EDITORIAL REVIEW ARTICLE

Complex Sleep-Disordered Breathing – Clinical Significance and Therapeutic Implications

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In the latest edition of International Classification of Sleep Disorders (ICSD-2), sleep-related breathing disorders have been classified into obstructive and central sleep apnea syndromes, sleep related hypoventilation/hypoxic syndromes due to congenital, idiopathic or medical conditions and other unspecified sleep-related breathing disorders(1).

Classically patients suffering from obstructive sleep apnea (OSA) have an anatomically small pharyngeal cavity due to multiple factors such as obesity, craniofacial anomalies, enlarged tonsils & adenoids and some endocrine disorders (2,3). The typical polysomnographic (PSG) features include repetitive episodes of apneas, hypopneas and flow limitations which are usually followed by electroencephalogram (EEG) arousals and variable degrees of oxygen desaturation(4). The disease is usually worse in the supine body position (5), rapid eye movement (REM) sleep and following bed time consumption of alcohol or sedative drugs (6,7). The treatment with nasal continuous positive airway pressure (CPAP) usually results in complete resolution of the disease (8,9).

Central sleep apnea syndromes (CSAS) include primary central sleep apnea and those due to Cheyne-Stokes breathing, high altitude periodic breathing, medical conditions and drugs (1). This condition is commonly seen in patients with congestive heart failure (10,11). The pathophysiology of central sleep apnea is complex and is thought to be associated with disorder of central respiratory control mainly due to dys-regulation of carbon dioxide (CO_2) homeostasis. Breathing during non rapid eye movement (NREM) sleep is totally under chemical control. In some genetically predetermined patients who have a highly sensitive hypocapnia-induced apneic threshold, apneas may be precipitated by small transient reduction in partial pressure of CO_2 in arterial blood ($PaCO_2$) below eupnoea and breathing may not resume until $PaCO_2$ has risen significantly above the eupneic levels (12,13,14,15). The characteristic PSG features include stereotyped repetitive episodes of periodic breathing with central apneas along with variable degree of oxygen desaturation (14). The disease is mainly observed in NREM sleep and improve dramatically during REM sleep which is in marked contrast to the pattern seen in OSA (15). Moreover, the response to treatment with nasal CPAP is also incomplete with significant residual central apneas (16).

Recently a few studies (17,18,20,24) and a case report (19) have highlighted the presence of a select group of patients who apparently have features of obstructive sleep apnea on PSG, but after the treatment with nasal CPAP is initiated, developed problematic central apneas or Cheyne-Stokes breathing. This pattern of abnormal sleep-disordered breathing has been termed by some authors as complex sleep apnea syndrome as a way to identify OSA patients with a clinically significant respiratory control component (17,18). The characteristic features of complex sleep apnea include symmetric short cycles of obstructions, NREM dominant disease and incomplete response to CPAP (18). When the CPAP pressure is gradually increased to eliminate obstructive

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events, periodic breathing or frank central apneas are induced before the flow limitation is completely eliminated. This phenomenon has been termed "break-point" and further increase in pressure above this point worsens the instability and reduction in pressure results in greater obstruction. The disease has remarkable stability during REM sleep at a relatively low pressure (18). The REM sleep is known to have an inhibitory effect on periodic breathing. The use of Bilevel positive airway pressure (Bilevel-PAP) also results in worsening of periodic breathing characterized by lengthening of respiratory event cycle timing and induction of frank central apneas. This is presumably due to further reduction in $PaCO_2$ levels below the apneic threshold.

Recently Medicare has framed diagnostic criteria for complex sleep apnea as newly appearing central apneas and hypopneas ($\geq$ 5/hour of sleep) in patients with primary OSA (AHI$\geq$ 5/hour of sleep) after initiation of treatment with nasal CPAP. There are limitations in making a diagnosis of complex sleep apnea with the standard PSG examination. This is due to difficulty in manually scoring central hypopneas in the presence of flow limitation which is commonly associated with these events. To overcome this difficulty, a new technique has been developed which involves the time series analysis of sleep stability states (17). It is based on the findings of recent work that NREM sleep fundamentally exists in stable and unstable forms which are independent of EEG stage and power. The stable form is characterized by prominent sinus arrhythmia, blood pressure dipping, stable arousal thresholds, absence of cyclic EEG activation complexes i.e. cyclic alternating pattern (CAP-EEG) and temporal stability of respiration. Unstable NREM sleep is characterized by periodic phasic EEG activation complexes (CAP-EEG), cyclic variation in heart rate and blood pressure that stays close to the waking levels, reduced and variable arousal threshold and temporal instability of respiration (17,21,22).

