second measurements was not significant. All measurements obtained in the study were expressed as
mean ± standard deviation (SD). The data was analysed using MATLAB version 1.0 and Excel 2007. To determine the correlation between OSA severity as indicated by AHI and SMM, linear and multiple regression models were applied.

Results

SMM values were calculated for all the subjects. The comparison of MM values between OSA and non-OSA groups showed an extremely statistically significant difference \((P<0.0001)\) with the OSA group having an average MM value of 67.30±11.95, while in the control group it was 55.43±7.80, as shown in Table 1. The results of the regression analysis showed that there was no significant correlation between the severity of OSA as indicated by AHI and SMM value in this sample of Indian OSA patients (Table 1). The line diagram for the distribution of patient’s AHI versus the calculated SMM value is depicted graphically in Graph 1, while the scatter plot of AHI against predicted values of SMM is shown in Graph 2.

The average age was 53.6±9.42 years. While the two groups had no significant difference in terms of height, the OSA patients were found to be significantly heavier than control subjects with a resulting statistically significant increase in BMI \((P<0.05)\), as shown in Table 2. The patients in the test group also had a statistically significant increase in NC \((P<0.05)\), when compared to the controls. The NC in the test group ranged from 34 to 45 cm, with an average of 41.11±2.05 cm for men and 37.55±3.53 cm for women. Table 2 presents the mean of general physical examination measurements of the two groups. All patients in the test group had varying degree of OSA, as confirmed by overnight PSG and symptoms of snoring and excessive daytime sleepiness. OSA severity was defined by the AHI. The AHI ranged from 5.6/h to 86.4/h with an average of 42.04±26.14 events per hour. In the test group, the ESS recorded a statistically significant increase \((P<0.05)\) and ranged from 9 to 20 with an average of 13±2.85 events per hour.

The comparison of mean intraoral values between OSA and controls is summarised in Table 3. Overjet was found to be larger in the controls when compared with the OSA sample, but analyses failed to detect statistically significant differences \((P>0.05)\). Statistically significant differences were found between the groups for the measurements of palatal height/depth \((P<0.05)\).

### Table 1

<table>
<thead>
<tr>
<th>S No</th>
<th>Parameter</th>
<th>Patients with OSA (Test Group: n=38)</th>
<th>Patients without OSA (Control Group: n=50)</th>
<th>P value (≤0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age, years</td>
<td>53.6±9.42</td>
<td>55.43±7.80</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>ESS score</td>
<td>13±2.85</td>
<td>5±0.80±0.91</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>3</td>
<td>Weight, kg</td>
<td>80.19±8.52</td>
<td>67.30±11.95</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>4</td>
<td>Height, m</td>
<td>1.60±0.03</td>
<td>1.60±0.09</td>
<td>1.00</td>
</tr>
<tr>
<td>5</td>
<td>Body mass index, kg/m²</td>
<td>24.7±4.81</td>
<td>24.8±4.85</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>6</td>
<td>Neck circumference, cm</td>
<td>39.8±4.56</td>
<td>36.1±4.53</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>7</td>
<td>Maxillary intercanine distance, mm</td>
<td>53.85±7.55</td>
<td>53.85±7.55</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>8</td>
<td>Maxillary intercanine distance, cm</td>
<td>53.85±7.55</td>
<td>53.85±7.55</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>9</td>
<td>Palatal height, mm</td>
<td>24.1±1.34</td>
<td>20.7±2.87</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>10</td>
<td>Overbite, mm</td>
<td>1.97±1.82</td>
<td>2.00±1.82</td>
<td>0.806</td>
</tr>
<tr>
<td>11</td>
<td>AHI, events/h</td>
<td>42.0±26.14</td>
<td>42.0±26.14</td>
<td>...</td>
</tr>
<tr>
<td>12</td>
<td>Morphometric model value</td>
<td>67.30±11.95</td>
<td>75.43±7.80</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of mean of general physical characteristics between test and control groups

<table>
<thead>
<tr>
<th>S no</th>
<th>Parameter</th>
<th>Test group (n=38)</th>
<th>Control group (n=50)</th>
<th>t (n=1)</th>
<th>P value (≤0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TH in m</td>
<td>1.64±0.01</td>
<td>1.62±0.05</td>
<td>2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>WH in kg</td>
<td>80.1±12.5</td>
<td>67.35±11.95</td>
<td>2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>BMI (kg/m²)</td>
<td>24.7±4.81</td>
<td>24.8±4.85</td>
<td>2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>NC in cm</td>
<td>39.8±4.56</td>
<td>36.1±4.53</td>
<td>2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>5</td>
<td>ESS</td>
<td>13±2.85</td>
<td>5±0.80±0.91</td>
<td>2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>6</td>
<td>AHI</td>
<td>42.0±26.14</td>
<td>20.7±2.87</td>
<td>2.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of mean intraoral measurements between test and control groups

<table>
<thead>
<tr>
<th>S no</th>
<th>Parameter</th>
<th>Test group (n=38)</th>
<th>Control group (n=50)</th>
<th>t (n=1)</th>
<th>P value (≤0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Overjet</td>
<td>1.97±1.82</td>
<td>1.8±1.82</td>
<td>1.97</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>AHI</td>
<td>24.1±1.34</td>
<td>20.7±2.87</td>
<td>2.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**OSA:** obstructive sleep apnoea. SMM: Stanford Morphometric Model.

Discussion

Sleep problems are common among primary care patients. The ability to identify patients at risk for OSA in a busy primary care setting is difficult. A study conducted in an Indian population estimated the prevalence of sleep-disordered breathing (SDB) among middle-aged urban Indian men to be at 19.5% and that of obstructive sleep apnoea–hypopnoea syndrome (SDB with excessive daytime sleepiness), to be 7.5%6.
On comparing the SMM values in this pilot study, we have been able to demonstrate statistically significant differences between the two groups. The comparison of MM values between OSA and non-OSA groups showed a highly statistically significant difference, with the OSA group having an average SMM value of 67.30, while in the control group it was 55.43. Kushida et al. have stated in their paper that, similar to other predictive models, the SMM is useful to screen and identify the more severe cases; these patients may then be prioritised for treatment. Furthermore, the authors also maintained the importance of PSG as an adequate tool for diagnosis. The average MM value in this sample of Indian OSA patients is only slightly lesser than that observed by Kushida et al. who found that patients with values equal to or more than 70, typically had OSA. The fact that the populations under our study group and in the study by Kushida et al., belong to different origins (Indian and North-Americans) and that there was no standardisation to account for ethnicity may explain the differences between both studies.

