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CLINICAL REVIEW

Peripheral neuropathology of the upper airway in obstructive sleep apnea syndrome

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SUMMARY

Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder that leads to significant morbidity and mortality without adequate treatment. Though much emphasis on the pathogenesis of OSAS has been placed on a narrow upper airway space and associated muscular factors, possible neuropathy of the upper airway has not been fully elucidated. Increasing peer reviewed evidence suggests involvement of neurologic lesions of the upper airway in OSAS patients.

In this article, we review the etiology and pathophysiology of OSAS, the evidence and possible mechanisms leading to upper airway neuropathy, and the relationship between upper airway neuropathy and OSAS. Further studies should focus on the long term effects of the upper airway neuropathy as related to the duration and severity of snoring and or apnea, and also on the potential methods of prevention and management of the neuropathy in sleep disordered breathing.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common, chronic disorder that is characterized by sleep fragmentation due to apnea, hypopnea, and repeated arousals resulting from partial or complete closure of the upper airway, and occurs in patients of all ages. An essential component in the pathogenesis of OSAS is an increase in upper airway resistance and obstruction that may result from either upper airway anatomical abnormalities or problems related to neuromuscular control of the upper airway.

Though the precise contributions of neuromuscular and anatomical factors on OSA pathogenesis are still debated,[1–3] it is clear that there is a significant role for neuromuscular response in keeping the upper airway patent.

Pathogenesis of OSAS

The human upper airway serves as a multipurpose structure for tasks of speech and deglutition, and as an air passage for breathing. Though the upper airway is composed of numerous muscles and soft tissues, it lacks a rigid support, particularly between the hard palate and the larynx. This lack of bony or cartilaginous support

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facilitates finely tuned phonation and articulation, but also makes the upper airway vulnerable to collapse, especially during physiological changes in sleep. In addition to the discrepancy between the anatomic space determined by physical exam and the severity of OSAS,[3] recent research has demonstrated that anatomical and neuromuscular factors might contribute to the upper airway narrowing and collapse, and thus to the development of OSAS.[1,2,4]

An anatomically narrow upper airway is more prone to collapse than a wider one. The soft tissue structures of the pharynx and their associated skeletal structures are important factors in determining the airway structure. Relevant skeletal structures include the mandible, the hard palate of the maxilla, and the position of the hyoid bone. These skeletal structures partly confine or malposition oral and pharyngeal soft tissues, including the lateral pharyngeal wall, adenotonsillar tissue, the tongue, the soft palate, and pharyngeal fat pads. Either excess soft tissue in the pharynx (as with tonsillar hypertrophy or submucosal edema in the lateral walls of the pharynx,[5] or as a result of obesity) and/or a small bony cage resulting from skeletal structures (as in retrognathia), can compromise the upper airway lumen in patients with OSAS.

During wakefulness, the cross-sectional area of the upper airway as measured by computed tomography and magnetic resonance imaging, is reduced in patients with OSAS compared to subjects without OSAS.[6,7] The arrangement of soft tissue structures is also altered in patients with OSAS, with a reduction in the lateral pharyngeal wall space playing a significant factor in OSAS pathogenesis compared to other soft tissue structures.[8] It is important to note, however, that imaging studies during wakefulness may not necessarily reflect the actual process of OSAS during sleep, particularly due to the influence of neuromuscular factors such as dilator muscle activity in the upper airway.

Obesity is a major risk factor for OSAS. It can result in increased neck circumference, parapharyngeal fat pads, and possibly fat deposition in the tongue.[9,10] An increase in the fat pad around the neck may decrease the upper airway space and possibly counteract the effects of upper airway dilator muscle activity to maintain upper airway patency, thus increasing likelihood of upper airway collapse.

Critical closing pressure (P_{crit})

The pressure at which the upper airway collapses during sleep is called the critical closing pressure (P_{crit}). In healthy subjects, a negative pressure (vacuum) must be exerted intraluminally to cause airway closure (negative P_{crit}). Patients with OSAS usually have a positive P_{crit}, meaning there is a tendency to collapse even without a negative pressure pulling on the pharyngeal walls. The role of upper airway anatomy in the pathogenesis of OSAS can be assessed by gauging P_{crit}. Under conditions of general anesthesia and muscle paralysis (thereby negating the role of neuromuscular factors), Isono and colleagues observed a positive P_{crit} in patients with OSAS as compared to control subjects.[11]

