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Diagnostic and therapeutic process of respiratory disorders during sleep

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Abstract

Introduction and purpose

Sleep apnea is a disturbance of sleep that affects about 10% of adult population and is not easily detected due to unspecific symptoms. The aim of this literature review is to present, respectively, obstructive sleep apnea and central sleep apnea symptoms and integrate the available data in the literature regarding the pathogenesis and treatment methods.

Materials and methods

A review of literature was performed using PubMed and Google Scholar database. The search criteria included keywords such as sleep apnea, obstructive sleep apnea treatment, central sleep apnea treatment.

State of knowledge

Sleep disturbances that involve breathing can be categorized as obstructive sleep apnea (OSA) and central sleep apnea. First one is associated with the obstruction of the upper airways and the second one – with malfunctioning breathing generator in the pontomedullary breathing pacemaker. Symptoms are unspecific which makes diagnostic process difficult. However, the right diagnosis and treatment may prevent patients from developing many cardiovascular diseases. Treatment options for OSA include: CPAP, reducing body weight, changing sleep position, braces and surgeries; for CSA: CPAP and acetazolamide.

Conclusions

OSA and CSA need to be further investigated in order to find more precise ways of diagnosis and treatment, as these diseases remain underreported. It is worth noting, that these conditions predispose to serious diseases, e.g. stroke. Therefore, developing new treatment techniques would beneficial for the health of population.

Keywords

sleep apnea, obstructive sleep apnea treatment, central sleep apnea treatment, sleep disorder

Introduction

Sleep is one of the natural states of human body that plays a tremendous role in circadian rhythm. Its characteristics include: reduced consciousness, immobility (with some exceptions

e.g. night walking), recurrence. This biological process is essential for humans to develop and maintain proper functioning of the body and mind. [1] Sleep is important in terms of cognition – studies showed that when infants and children sleep directly after a learning period, they have a better consolidation of knowledge. [2] Unfortunately, many conditions may negatively influence sleep, which results in decreased sleep duration and poor sleep quality. One of the most commons diseases that disrupt sleep is obstructive sleep apnea (OSA) because an upper airway obstruction may cause hypoxemia, awakenings or activation of the sympathetic nervous system. All those elements lead to sleep worsening. [3] OSA should be considered as a serious issue associated with health of middle-aged and senior patients. Some reports say that 10 to 20% of that population might be affected. [4] Studies also suggest that OSA may be a risk factor or intensify symptoms of many diseases, such as insomnia, neurocognitive deficits, cardiovascular conditions, gestational diabetes, stillbirth and more. [3,4,5] Less frequent sleep disturbance is central sleep apnea (CSA). Its symptoms result from lack or reduction of respiratory effort. CSA may occur as Cheyne-Strokes breathing or during opioid treatment and some cardiac, renal and neuromuscular diseases. [6] One of the most popular ways of managing OSA and CSA is CPAP, however it is not equally effective in every circumstance. [3,6] The aim of this review is to present characteristics of OSA and CSA and latest advances in treating these conditions.

How to breath during sleep?

Breathing is a process that allows gas exchange, supplying oxygen from atmospheric air and removing carbon dioxide from the body. It is a mechanical process involving alternating cycles of inhalation and exhalation which allows gas exchange in the alveoli. Oxygen is transported to all cells of the body, where it participates in the production of energy in the process of cellular respiration. Proper breathing requires open airways and proper functioning of the diaphragm and intercostal muscles. Breathing also enables laughter, speech, sneezing, yawning, coughing, expressing emotions or thermoregulation. Both the depth and frequency of breathing are controlled by the breathing center located in the brainstem. More and more structures responsible for the breathing process are being discovered, including the breathing central pattern generator (bCPG) responsible for the regulation of breathing and gas exchange [7,9]. The most important part of bCPG is the preBötzinger complex (preBötC). The loss of neurons from the preBötC region has been associated with respiratory disorders, sleep apnea, changes in breathing patterns and even death during sleep [10]. Changes in the partial pressure of oxygen and carbon dioxide in the blood are recognized by chemoreceptors located

in the medulla oblongata, aorta and carotid arteries. Chemoreceptors recognize changes in the pH of arteria blood and adjust the respiratory mechanism accordingly, leading in extreme cases to hyper- or hypoventilation. The same mechanisms operate during sleep.