The results of the linear and multiple regression analysis indicate that there is no significant correlation between OSA severity as indicated by AHI and the values of SMM in this sample of Indian OSA patients. Although there was a significant difference between the groups, we were unable to establish a cutoff point according to disease severity, as the values were very similar and did not increase linearly from the non-apnoeic to the mild, moderate and severe OSA groups. However, 13 (43%) of the 30 test subjects showed an increase in AHI value with increase in their predictive MM value.

Many studies have been done assessing craniofacial characteristics in OSA patients using cephalometrics, computed tomography, magnetic resonance imaging and acoustic reflection. Although there is controversy in the results, craniofacial alterations most closely related to the occurrence and severity of OSA are: retroposition of the maxilla, shortening of the mandibular body, inferiorly displaced hyoid bone, retrognathism, dental occlusion class II and narrow, arched hard palate.

Different clinical prediction rules have been described in the literature. Scientists have used various factors to predict a person’s risk of having OSA, based on their demographics, symptoms and BMI. Using these factors, scientists have been able to correctly identify 76% to 96% of patients who have OSA and 13% to 54% of patients who do not have OSA. A comprehensive comparative effectiveness review carried out by the US Department of Health and Human Services has concluded that of the available models, the MM by Kushida et al. gave near perfect discrimination between OSA and non-OSA subjects.

No data are available on the applicability of the predictive SMM in patients with OSA from the Indian subcontinent and a Medline search confirms that this is the first study evaluating the correlation between SMM values and the severity of OSA, from this country. There has been only one previous Indian study in which a

Graph 1: Line diagram for the distribution of patient’s AHI versus calculated Stanford Morphometric Model values

Graph 2: Scatter plot of AHI against predicted values of Stanford Morphometric Model
diagnostic model was derived and validated for the prediction of OSA in subjects presenting with non-sleep-related complaints. In the previous study carried out at a tertiary care centre, gender, relative-reported snoring index and choking index were found to be significant, independent predictors of OSA. The results of the present study indicate that the relatively easier morphometric measurements afforded by the SMM, enable faster screening for OSA in a primary health care setting. Other studies worldwide have also validated the applicability of SMM in identifying OSA in clinical practice, with the separation value between subjects with or without OSA being 70,12,13.

A level I overnight PSG is considered the gold standard in the diagnosis of sleep apnoea. The PSG device used in this study meets the requirements of the consensus statement of the American Thoracic Society (1996). Plaster study models were used for the intraoral measurements in this study, since they are a standard component of orthodontic records and they are fundamental to diagnosis and treatment planning, case presentations, evaluation of treatment progress and results, besides record keeping. The dental arch dimensions were measured on study models made of dental stone, by means of digital vernier callipers. Compared to dividers, studies have shown that by using sliding manual/digital vernier callipers, accurate measurements could be made from the study models in all three dimensions. Although some new methods like geometric morphometrics provide excellent possibilities for morphological analysis, distance measurements on dental casts were calculated because most clinicians are familiar with the method used in this study.

In the present study, statistically significant differences were found between the two groups for the measurements of palatal height/depth (P<0.05) with the mean palatal depth in patients being greater than the mean palatal depth of the controls. The method used by Kushida et al. and in subsequent studies for measurement of palatal depth was found to be subjective and difficult to standardise for a large group. A new method for measurement of palatal depth was resorted to, because it is difficult to measure palatal depth with 20° mouth opening and from the dome of the tongue in all cases. In order to standardise the measurement of palatal depth in this study, the study models were trimmed until the distal contact point of the upper first molars showed up on the edge. Distance from the mid-deepest part of the palate to the line connecting the left and right distolinguclus tips of the upper first molars was taken as palatal depth.

The minimum age of the subjects in this study was chosen on the basis of previous studies, which have reported that molar and canine arch widths do not change after 13 years of age in females and 16 years of age in males. Therefore, it was assumed that the arch widths of the subjects studied were fully developed. The strength of the present study is the inclusion of a relatively large group of Indian patients with OSA, who underwent a limited hospital-based sleep study, matched with control subjects for age and gender. This study highlights the importance of matching subjects for age to prevent any age-related morphological changes from confounding the results.

**Study limitations**

This is a cross-sectional study based on enrolment of patients attending one hospital clinic. As expected, the patients in this study only represent at best the patients attending this clinic. Further research is necessary to generalise the results to the general population and other ethnicities. Another limitation of this study was that PSG was not carried out for the controls, due to ethical considerations and the prohibitive expense of the procedure. This is usually the case with studies incorporating normal controls who do not exhibit any symptoms of OSA.

**Conclusion**

1. There is no significant correlation between OSA severity as indicated by AHI and the SMM values in this sample of Indian OSA patients.
2. The SMM proposed by Kushida et al. is applicable to the selected sample in clinical practice.
3. The average predictive MM value for OSA in this sample of Indian patients is only slightly lesser than that observed by Kushida et al.

**References**


Prevalence of Depression and Anxiety in Patients with Sleep-Disordered Breathing and its Correlation with Disease Severity

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Doi: 10.5958/j.0973-340X.7.2.012

Abstract

Objective: Primary objective of the study was to assess the prevalence of depression and anxiety among obstructive sleep apnoea (OSA) patients presenting to the sleep clinic of Safdarjung Hospital. Secondary aim was to study the correlation between and severity of depression, anxiety and respiratory disturbance index (RDI) and to see any relation with gender.