Though patients with OSAS have an elevated/positive P_{crit}, their airway remains open during wakefulness. Further evidence suggests that mechanical loads to narrow the upper airway may account for only one-third of the variability in sleep apnea severity.[12] In a study by Patil and colleagues, evaluating the relative contribution of mechanical loads (such as obesity or narrow upper airway anatomy – i.e., passive P_{crit}) and dynamic neuromuscular response (active P_{crit}) to pharyngeal collapse during sleep, found that the sleep apnea patients had elevated passive P_{crit} compared to normal subjects. Dynamic upper airway responses were depressed in sleep apnea patients as indicated by their inability to lower active P_{crit} in response to upper airway obstruction.[13] Some normal subjects also had elevated passive P_{crit} suggesting elevated mechanical loads, but did not develop sleep apnea as their dynamic response to upper airway obstruction. Therefore, increased mechanical loads and blunted neuromuscular responses are both required for the development of OSAS.[13]

Neuromuscular factors

There are various neuromuscular factors that play a role in maintaining upper airway patency, both during wakefulness and during sleep in healthy subjects. Upon inhalation, the upper airway is subjected to negative pressure generated by respiratory muscle activity. The negative pressure reflex of the upper airway opposes the negative collapsing effect by activating the upper airway dilator muscles.[14–16] The negative pressure reflex is mediated primarily by mechanoreceptors within the pharynx. Therefore an intact neuromuscular circuit is of paramount importance to maintain upper airway patency. One or more of these pathways can be affected in patients with OSAS.

In fact, the dynamic neuromuscular factors of the upper airway differ between OSAS patients and normal subjects, even in wakefulness. Anatomically narrow upper airways during wakefulness require increased genioglossus muscle activity to overcome the mechanical overload. Similar dynamic neuromuscular responses during sleep can compensate for upper airway mechanical loads and stabilize airway patency.[17,18] A blunted response in such situations with increased upper airway mechanical load can predispose an individual to OSAS. Therefore, further examination of the dynamic neuromuscular response is required to properly elucidate the pathogenesis of OSAS.[1,4] A lesion, such as a peripheral neuropathy of the upper airway could therefore predispose to OSAS.

Evidence for neuropathy of the upper airway

Afferent sensory receptors

There are different types of sensory receptors in the upper airway. These receptors respond to pressure, respiratory muscle drive, cold, heat, irritants, and other chemicals. Among these receptors, the mechanoreceptors of the upper airway have been well studied.

The mechanoreceptors of the upper airway respond to changes in airway pressure, airflow, temperature, and to upper airway muscle tone.[19] Though there is no direct evidence that these receptors are affected in OSAS, there is indirect evidence that these receptors play a role in maintaining upper airway patency. Animal models have demonstrated augmented activity in the genioglossus muscle with negative upper airway pressure generation, which could be blocked by sectioning the superior laryngeal nerve or by applying topical anesthesia.[15,20] Similarly, diversion of tidal volume away from these mechanoreceptors through tracheostomy, promoted pharyngeal closure, which was restored with application of phasic pharyngeal pressures.[21]

Human studies have also demonstrated increased pharyngeal airflow resistance compromising upper airway patency both during normal sleep and in wakefulness, when the pharynx and glottis were anesthetized with topical lidocaine.[22] Similar results were seen in normal adult male subjects when the oropharyngeal and nasal mucosa were anesthetized,[23,24] and the same were noted in snorers with increased frequency of obstructive hypopneic and apneic events.[25] Apnea induction leading to electroencephalographic (EEG) arousals occurred more rapidly when upper airway mechanosensory receptors were exposed to pressure fluctuations in animal models and normal humans compared to when they were not.[26,27] Application of topical anesthesia to the upper airway in OSA patients, resulted in a delay of apnea-induced EEG arousals

and an increase in apnea duration.[28] Though these studies do not directly implicate the role of mechanoreceptors in the pathogenesis of OSA, they suggest lesions such as neuropathy in these areas could contribute to upper airway collapse.