The unstable form of NREM sleep in normal healthy individuals is confined to sleep onset and during transitions from NREM to REM sleep (21). However the proportion of unstable form of NREM sleep significantly increases in the patients suffering from sleep disordered breathing. In other words the presence of CAP-EEG is strongly suggestive of breathing instability. Since it is often difficult to identify CAP cycles because of great individual and age dependent variability in the amplitude of EEG complex (21,22), an electrocardiogram (ECG) based method of characterizing sleep stability states has been developed by mathematically combining heart rate and respiratory (through amplitude modulation of R waves) variability. This generates a measure of cardiopulmonary coupling which is independent of EEG sleep stages (23). Stable state is characterized by high frequency cardiopulmonary coupling whereas the unstable form of NREM sleep which is frequently associated with sleep disordered breathing is characterized by low frequency couplings. The spectral analysis of low frequency coupling has lead to recognition of two patterns i.e. single narrow peak and multiple broad peaks (23). It has been observed that patients with pure obstructive sleep apnea have multiple broad peaks due to event-to-event variability in cycle length, whereas, patients of complex sleep apnea have narrow single spectral band cardiopulmonary coupling. This is due to stereotyped repetitive cycles of central apnea and periodic breathing of constant lengths due to oscillatory respiratory control.

The treatment of complex sleep apnea involves the careful application of nasal CPAP, as higher pressure may precipitate central events and hence, some degree of flow limitation should be accepted. This may result in partial resolution of disease with residual symptoms. In one study comparing the efficacy of CPAP treatment between patients with OSA and complex sleep apnea, no difference was found in the degree of sleepiness and CPAP compliance. However, patients with complex sleep apnea had more interface problem and required more frequent follow-up than OSA patients (24).

The role of supplemental oxygen in the treatment of complex sleep apnea is controversial but has been used with some success in patients with congestive heart failure. Some patients may notice an improvement in sleep quality but this may be due to placebo effect (25,26).

Recently newer strategies to minimize hypocapnia during sleep have been developed. These include the use of non-vented mask, the use of enhanced expiratory rebreathing space (EERS) (27) and the controlled increase of CO_2 concentrations in the inhaled air (28,29). The latter involves the use of the positive airway pressure gas modulator.

Keeping in view the difficulties in treatment and special additional requirements besides nasal CPAP, it is very important to recognize complex sleep apnea. The exact prevalence of complex sleep apnea is not known. In one study of 223 consecutive patients, 15% had complex sleep apnea and the clinical characteristics of

most of the patients were similar to those with OSAS until nasal CPAP was applied. No definite clinical risk factors which could predict the emergence of complex sleep apnea were identified (20).

The presence of complex sleep apnea should be strongly suspected in patients who have residual symptoms after treatment with nasal CPAP and in whom other causes of failure of treatment such as poor mask fit, mask & mouth leakage, nasal congestion, inadequate hours of use per night and comorbid conditions like narcolepsy, depression and sleep deprivation have been excluded. In such patients the presence of occult or frank cardiac failure should be carefully ruled out. The treatment of the underlying conditions can significantly improve the symptoms and overall outcome of these patients.

In summary, complex sleep disorder breathing is a distinct sub group of sleep apnea which demonstrates that both anatomical and respiratory control mechanism are working in a complex manner simultaneously in the pathogenesis of the disease. It is very important to recognize these patients as they tolerate nasal CPAP poorly and continue to have residual symptoms. Further studies are required to know the exact prevalence of complex sleep disordered breathing in OSA patients as it will have a tremendous impact on the future guidelines for the selection of appropriate diagnostic and treatment modalities.

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