Study design: Case-control study.

Materials and Methods: One hundred seventy-two patients with OSA were evaluated before treatment and compared with controls by using the Patient Health Questionnaire-9 (PHQ-9) and anxiety on the basis of General Anxiety Disorder Assessment-7 score (GAD-7). Based on these scores, depression and anxiety were categorised as mild, moderate and severe, respectively. OSA was assessed by Epworth Sleepiness Scale, and polysomnography was used for sleep scoring and classified to mild, moderate and severe OSA by RDI.

RESULTS: Depressive symptoms were identified in 14% (25 of 172) of controls, and 36.4% (62 of 172) of patients with OSA by using PHQ-9 screening (P<0.006). Anxiety was identified in 19.2% (33 of 172) OSA patients as compared to 6.7% of controls. Evaluation of the patients with OSA compared to the control group showed depression and anxiety to be significantly more common in OSA patients than in controls (P-values 0.006 and 0.01, respectively). Overall, 41.9% and 58.1% of men and women, respectively, with OSA had elevated PHQ-9 scores; 05% and 11% of male and female control patients, respectively, exhibited depressive symptoms (P<0.001). In all, 75.75% patients were female OSA cases with symptoms of anxiety (25 of 33), while 24.25% were male (P<0.02) as screened by GAD-7 scores. Analysis of depression scores by OSA disease severity category found significant difference in depressive symptoms between participants with mild OSA, moderate OSA and severe OSA (P-value <0.006). In this study, the association between OSA disease severity (as determined from the RDI) and PHQ-9 on univariate analysis (P ¼ .04.00) was significant, with association found (P-value<0.003) on multivariable analysis, after controlling for sex. Partial linearity was noted. Analysis of anxiety scores by GAD-7 scores found no significant difference

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Introduction

Obstructive sleep apnoea (OSA) is a common disease, characterised by repetitive upper airway obstruction during sleep and associated with increased morbidity and mortality and diminished quality of life. Obstructive sleep apnoea syndrome (OSAS) is a common disease, affecting about 2%-4% of the adult population. Tiredness, daytime sleepiness, headache and obesity are common symptoms of OSAS, which often lead to inactivity and cardiovascular or other organ manifestations. Some of the symptoms of OSAS resemble symptoms associated with anxiety and depressive conditions. However, clinicians may have problems differentiating psychiatric disease from symptoms related to organic diseases. Most case–control studies have reported increased prevalence rates of depression in OSA patients compared to controls, but other studies indicate no differences. Further, the relationship between OSAS and depressive symptoms may be moderated by factors such as gender and OSAS severity. The prevalence of depression in people with OSA ranges from 7% to 63%. Although many of these rates reflect the variable composition of the clinical populations studied, they are consistently higher than rates of depression found in community samples (3%-5%) or in the primary care setting (5%-10%). In addition, rates among women appear to be higher than rates in men within the same cohorts.

The direction of the association is unclear because there is significant overlap in the symptoms of OSA and depression, including fatigue, decreased libido and poor concentration, which are common to both conditions and not specific for either. The purpose of this study was to determine whether a relationship exists between depression, anxiety and OSA, disease severity, in patients with OSA presenting to our sleep clinic as compared with controls.

Materials and Methods

Methods

Primary aim of the study was to assess the prevalence of depression among OSA patients presenting to the sleep clinic of Safdarjung Hospital. Secondary aim was to study the correlation between respiratory disturbance index (RDI) and severity of depression and anxiety and to see any relation with gender.

Study Design

It was a case–control study involving 172 patients visiting the sleep clinic of Safdarjung Hospital being evaluated for SDB. Depression was assessed on the basis of Patient Health Questionnaire-9 (PHQ-9) and anxiety on the basis of General Anxiety Disorder Assessment-7 score (GAD-7).

Epworth Sleepiness Scale (ESS) was used for assessing daytime sleepiness. This used self-administered scale with eight items about how easily the respondent would fall asleep in different situations. The items were scored on a 0–3 scale, which were added to give an overall score of 0–24. Higher scores indicate more sleepiness. ESS score 2–10 was considered ‘normal’ and ≥10 indicative of pathological sleepiness. OSAS was diagnosed with a full night of in-laboratory, clinical polysomnography evaluating the following physiological and respiratory variables: central and occipital EEG, oblique EOG, submental and tibialis EMG activity, ECG, nasal and oral airflow via nasal pressure transducer and thermistor, thoracic and abdominal excursions with peizo belts and continuous oxygen saturation. Sleep stage...
was scored by trained technicians using standard criteria\textsuperscript{19}. Apnoeas and hypopnoeas were scored using recommended guidelines. An apnoea was defined as the cessation of airflow for 10 s or longer. Hypopnoea was defined as a 30\% decrease (from baseline) in airflow or chest wall movement for at least 10 s, accompanied by an oxygen desaturation of 4\% or greater. This definition also included respiratory effort–related arousals (RERAs), whereby arousals were identified in the setting of heavy snoring without hypoxaemia or discernible reductions in airflow. Thus, SDB severity was measured by the RDI, an index of apnoeas–hypopnoeas and RERAs, divided by the total sleep time. OSA severity was defined according to the criteria of the American Academy of Sleep Medicine, with mild OSA defined as 5–14 events per hour, moderate as >15 to <30 events per hour and severe OSA defined as 30 events per hour\textsuperscript{16}.

The PHQ-9 scale was used to assess depression. It is a reliable instrument in screening for clinical depression in many different settings and populations\textsuperscript{20}. It incorporated DSM-IV criteria questions as a self-report tool. The scale was self-administered and as 10 items scored on a 0–3 scale. Scores on the items were summed to give a score to comprise the depression score. Hence, scores range 0–21, with higher scores indicated more symptoms of depression. A score greater than or equal to 10 correlated with major depression with a sensitivity and specificity of 88\%, respectively, hence, patients with a score of more than 10 were assigned to have depression. Those with scores of 10, 15 and greater than or equal to 20 were classified to have mild, moderate and severe depression, respectively\textsuperscript{20}.