Upper airway mucosa

Larsson and colleagues tested temperature thresholds for heat and cold on the tonsillar pillars of control subjects (who did not snore) and patients with OSAS. They found significant differences in patients with OSAS (6 of the 15 patients); they were unable to differentiate between heat and cold. No differences were found at the tip of the tongue, indicating a very local sensory dysfunction.[29] Friberg and colleagues also found differences in vascular reactivity in the soft palatal mucosa using electrical stimulation in subjects with habitual snoring and OSA patients when compared with normal control subjects.[30] The normal response of vasodilation was exaggerated in habitual snorers and patients with mild OSAS compared to normal control subjects, and patients with severe OSA exhibited a marked reduction in reactivity. The latter finding could be explained by an almost complete loss of afferent C fibers. The exaggerated response in habitual snorers and mild OSA patients may be the result of minor lesions with consequent reinnervation, leading to increased sensitivity to mechanical stimuli.[31]

Kimoff and colleagues have found further substantiated sensory dysfunction in OSAS patients and in non-apneic snorers when compared with non-snoring control subjects when they studied two-point discrimination and vibratory sensation in the upper airway mucosa.[32] No significant differences were found between snorers and OSA patients. When 16 OSAS patients were retested after continuous positive airway pressure (CPAP) treatment, vibration thresholds had significantly improved, although the two-point discrimination did not change. Guilleminault and colleagues[33] also showed that patients with OSA had an impairment of their palatal sensory input, with a significant decrement in two-point discrimination when compared with patients with upper airway resistance syndrome (UARS) and normal control subjects.

Using endoscopic sensory testing, Nguyen and colleagues[34] showed mucosal sensory function impairment in multiple sites of the upper airway including the velopharynx and the upper larynx, more particularly at the level of the aryepiglottic eminence in OSA patients. The impairment did not appear to be restricted to the oropharyngeal/laryngeal mucosa. They noted no differences in sensory threshold between OSAS patients and matched controls when endoscopic sensory testing was delivered on the lips. Furthermore, these investigators also demonstrated a significant correlation between the severity of laryngeal mucosal dysfunction and the severity of OSA. These studies at least inform us that there is evidence for mucosal lesions involving the upper airway in OSA patients.

Motor deficits

Pharyngeal dilator muscles are important to maintain patency of the upper airway. Patients with narrow upper airway (commonly found in OSAS patients) have shown increased activity of these pharyngeal dilator muscles during wakefulness, such as the genioglossus and tensor palatini muscles, to maintain patency of the upper airway compared to controls.[35,36] This increased activity of the pharyngeal dilator muscles, particularly the response of the genioglossus muscle to negative pressure applied during wakefulness is not impaired in OSAS patients compared to control subjects.[37,38] During sleep onset, the decrease in upper airway pharyngeal dilator muscle activity appears to be related to a decrease in wakefulness stimuli to breathe rather than to a loss of negative pressure upper airway responsiveness.[39] Therefore, insufficient muscle tone due to neurologic lesions or discoordinate activation of different pharyngeal muscles may predispose to collapse of the upper airway, and in fact, Saboisky et al.[40] found significantly longer motor unit action potentials and larger mean areas of motor unit potentials in OSAS patients than in control healthy subjects when testing the multi-unit electromyography (EMG) of the genioglossus muscle.

Mortimore and colleagues demonstrated reduced palatal muscle activity in response to negative pressure pulses in awake OSA patients when compared with controls.[41] The evidence for motor neuron lesion and actual damage to the upper airway muscles themselves that could lead to partial paresis of the pharyngeal dilator muscles, is still debated. Swedish researchers began systematic biopsy of the palatal tissues in the early 1990s, particularly from OSAS patients who underwent uvulopalatopharyngoplasty (UPPP). Edstrom and colleagues found atrophy and an abnormal distribution of fiber types in the palatopharyngeal muscles, suggesting a neurogenic alteration.[42] These findings were subsequently confirmed by Woodson and colleagues who found disruptive changes with atrophy in the muscle fibers of the soft palate in OSA patients and heavy snorers when compared with non-snorers, under light microscopy.[43] In addition, under electron microscopy, they found degenerative changes in the neurons from the soft palate and uvula of OSA patients. Friberg and colleagues compared biopsies of palatopharyngeus muscle from non-snoring controls, habitual snorers, and OSA patients, and found that the degree of muscle pathology increased in parallel with the proportion of obstructive breathing during sleep.[44] All patients with OSA exhibited histologic abnormalities, including signs of motor neuron lesions. A recent study by Eckert and colleagues using respiratory sensory processing properties found tongue protrusion force to be greater in OSAS than in controls during wakefulness, however, OSAS patients were at higher risk for muscle fatigue, which subsequently may lead to OSAS disease progression.[45]

Thus far, there is evidence of neuropathy involving the upper airway in some patients with snoring and in most patients with OSAS. However, there is no clear-cut evidence that these lesions increase in parallel with the clinical progression from habitual snoring to OSAS.