The GAD-7 score was calculated by assigning scores of 0, 1, 2 and 3 to the response categories of “not at all,” “several days,” “more than half the days” and “nearly every day,” respectively, and adding together the scores for the seven questions\textsuperscript{21}. Scores of 5, 10 and 15 are taken as the cutoff points for mild, moderate and severe anxiety, respectively.

The control population was also chosen among populations attending Outpatient Department in Safdarjung Hospital but with ESS of <10.

Statistical analysis was made by mean, standard deviation percentages. Independent variables like age at time of survey and sex were included. The Fisher exact test was used to compare demographics between OSA and control patients, and the Mann–Whitney U-test was used to compare differences in PHQ-9 and GAD scores between OSA and control patients. Spearman correlation analysis was used to evaluate correlations between factors. Multivariable linear regression analysis was used to examine the data and describe the relationship between OSA, depression, anxiety and sexes. Results of univariate and multivariate analysis are presented as\textit{P}-values and\textit{r}-values. Simple linear regression models were also fitted for each individual factor. Data analyses were conducted using SPSS 11.5 (SPSS, Inc., Chicago, IL). Significance level was set at 0.05 for all analyses.

\textbf{Results}

A total of 172 patients were surveyed. This group was compared with a group of 172 controls who presented to the Department of Respiratory, Critical Care and Sleep medicine for non-sleep-related disease. There was no significant difference between groups with respect to age (Table 1).

The OSA patients differed from controls in that there were less male patients in the OSA group (54.07\%) than in the control group (56.3\%). Patients with OSA differed significantly from controls in regard to mean PHQ-9 and GAD-7 scores for depression and anxiety, respectively (Table 1).

Depressive symptoms were identified in 14\% (25 of 172) of controls, and 36.4 \% (62 of 172) of patients with OSA by using PHQ-9 screening (\textit{P}<0.006). Anxiety was identified in 19.2\% (33 of 172) of OSA patients as compared to 6.7\% of controls. Evaluation of the patients with OSA compared to the control group showed depression and anxiety to be significantly more common in OSA patients than in controls (\textit{P}-values=0.006 and 0.01, respectively). Overall, 41.9\% and 58.1\% of men and women, respectively, with OSA had elevated PHQ-9 scores; 05\% and 11\% of male and female control patients, respectively, exhibited depressive symptoms (\textit{P}<0.001). In all, 75.75\% patients were female OSA cases having symptoms of anxiety (25 of 33), while 24.25\% were male (\textit{P}<0.02) as screened by GAD-7 scores.

Analysis of depression scores by OSA disease severity category found significant difference in depressive symptoms between participants with mild, moderate and severe OSA (\textit{P}-value<0.006).

In this study, the association between OSA disease severity (as determined from the RDI) and PHQ-9 on univariate analysis (\textit{P}<0.00) was significant, with association found (\textit{P}<0.13). But on multivariate analysis,
Prevalence of Depression and Anxiety in Patients with Sleep-Disordered Breathing and its Correlation with Disease Severity

after controlling for sex, partial linearity was noted (Figure 6).

Analysis of anxiety scores by GAD-7 scores found no significant difference in anxiety symptoms between subgroups with mild, moderate and severe OSA (P-value<0.23) on univariate analysis. However, on multivariate analysis, ruling out confounding factor like sex was significant (P-value<0.003; Figure 1).

On comparing the depression scores between two sexes, no significant difference was seen (P-value <0.33). However, on comparing anxiety scores between two sexes, significantly higher scores were seen among females (P-value <0.004).

Table 1: Comparison of demographic characteristics of patient and control population

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>OSA (n=172)</th>
<th>Control (n=172)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>50.59±10.8</td>
<td>50.12±9.4</td>
<td>0.99</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>93 (54.07)</td>
<td>97 (56.3)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>79 (45.9)</td>
<td>75 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Depression PHQ-9 &gt;10</td>
<td>62 (36.4)</td>
<td>25 (14.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Anxiety GAD-7 &gt;10</td>
<td>33 (19.2)</td>
<td>12 (6.9)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

GAD-7: General Anxiety Disorder Assessment-7 score; PHQ-9: Patient Health Questionnaire-9; OSA: Obstructive sleep apnoea

Table 2: Comparison of prevalence of depression and anxiety according to disease severity in OSA population and control population

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control Moderate</th>
<th>Moderate</th>
<th>Severe</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed n (%)</td>
<td>25 (14.5)</td>
<td>19 (30.9)</td>
<td>13 (20.9)</td>
<td>30 (48.3)</td>
</tr>
<tr>
<td>Anxious n (%)</td>
<td>12 (6.9)</td>
<td>11 (33.3)</td>
<td>8 (24.2)</td>
<td>12 (36.6)</td>
</tr>
</tbody>
</table>

OSA: Obstructive sleep apnoea

Figure 1: Comparison of prevalence of depression according to disease severity in obstructive sleep apnoea (OSA) population and control population. MOD: moderate; SEV: Severe.

Table 3: Severity of depression and anxiety in male and female sexes of OSA population

<table>
<thead>
<tr>
<th>Depression</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>16 (16.2)</td>
<td>6 (6.3)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>23 (29.9)</td>
<td>7 (9.1)</td>
<td>4 (5.2)</td>
</tr>
</tbody>
</table>

OSA: Obstructive sleep apnoea

Figure 2: Comparison of prevalence of anxiety according to disease severity in obstructive sleep apnoea (OSA) population. MOD: moderate.

Table 3: Severity of depression and anxiety in male and female sexes of OSA population

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>1 (1.1)</td>
<td>4 (4.2)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>9 (11.7)</td>
<td>13 (16.9)</td>
<td>3 (3.9)</td>
</tr>
</tbody>
</table>

MOD: moderate; OSA: obstructive sleep apnoea.
On comparison with anxiety and OSA, $P$-value $>0.05$ and $r$-value $=0.69$ implies absence of any colinearity.

Discussion

Depression in OSA patients was much more common in this study (36%) than in a recent report by Chandra et al. looking at the prevalence of depression in patients with sleep apnoea seen in the general practice setting (14%)\(^{12}\).

To better understand the relationship between sleepiness and mood disorders, researchers have evaluated the effects of acute sleep deprivation (24 h) on healthy adults without pre-existing mood disorders and have found that depression and anxiety are elevated after acute sleep deprivation\(^{25}\). Correlation has also been seen between increased levels of sleepiness and increasing depressive symptoms, a finding which suggests that there may be a causal relationship between the two conditions\(^{36}\). Although little is known about the effects of chronic sleep deprivation or sleep restriction on the incidence of mood disorders, several studies have suggested that the relationship between the two is complex and that sleepiness may in fact be more than a symptom of depression; rather, sleepiness instead may contribute to the development of depression\(^{27,28}\). In addition, recent studies have looked at the effect of chronic sleep restriction/deprivation on the brain chemistry of rats and found that the changes in neurotransmitter receptor systems and neuroendocrine reactivity are similar to those seen in depression\(^{29}\). OSA is associated with elevated levels of the cytokines IL-6 and tumour necrosis factor\(^{30,31}\). These cytokines have been proposed as the mediators of daytime sleepiness in this condition. Administration of a tumour necrosis factor antagonist has been shown to dramatically reduce the level of daytime sleepiness in patients with OSA\(^{32}\). Major depression has also been shown to be associated with an immune response involving proinflammatory cytokines IL-1, IL-6\(^{33}\). While these studies involve small numbers of subjects and do not imply causation, they do suggest a possible shared pathway between abnormalities in central and peripheral neurotransmission of serotonin\(^{34}\). Serotonin is also thought to be involved in the sleep dependant reduction in output to the upper airway dilator muscles, particularly, the hypoglossal nucleus, although this pathway is extremely complex, with multiple receptor subtypes\(^{35}\). The exact role of serotonin in the hypoglossal nucleus has also not been characterised. Again this may suggest a shared pathway. A further possibility is an as yet uncharacterised underlying causal mechanism for both OSA and depression. Overall, similar factors may be causative for both OSA and depression, with links between the two still uncertain. In our study also we could not establish the nature of the relationship\(^{36}\).

Gender appears to moderate the relationships between apnoea severity, depression and anxiety. Men only showed an insignificant association with depression. On the other hand, Women only showed a relationship with depression, independent of apnoea severity. However, in our study, gender-specific relation was found
with anxiety rather than depression.

These findings suggest that men and women with apnoea manifest depressive symptoms differently. Pillar et al.\(^9\) found that women with OSAS scored higher on depression and anxiety scales than did men with OSAS. They attributed these findings in part to basic gender differences in personality, suggesting that women tend to focus more on their symptoms than do men\(^5,38\).

Given these findings, the gender-specific manifestation of depression and the mechanisms underlying these relationships deserves closer attention.

Noting that early studies showing links between depressive symptoms and sleep fragmentation or hypoxia in OSA had small numbers of patients and did not control depressive symptoms and sleep fragmentation or hypoxia underlying these relationships deserves closer attention.

manifestation of depression and the mechanisms et al.\(^{12}\) later compared the effects of Continuous Positive Airway Pressure CPAP and oxygen therapy on depressive symptoms in a controlled randomised trial in 38 people with OSA. While other arms showed no significant effect, the oxygen therapy arm showed significant reduction in psychological symptoms. Authors concluded that in patients with OSA, hypoxaemia may play a stronger role than sleep disruption in depression. In contrast, a case–control study\(^{39}\) showed psychological symptoms to be correlated with sleep fragmentation but not with oxygen desaturation. Thus, the actual relationship between depression, anxiety and sleep is not clear. In our study also we could not establish any such causal relation.

Our study has several limitations. First, based on the nature of our correlational analyses, causation cannot be inferred. Second, there was no significant correlation between severity of OSA and anxiety, may be due to a smaller population of study as compared with that of the population with depression.

**Conclusions**

Patients with OSA are more likely to have depressive and anxiety symptoms compared to controls (37\% versus12\% and 19.18\% versus6.9\%) regardless of their sex. OSA disease severity (measured by the RDI) is a predictor of PHQ-9 scores but not that of anxiety score predictor (GAD-7). Sex-related prevalence shows an increase with female sex but there is no correlation with severity of depression but there is a positive correlation with anxiety scores. However, we could not establish whether the relation between depression, anxiety and OSA is causal or not, further studies are required to establish that. Thus, any patient presenting with depression and anxiety should be evaluated for OSA and vice versa.

**References**


15. **PHQ-9 & GAD-7 questionnaires**


Burnout in ICU Caregivers: A Multicenter Study of Factors Associated to Centers

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Rationale: The stressful work environment of ICUs can lead to burnout. Burnout can impact on the welfare and performance of caregivers, and may lead them to resign their job. The shortage of ICU caregivers is becoming a real threat for health care leaders.

Objectives: To investigate the factors associated with burnout on a national level in order to determine potential important factors.

Methods: Prospective, multicenter, observational survey of all caregivers from 74 of the 92 Swiss ICUs, measuring the prevalence of burnout among the caregivers and the pre-specified center-, patient and caregiver-related factors influencing its prevalence.

Measurements and Main Results: Out of the 4322 questionnaires distributed from March 2006 to April 2007, 3052 (71%) were returned, with a response rate of 72% by center, 69% from nurse assistants, 73% from nurses and 69% from physicians. A high proportion of female nurses among the team was associated with a decreased individual risk of high burnout (OR 0.98, 95% CI:0.97–0.99 for every %). The caregiver-related factors associated with a high risk of burnout were being a nurse-assistant, being a male, having no children and being under 40 years old.

Conclusions: The findings of this study seem to open a new frontier concerning burnout in ICUs, highlighting the importance of team composition. Our results should be confirmed in a prospective multicenter, multinational study. Whether our results can be exported to other medical settings where team-working is pivotal remains to be investigated.