Possible causes of UA neuropathy in OSAS: vibration, desaturation or inflammation?

The exact cause of neuropathy in OSAS patients is not fully understood. Most OSAS patients snore due to vibration of upper airway soft tissues resulting from a narrow or partially occluded upper airway.[46] Persistent vibratory trauma resulting in nerve impairment affecting the hands and arms of workers, have been well documented.[47] This occurs due to prolonged exposure to vibrating tools. Therefore, it is possible that the same type of vibratory trauma may be induced in the upper airway due to long term snoring.[30]

Also, OSAS patients are exposed to intermittent hypoxia due to partial or complete closure of the upper airway during sleep. Hypoxia can also affect both the central and peripheral nervous systems and possibly result in neuropathic lesions through mechanisms such as inflammation.

Vibration

Hand arm vibration syndrome (HAVS) is found in workers exposed to long term vibration such as road construction workers using jack-hammers and other vibratory power tools. Studies show that sensory nerve conduction velocity was decreased in these workers compared to healthy controls.[48–51] Impairment of sensory

perception has also been noted and typically the warm perception threshold was elevated while cold perception threshold was lowered, implying a decrease in sensitivity to thermal stimuli.[52–54] Vibration perception threshold was also increased in those exposed to vibration. Pathological studies revealed structural changes in nerve fibers including demyelination and interstitial and perineural fibrosis in the wrists,[55] suggesting nerve injury was induced by exposure to vibration. Vibration can also cause myopathy and vascular lesions in surrounding tissues, such as vibration-induced Raynaud's phenomenon, which is caused by endothelial dysfunction in blood vessels.[56,57] Vibration can cause endothelial damage, increase plasma levels of oxidative stress markers, create an imbalance in vasoactive factors, and impair vascular smooth muscle responses.[58,59]

Heavy snoring induces stretching and low-frequency vibration of the pharyngeal tissues.[60] It is well-known that long term exposure to a low-frequency vibration causes histological changes in the peripheral nerves of upper airway in humans.[43,61] Powell et al.[62] observed turbulent airflow in the upper airway in OSAS patients. As turbulence increased, airflow became chaotic and caused flow separations and vortices or eddy flows in the upper airway. There are three important metrics concerning dynamic airflow: Axial velocity, mean static pressure, and wall shear stress. These metrics enable airflow to negatively affect the soft tissues of the upper airway by vibration, snoring and inflammation.

Whether upper airway neuropathy in patients with OSAS is caused directly by vibration or is secondary to peripheral tissue injury is still under debate. In HAVS, neuropathy is not only caused by vibration, but also by other factors such as the temperature of the work place. Animal models have directly examined injury due to vibration, and demonstrated that rat tail vibration, for example, could cause arterial damage to the smooth muscle and endothelial cells, and blood flow changes similar to vasoconstriction.[63,64] Tail vibration also resulted in permanent impairment of nerve function.[65] Increased levels of oxidative stress markers and inflammatory reactions were also found in animal studies, suggesting that vibration could cause damage through mechanisms of free radicals and inflammatory changes.[66–68] Vibration itself can cause direct damage to the nerve, while free radical formation and inflammation is related to vibration-induced injury.

Hypoxia

Intermittent hypoxia can result in increased release of inflammatory factors and oxidative stress. Animal studies showed that intermittent hypoxia could reduce the activity of motor neurons of upper airway muscles,[69] as well as increasing levels of reactive oxygen species. These levels could be reduced by the use of prophylactic antioxidants,[70] suggesting oxidative stress participates in hypoxia-induced nerve damage of the upper airway. In patients with OSAS, the production of reactive oxygen species in leukocytes increased[71–73] and the markers of oxidative stress were also elevated.[72,74–76] In fact, in a recent animal model study, it was shown that oxidative stress contributes to impaired upper airway muscle endurance and subsequently cause nerve tissue damage.[77]

Inflammation

A number of reports on patient data strongly suggest that snoring is a source of upper-airway injury, including inflammation, loss of sensitivity, muscle and nerve dysfunction, and sensory neuropathy.[33,34,78,79] Snoring is caused by vibration of the soft structures of the upper airway. A recent in vitro study showed that vibration with amplitude and frequency typical of snoring can trigger a proinflammatory cascade in bronchial epithelial cells.[64] Boyd and colleagues reported a significant increase in inflammatory cell infiltration of the upper airway in patients with OSAS, which encompasses both the mucosal and muscular layers.[80] The inflammatory cell infiltration of skeletal muscle, together with production of proinflammatory mediators, such as cytokines and oxygen free radicals, can cause significant muscle weakness.[79] For instance, tumor necrosis factor-α and nitric oxide are both known to have direct inhibitory effects on the force-generating capacity of muscle fibers.[81,82] In addition, models of peripheral neuropathy have shown that the presence of non–neural-specific activated inflammatory cells can induce or worsen neuropathy.[83,84] Under these conditions, neural toxicity appears to be mediated via direct cytotoxic inflammatory cell-induced axonal injury, as well as by cytokines such as tumor necrosis factor-α, which can induce Wallerian degeneration.[83,84] Therefore, inflammatory cells within the upper airway of patients with OSAS have the potential to produce contractile dysfunction of upper airway dilator muscles and degeneration of nerve fibers. Other studies have shown markers of inflammation and oxidative stress, including plasma and exhaled mediators such as intercellular adhesion molecule 1 (ICAM-1), interleukin (IL)-8, IL-6, and 8-isoprostane, were higher in OSAS patients than control groups.[85–87]

Obesity may cause OSA and UA inflammation,[88] however, the specific effect of sleep apnea on UA inflammation in the absence of obesity is still debated. This is mainly due to the fact that OSAS patients were normally more obese in comparison to control subjects in past studies.[85,87] Even in stratified study design, the roles of OSAS and obesity on inflammation could not properly be distinguished.[86]

Assessment of neuropathology: neural morphology (histology) and functional assessment

Morphological (histological) assessment: light & electron microscope

The sub-occlusive stage of habitual snoring usually precedes the development of OSAS, but the pathophysiological mechanisms underlying this progression are not known. Histological changes indicative of a denervation process of the efferent pathways to the palatopharyngeus muscle was demonstrated in OSAS patients[42] and has been explained above. Furthermore, focal degeneration of myelinated nerve fibers was shown in the uvula of severe OSAS patients, and an afferent nerve lesion with impaired temperature sensitivity thresholds was also indicated in the soft palatal mucosa of OSAS patients.[29] Some afferent nerve endings, in particular polymodal nociceptors, are responsible for propagating mechanical, chemical and thermal stimuli, as well as causing vascular reactions after stimulation. The vascular reaction has been shown to be caused by a release of calcitonin gene-related peptide (CGRP) and substance P (SP). CGRP and SP have previously been demonstrated in the human uvula mucosa by immunohistochemical staining.[89] Friberg et al.[44] also showed abnormal vascular reactions after afferent nerve stimulation of the uvula mucosa in sleep apneics compared to controls, indirectly indicating an afferent nerve lesion. This study indicated that in OSAS patients, there were increased levels of protein-gene product 9.5 (PGP 9.5), CGRP and SP.[30] Whereas PGP 9.5 is a general marker for nerve fibers, the neuropeptides CGRP[90] and SP[91] are in the skin and mucous membranes and are generally assumed to be present mainly in sensory nerve fibers of the C and A-delta type.[92] Sprouting may occur as a regenerative response, resulting in an increased number of nerves containing neuropeptides CGRP and SP. The possible role of sensory fibers in the wound healing process has been studied, and SP was shown to have a stimulatory effect on connective tissue

Table 1
Functional and morphological assessment of upper airway in OSAS.