Keywords: critical care; job satisfaction; multicenter; intensive care unit management; intensive care unit organization

Developing quantitative physiological phenotypes of sleep apnea for epidemiological studies.

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Existing physiological databases have not been sufficiently detailed to provide relevant and important information.
for characterizing the pathophysiology of obstructive sleep apnea. Critical collapsing pressure (P(CRIT)) is a standard method for determining upper airway patency during sleep, however is labor intensive and prohibits large-scale studies. Based on previously published data indicating R(US) does not significantly vary between groups, our aim was to develop an approach to estimate the P(CRIT) from airflow at atmospheric pressure (V(atm)). In a dataset of 126 subjects, where P(CRIT) and R(US) were measured using standard techniques. We then determined the minimum sample size required to estimate the R(US) mean and variance by utilizing a bootstrap procedure (30 times for n=3 to 126). We first estimated the minimum number of subjects needed for obtaining a group for a two-tailed (z=1.96) standard error for R(US) in the population. Then in 75 individuals, quantitative estimates of airflow were obtained at atmospheric pressure. Using the estimated R(US) and atmospheric, we determined an estimated P(CRIT) (ªP(CRIT)). Bland-Altman plots were generated to determine the agreement between the measured P(CRIT) and ªP(CRIT). For the entire population the mean ± SEM R(US) was 23 ± 1 cmH(2)O/L/s (± 95% CI: 21, 25). ~40 subjects represent the minimum sample required to estimate the population variance within ± 2 SEM. In the subsample with atmospheric flow measurements, a linear regression model (ªP(CRIT) [cmH(2)O] = V(atm) [L/s]x-23 [cmH(2)O/L/s]), ªP(CRIT) ranged from 0 to -9.6 cmH(2)O. In the Bland-Altman analysis there was no mean difference between the measured P(CRIT) and ªP(CRIT) (-0.01 cmH(2)O; p=0.8) with upper and lower limits of agreement at ± 2.3 cmH(2)O. The variance of upstream resistance approaches a constant value in groups with approximately 40 subjects. Utilizing a fixed upstream resistance to estimate P(CRIT) from the airflow at atmospheric pressure agrees with the measured values. These data suggest that measurements of quantitative airflow during standard polysomnography can be used to determine upper airway properties in large cohorts.

Polymorphisms in the 5-HTR2A gene related to obstructive sleep apnea syndrome.

[Article in English, Portuguese]

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Obstructive sleep apnea syndrome (OSAS) is one of the most complex disorders of sleep; it involves several genetic factors that contribute to the phenotype.

Serotonin (5-HT) regulates a variety of visceral and physiological functions, including sleep. Gene 5-HTR2A polymorphisms may change the transcription of several receptors in the serotoninergic system, thereby contributing to OSAS.

AIM: To investigate the prevalence of T102C and -1438G/A polymorphisms in the 5-HTR2A gene of patients with and without OSAS.

MATERIAL AND METHOD: A molecular study of 100 index-cases and 100 controls of both genders. DNA was extracted from blood leukocytes samples and the regions that enclose both polymorphisms were amplified with PCR-RFLP.

STUDY DESIGN: A cross-sectional case study.

RESULTS: There was a significant prevalence of males in index cases compared to controls (p<0.0001). No significant genotypic differences between cases and controls were found in T102C polymorphisms (p=1.000). There were significant differences between the AA genotype of -1438G/A polymorphisms and patients with OSAS (OR:2.3; CI95%:1.20-4.38, p=0.01).

CONCLUSION: Serotonergic mechanisms may be related to OSAS. There were no differences in the prevalence of T102C polymorphisms in patients with OSAS and the control group. There is evidence of an association between the -1438G /A polymorphism and OSAS.
Heritability and mortality risk of insomnia-related symptoms: a genetic epidemiologic study in a population-based twin cohort.

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STUDY OBJECTIVES: Our aim was to estimate heritability in phenotypic insomnia and the association between insomnia and mortality.

DESIGN: Representative follow-up study.

PARTICIPANTS: 1990 survey of the Finnish Twin Cohort (N = 12502 adults; 1554 monozygotic and 2991 dizygotic twin pairs).

MEASUREMENTS: Current insomnia-related symptoms (insomnia in general, difficulty in initiating sleep, sleep latency, nocturnal awakening, early morning awakening, and non-restorative sleep assessed in the morning and during the day) were asked. Latent class analysis was used to classify subjects into different sleep quality classes. Quantitative genetic modelling was used to estimate heritability. Mortality data was obtained from national registers until end of April 2009.

RESULTS: The heritability estimates of each symptom were similar in both genders varying from 34% (early morning awakening) to 45% (nocturnal awakening). The most parsimonious latent class analysis produced 3 classes: good sleepers (48%), average sleepers (up to weekly symptoms, 40%), and poor sleepers (symptoms daily or almost daily, 12%). The heritability estimate for the cluster was 46% (95% confidence interval 41% to 50%). In a model adjusted for smoking, BMI, and depressive symptoms, the all-cause mortality of poor sleepers was elevated (excess mortality 55% in men and 51% in women). Further adjustment for sleep length, use of sleep promoting medications, and sleep apnea-related symptoms did not change the results.

CONCLUSIONS: Insomnia-related symptoms were common in both genders. The symptoms and their clusters showed moderate heritability estimates. A significant association was found between poor sleep and risk of mortality, especially in those with somatic disease.

Asthma-related comorbidities.

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Centre de Recherche de l’Institut Universitaire de Cardiologie et de Pneumologie, de Québec, 2725, Chemin Sainte-Foy, QC, G1V 4G5, Canada. lpboulet@med.ulaval.ca

Asthma is often associated with various comorbidities. The most frequently reported asthma comorbid conditions include rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hormonal disorders and psychopathologies. These conditions may, first: share a common pathophysiological mechanism with asthma; second: influence asthma control, its phenotype and response to treatment; and third: be more prevalent in asthmatic patients but without obvious influence on this disease. For many of these, how they interact with asthma remains to be further documented, particularly for severe asthma. If considered relevant, they should, however, be treated appropriately. Further research is needed on the relationships between these conditions and asthma.