Author	Method	Position
I. Functional Assessment		
Friberg et al. (1998)[30]	Laser Doppler perfusion monitoring, combined with electrical stimulation	Mucosa of soft palate
Kimoff et al. (2001)[32]	Two-point discrimination and vibratory sensation thresholds	Two point discrimination: soft palate; Vibratory sensation: tonsillar pillars v.s. hand, lip
Guilleminault et al. (2002)[33]	Two-point discrimination	Soft palate
Nguyen et al. (2005)[34]	Air-pressure pulses detection	Oropharynx, velopharynx, hypopharynx and larynx
Dematteis et al. (2005)[79]	Airflow rates detection	Soft palate
Hagander et al. (2009)[97]	Vibration detection threshold and cold detection threshold	Tonsillar pillars, tongue v.s. lip and finger
Sunnergren et al. (2011)[96]	Quantitative cold sensory testing	Soft palate v.s. lip
II. Morphological (Histological) Assessment		
Woodson et al. (1991)[43]	Electron microscopy/ Light microscopy: stained with hematoxylin and eosin/thin sections were stained with lead citrate and uranyl acetate	Soft palate and uvula
Edstrom et al. (1992)[42]	Light microscopy: stained with hematoxylin-eosin and modified trichrome for adnosine triphosphatase (ATPase) and NADH-TR	Cranial part of the palatopharyngeal
Hauser-Kronberger et al. (1995)[89]	Macro- and microscopy: modified immunogold- silver staining (IGSS) technique/immunofluorescence methods	Soft palate
Sekosan et al. (1996)[94]	Point counting in five randomly selected high-power microscopic fields (×100)	Uvula mucosa

cell growth.[93] This effect of SP could be a mechanism underlying the formation of a thick mucosa as seen in some OSAS patients in a study by Sekosan et al.[94] Apart from mitogenic effects, sensory neuropeptides may contribute to the inflammatory response in the skin.[95] Inflammation of the uvula mucosa in patients with OSAS has been demonstrated,[94] and it has been suggested that the inflammation contributed to the occlusion of the upper airways seen during sleep in patients with OSAS. In summary, habitual snoring is at the beginning of a spectrum of a progressive disease, which in susceptible individuals, can progress to OSAS. Furthermore, local neurogenic lesions are a possible contributory factor to the collapse of the upper airways seen in patients with OSAS.

Functional assessment

In addition to morphological evidence of neuropathology in the upper airway, abnormal neural function has also been found in patients with OSAS.

Guilleminault et al.[33] showed a significant decrement in two-point discrimination of the palate in patients with OSAS