Sleep disturbances in children with attention-deficit/hyperactivity disorder.

Spruyt K, Gozal D.

Department of Pediatrics, Comer Children’s Hospital, Pritzker School of Medicine, The University of Chicago, Chicago, Illinois 60637, USA.

In this article, we advocate the need for better understanding and treatment of children exhibiting inattentive, hyperactive, impulsive behaviors, by in-depth questioning on sleepiness, sleep-disordered breathing or problematic behaviors at bedtime, during the night and upon awakening, as well as night-to-night sleep duration variability. The relationships between sleep and attention-deficit/hyperactivity disorder (ADHD) are complex and are routinely overlooked by practitioners. Motricity and somnolence, the most consistent complaints and objectively measured sleep problems in children with
ADHD, may develop as a consequence of multidirectional and multifactorial pathways. Therefore, subjectively perceived or reported restless sleep should be evaluated with specific attention to restless legs syndrome or periodic limb movement disorder, and awakenings should be queried with regard to parasomnias, dyssomnias and sleep-disordered breathing. Sleep hygiene logs detailing sleep onset and offset quantitatively, as well as qualitatively, are required. More studies in children with ADHD are needed to reveal the 24-h phenotype, or its sleep comorbidities.


Residual sleepiness in obstructive sleep apnoea: phenotype and related symptoms.
Vernet C, Redolfi S, Attali V, Konofal E, Brion A, Frijia-Orvoen E, Pottier M, Similowski T, Arnulf I.

Sleep Disorders Unit, UMR 975, National Reference Centre for Narcolepsy and Hypersomnia, Paris, France.

The characteristics of residual excessive sleepiness (RES), defined by an Epworth score >10 in adequately treated apnoic patients, are unknown. 40 apnoic patients, with (n = 20) and without (n = 20) RES, and 20 healthy controls underwent clinical interviews, cognitive and biological tests, polysomnography, a multiple sleep latency test, and 24-h sleep monitoring. The marked subjective sleepiness in the RES group (mean ± sd score 16.4 ± 3) contrasted with moderately abnormal objective measures of sleepiness (90% of patients with RES had daytime sleep latencies >8 min). Compared with patients without RES, the patients with RES had more fatigue, lower stage N3 percentages, more periodic leg movements (without arousals), lower mean sleep latencies and longer daytime sleep periods. Most neuropsychological dimensions (morning headaches, memory complaints, spatial memory, inattention, apathy, depression, anxiety and lack of self-confidence) were not different between patients with and without RES, but gradually altered from controls to apnoic patients without and then with RES. RES in apnoic patients differs markedly from sleepiness in central hypersomnia. The association between RES, periodic leg movements, apathy and depressive mood parallels the post-hypoxic lesions in noradrenaline, dopamine and serotonin systems in animals exposed to intermittent hypoxia.


Daytime sleepiness and REM sleep characteristics in myotonic dystrophy: a case-control study.
Yu H, Laberge L, Jaussent I, Boyard S, Scholtz S, Raoul M, Pages M, Dauvilliers Y.

Service de Neurologie, Hôpital Gui-de-Chauliac, 80 avenue Augustin Fliche, Montpellier cedex 5, France.

STUDY OBJECTIVES: Excessive daytime sleepiness (EDS) and high daytime REM sleep pressure are important sleep features of myotonic dystrophy (DM1). Small and uncontrolled studies have focused on EDS phenotype; none have focused on nocturnal REM sleep characteristics in DM1. Our objectives were to compare polysomnographic and multiple sleep latency test (MSLT) parameters, and both tonic and phasic components of REM sleep between DM1 and controls.

DESIGN AND PATIENTS: Forty consecutive DM1 patients and 40 sex- and age-matched controls were included. All subjects underwent overnight polysomnography followed by a MSLT.

RESULTS: About 80% of DM1 patients complained of EDS through clinical interview: 31.4% had Epworth scores > 10, and 12.5% had objective sleepiness (latency < 8 min). Higher apnea and central apnea indexes, and a greater proportion of subjects with severe apnea/hypopnea syndrome were found in DM1. The number of SOREMP differed between DM1 and controls, one and two SOREMPs being present in 47.5% and 32.5%, and one control had one SOREMP. Higher percentages of slow wave sleep and REM sleep were found in DM1. DM1 patients had significantly more PLMW, PLMS in both NREM and REM sleep, and PLMS-associated microarousals. Higher REM density was found in DM1 with similar tendencies for either REM sleep without atonia or phasic EMG activity.

CONCLUSIONS: This is the first case-control sleep study in DM1 to demonstrate higher frequency of daytime sleepiness and abnormalities in REM sleep.
regulation, with an increased daytime and nighttime REM sleep propensity, REM density, and PLMS. These data suggest a primary central sleep regulation dysfunction in DM1.


Systems biology analyses of gene expression and genome wide association study data in obstructive sleep apnea.


Center for Proteomics & Bioinformatics, Case Western Reserve University (CWRU), Cleveland, Ohio, 44106, USA. yxl442@case.edu.

The precise molecular etiology of obstructive sleep apnea (OSA) is unknown; however recent research indicates that several interconnected aberrant pathways and molecular abnormalities are contributors to OSA. Identifying the genes and pathways associated with OSA can help to expand our understanding of the risk factors for the disease as well as provide new avenues for potential treatment. Towards these goals, we have integrated relevant high dimensional data from various sources, such as genome-wide expression data (microarray), protein-protein interaction (PPI) data and results from genome-wide association studies (GWAS) in order to define sub-network elements that connect some of the known pathways related to the disease as well as define novel regulatory modules related to OSA. Two distinct approaches are applied to identify sub-networks significantly associated with OSA. In the first case we used a biased approach based on sixty genes/proteins with known associations with sleep disorders and/or metabolic disease to seed a search using commercial software to discover networks associated with disease followed by information theoretic (mutual information) scoring of the sub-networks. In the second case we used an unbiased approach and generated an interactome constructed from publicly available gene expression profiles and PPI databases, followed by scoring of the network with p-values from GWAS data derived from OSA patients to uncover sub-networks significant for the disease phenotype. A comparison of the approaches reveals a number of proteins that have been previously known to be associated with OSA or sleep. In addition, our results indicate a novel association of Phosphoinositide 3-kinase, the STAT family of proteins and its related pathways with OSA.