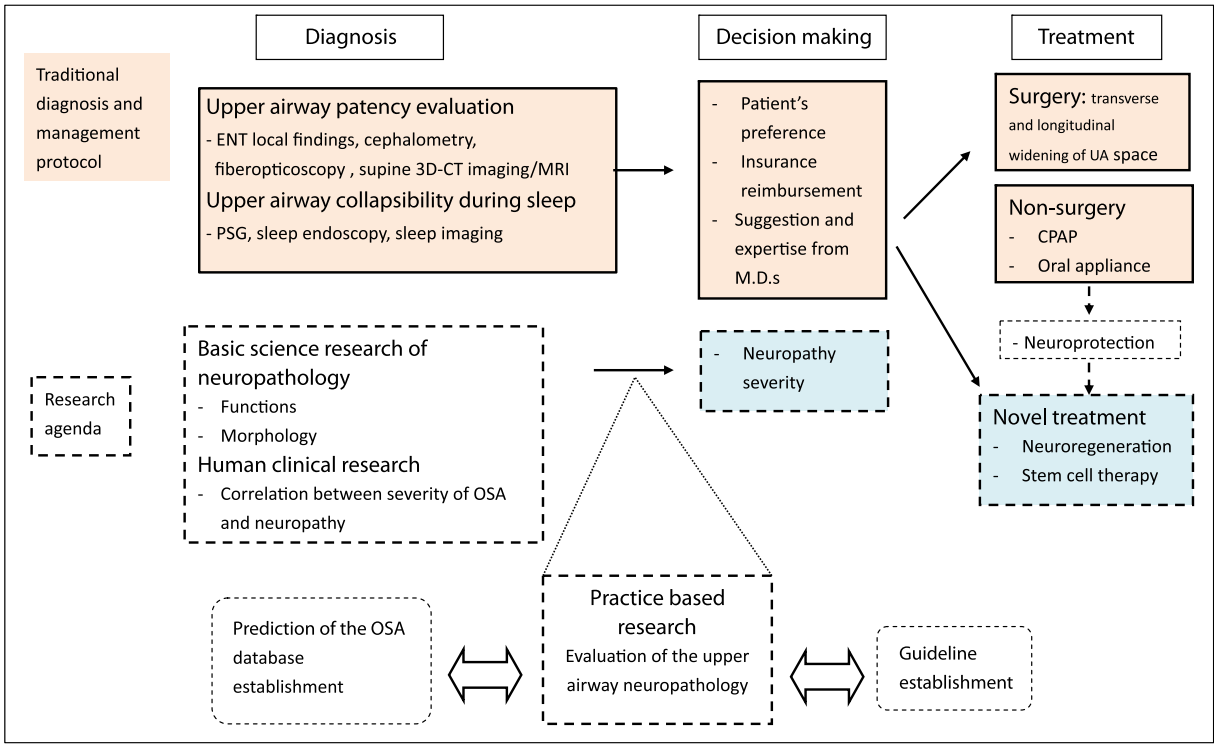

Fig. 1. Proposed diagnosis and management of OSAS in terms of upper airway neuropathy. Red squares indicate the traditional diagnosis and management protocol; Blue squares with dash frames indicate additional steps of clinical protocol based on upper airway neuropathy; Dashed squares show the proposed research agenda and clinical practice of upper airway neuropathy in OSAS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

compared to upper airway resistance syndrome (UARS) and normal subjects, indicating an impaired sensory transmitting process in OSAS. Furthermore, there was no difference in the discrimination in UARS and normal subjects. This might infer a shorter period and/or lesser degree of snoring, and thereby less vibration induced trauma, in UARS and normal subjects. However, Dematteis et al.[79] found an increased sensory threshold which correlated with the severity of sleep-disordered breathing by applying graded topical mucosal anesthesia between different subgroups, including severe, moderate, mild sleep disordered breathing and normal groups. Through use of an endoscope, these findings were also supported for laryngeal and velopharyngeal sensory thresholds.[34]

Similar to two-point discrimination and vibration detection, sensitivity to temperature was also impaired in patients with OSAS.[96] Compared to vibration detection thresholds, cold detection thresholds seemed to give more discriminative results.[97] Saboisky et al.[40] tested the multi-unit electromyography (EMG) in genioglossus in patients with OSAS and healthy subjects and found significantly longer motor unit action potentials and larger mean areas of motor unit potentials in OSAS patients than in control subjects.

Table 1 shows the functional and morphological assessment of upper airway in OSAS; results indicate impairment of the function and change in the morphology of the upper airway nerve in OSAS.

Conclusion

Apart from anatomical narrowing of the upper airway as a pathogenetic mechanism in the development of OSAS, there is mounting evidence to suggest the role of neuropathy in the upper airway as well.[77,98,99] Both the vibration caused by snoring and the hypoxia caused by intermittent upper airway collapse may affect nerves in the upper airway. These changes can impair the normal function of the upper airway mucosa (sensory) and the pharyngeal dilator muscles (motor), rendering the upper airway prone to collapse. Although we can currently observe the morphological changes of the nerve fibers and the functional impairment in the upper airway, these results are seen after years of evolution and might be missing the initial steps. Whether or not the nerve injury was the initial step in the pathogenesis of OSAS and subsequent deterioration remains unknown due to lack of longitudinal evidence on the progression of OSAS from children to adults.

Upper airway neuropathology could be a crucial factor in the pathogenesis of OSAS. Evaluation of nerve impairment might eventually be valuable during the diagnosis and formation of a treatment plan (Fig. 1). Likewise, future treatments focusing on methods to reduce or reverse neuropathy in addition to enhancing caliber of the upper airway may help to treat OSAS. These concepts regarding the roles of neuropathology on OSAS and its treatment warrant further investigations.

Practice points

1) Evaluation of upper airway neuropathology in OSAS has often been disregarded in daily clinical practice.
2) Current literature supports the presence of upper airway neuropathology in OSAS.
3) Abnormal anatomical factors alone do not explain the pathogenesis of OSAS, and therefore may explain the reasons for not reliably predicting surgical success in the treatment of OSAS.
4) In addition to anatomic factors, understanding and evaluating the upper airway neuropathology might provide information to identify good surgical candidates for the treatment of OSA.

Research agenda

Though there is evidence that vibration, hypoxia and inflammation may result in upper airway neuropathology, the mechanism is not fully understood, and will require further study. Clarifying the role of neuropathy in the pathogenesis of OSA might help to address management options.

1) Morphological changes and neural function impairment are noted in patients with OSA, though the method of assessment is not well established. Studies are needed to identify the biomarkers of upper airway neuropathy.
2) More evidence is needed to establish the relationship between the severity of upper airway neuropathy and OSAS.
3) More conscientious research is required to evaluate the severity of upper airway neuropathy and surgical success or failure.
4) Novel treatments such as neuroprotection, neurogenesis or stem cell therapy that focus on reducing or reversing the upper airway neuropathology might be the future direction of management for OSAS.

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