Cost-effectiveness of adenotonsillectomy in reducing obstructive sleep apnea, cerebrovascular ischemia, vaso-occlusive pain, and ACS episodes in pediatric sickle cell disease.

Tripathi A, Jerrell JM, Stallworth JR.

Department of Epidemiology and Biostatistics, University of South Carolina Arnold School of Public Health, Columbia, SC, USA.

In children with sickle cell disease (SCD), adenotonsillar hypertrophy or recurrent tonsillitis are frequently linked with an increased risk of obstructive sleep apnea, cerebrovascular ischemia, or frequent pain episodes and often require an adenoidectomy and/or tonsillectomy. Interventions designed to prevent these complications, control vaso-occlusive pain episodes, and avoid hospitalizations may reduce the significant personal and economic burden of SCD. This study compares episode recurrence and treatment costs for cerebrovascular ischemia, vaso-occlusive pain, acute chest syndrome (ACS), and obstructive sleep apnea in children who had an adenotonsillectomy (A/T surgery, N = 256; 11.7%) and a matched cohort of those who did not (N = 512; 23.3%) from a cohort of 2,194 children and adolescents with SCD from South Carolina's Medicaid system. A/T surgery was associated with a significantly reduced rate of visits over time for obstructive sleep apnea and cerebrovascular ischemia (e.g., stroke, transient ischemic attacks), but not with any change in the rate of visits for vaso-occlusive pain or ACS/pneumonia visits. The rate of mean acute (emergency and inpatient) service costs was significantly decreasing over time after an increase about the time the A/T surgery was performed. The cost-effectiveness of adenoidectomy and/or tonsillectomy for treating obstructive sleep apnea and preventing cerebrovascular ischemia without increasing vaso-occlusive pain episodes or long-term acute service costs
in routine clinical practice settings was demonstrated. The matched control group of SCD patients without A/T surgery contained more patients with severe vaso-occlusive pain episodes, ACS visits, and higher mean total costs over time and appears to represent a different phenotype of children with SCD.


**Polymorphisms of the noggin gene and mandibular micrognathia: a first approximation.**

**Gutiérrez SJ, Gómez M, Rey JA, Ochoa M, Gutiérrez SM, Prieto JC.**

Dental Research Center, School of Dentistry, Javeriana University, Bogotá, Colombia. s.gutierrez@javeriana.edu.co

Mandibular micrognathia is a deficiency in mandibular growth that prevents tooth contact during mastication, interferes with phonation and even causes sleep apnea. Studies show that mutant mice for chd (chordin) and nog (noggin) genes, which are modulators of the Bone Morphogenic Protein (BMP), had mandibular defects ranging from mandibular hypoplasia to micrognathia and agnathia. The human NOG gene was the first BMP antagonist identified and it is essential for various late events in mandibular development, which require modulation of the BMP activity. The aim of this work was to determine the presence of NOG gene polymorphisms in families with mandibular micrognathia and analyze its phenotype. Four families with mandibular micrognathia were included in this study. Blood samples were taken from the participating individuals through venipuncture and DNA was extracted. The fragments of interest were amplified using the Polymerase Chain Reaction (PCR) and the Single Nucleotide Polymorphisms (SNPs) of the NOG gene reported in the NCBI data base were analyzed through direct sequencing. The SNP rs1348322 was present in homozygote form in the subjects from all the families, where Cytosine is changed to Adenine in position 112 of the exon of the NOG gene. The SNP rs1236187 did not show any clear result. This result suggests that there may be population polymorphism, or markers that are seldom polymorphic for our population. It is therefore necessary to continue with the search for the relationship of the NOG gene with mandibular micrognathia.


**Non-synonymous polymorphism in the neuropeptide S precursor gene and sleep apnea.**


Respiratory Diseases Research Unit, IRB Lleida, Lleida, Spain.

BACKGROUND: Obstructive sleep apnea syndrome (OSAS) is a complex disease with a strong genetic basis. One of the primary molecular domains affected by OSAS is sympathetic activity. Neuropeptide S (NPS) plays an important role in the regulation of the sleep-wakefulness cycle, anxiety states, and daytime sleepiness. It is important to study neuropeptides related to sympathetic activity regulation and how their function could be modified by genetic variants affecting the expression of these molecules.

OBJECTIVES: We investigated the association of the non-synonymous polymorphism rs4751440 in the NPS precursor gene with OSAS and certain variables related to OSAS (daytime sleepiness, body mass index (BMI), insulin resistance, and blood pressure). This polymorphism causes an amino acid substitution in exon 3 of the human NPS precursor gene.

PATIENTS AND METHODS: We included 253 OSAS patients and 70 healthy subjects. Genotyping was done by polymerase chain reaction using specific flanking primers and agarose gel electrophoresis. Daytime sleepiness, BMI, plasma levels of high-density lipoprotein, glucose, total cholesterol, insulin, triglycerides, and the homeostasis model assessment index were also determined.

RESULTS: A similar genotypic and allelic distribution was found in OSAS patients and controls. The risk of OSAS was not associated with the rs4751440 polymorphism. There was no significant interaction between daytime sleepiness or metabolic variables and the rs4751440 polymorphism.

CONCLUSION: Genotypic and allelic frequency distribution of the rs4751440 polymorphism was similar in OSAS patients and controls. In this population-based
study, we could not show a significant association between rs4751440 polymorphism and susceptibility to OSAS or certain phenotypes related to OSAS (daytime sleepiness, BMI, systolic blood pressure, and insulin resistance) with the exception of diastolic blood pressure.
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