Physiological sleep consists of two phases: nREM (non-rapid eye movement) and REM (rapid eye movement). The sleep phases are arranged in cycles, usually there are 4 or 5 cycles that normally last 90-120 minutes each. The nREM phase consist of 4 stages: N1, N2 which represent light sleep and N3, N4 which reflect deep sleep (slow-wave sleep). After the transition from wakefulness to sleep, metabolic rate and minute ventilation decreases, which is mainly due to GABAergic neurons. As sleep depth increases, minute ventilation decreases but resistance in the upper airways increases. This is caused by a reduction in the tension of the pharyngeal muscles, especially in the area of the epiglottis and the genioglossus muscle [8,10]. During the REM phase, the activity of the cerebral cortex increases, sleep dreams appear and the breathing pattern changes, which depends on eye movements. The onset of the REM phase is associated with an increase in neuronal impulses in the dorsal part of the pons, which respond to the increase in glutamate concentration and increased activity of the sympathetic nervous system [10]. L-glutamic acid causes significant atony of the muscles of the upper respiratory tract and promotes their collapse. The respiratory volume during REM sleep can either increased or decreased. There are sudden changes in the amplitude and frequency of breathing, and breathing becomes irregular. Apnea of central origin mat appear, lasting 10-20 seconds, this is a physiological phenomenon and does not negatively affect the functioning of the body.

Obstructive sleep apnea (OSA)

Apnea is the loss of airflow through the respiratory tract for more than 10 seconds. There are obstructive, central and mixed apneas. Obstructive sleep apnea is characterized by recurrent episodes of partial or complete upper airways obstruction, resulting in a repeated decrease in the partial pressure of oxygen (PO2), which causes hypoxia, a decrease in blood pH, leading to awakening during sleep. A high frequency of asleep apneas may disturb the quality of sleep, which contribute to negative health consequences, including: excessive daytime sleepiness or increased cardiovascular risk [14,15]. OSA affects 14-34% of men and 5-17% of women in the general adult population and approximately 2% in children from 2 to 8 years old. The 5-year incidence is about 7%-11% for OSA in middle-aged adults [11,12,16].

During slow-wave sleep (nREM stage 3,4) and during REM sleep, the muscle tone of the vast majority of skeletal muscles is almost completely relieved. The throat and neck muscles are relaxed as well. It causes the tongue, epiglottis and soft plate to collapse and the airway to narrow or completely close. With a decrease in respiratory ventilation, the level of oxygen in the blood decreases too. This situation provokes a sudden awakening of the patient from sleep. This does not have to cause a complete awakening, often it is only switch from deep to light sleep and patients do not remember the moment of awakening. That is enough to automatically restore general muscle tone, the airways open and blood-oxygen level increases [13]. Then the patient falls into deep sleep, which obstructs the air flow, after which he wakes up again, and the whole cycle repeats itself. In one night, it may be even 30 such cycles per every hour of sleep.

Many people with OSA are not aware of their breathing disorders during sleep, even after waking up. Sleep symptoms such as snoring, stopping breathing or choking during sleep may be undetectable; especially when people sleep alone. When symptoms persist for years, over time patients get used to symptoms such as morning headaches or fatigue. Obesity is a major risk factor for OSA, especially with body mass index (BMI) >35 kg/m2. Other risk factors include: family history of OSA, male gender, older age, tonsillar hypertrophy, retrognathia, acromegaly, Down syndrome, decreased muscle tone or alcohol consume [11,17]. The most common symptom, occurs in 90% of patients with OSA is excessive sleepiness. Many patients also report tiredness, impaired concentration, fatigue, lack of energy. Typical signs of OSA also occur at night, these include gasping, choking, nocturia, problems with falling asleep and waking up during sleep. Habitual snoring presents 60% of patients. Moreover, chronic morning headaches and gastroesophageal reflux occur twice as often in patients with OSA as in the general population. The headaches that patients experience appear immediately upon waking, are characterized by bilateral headache and disappear within a few hours later. There is a strong association between OSA and cardiovascular or metabolic diseases. OSA is a risk factor for hypertension, arrhythmias, stroke, heart failure, coronary artery disease, pulmonary hypertension, diabetes mellitus and lipid disorders. There are many interconnected pathophysiological mechanisms that play a role in causing hypertension and cardiovascular disease in individuals with OSA. Recent study show, that about 80% patients with resistant hypertension, atrial fibrillation, type 2 diabetes suffer from OSA [16]. The risk of stroke in patients with OSA is twice as high as in patients without OSA [14]. Exposure to repeated episodes of hypoxia during sleep leads to increase activity of the sympathetic nervous system.

It causes increase in blood pressure and vascular resistance. Moreover, patients with OSA have higher levels of endothelin-1 and inflammatory markers which is associated with the occurrence of hypertension, cardiovascular disease, obesity and metabolic dysregulation [14,15].

Screening of patients should include a detailed medical history that takes into account the characteristic symptoms of OSA, risk factors and include a physical examination with particular emphasis on anatomic abnormalities of the upper airway. There are also many questionnaires to help make a diagnosis, such as the Berlin Questionnaire or the STOP-Bang questionnaire. However, the most commonly used is the Epworth Sleepiness Scale (ESS), which assesses the probability of falling asleep in various everyday situations. A score >10 indicates excessive sleepiness and score >14 indicates pathological sleepiness. The severity of OSA is determined by the apnea-hypopnea index (AHI), which measures the number of breathing disorders events per hour. An AHI less than 5 events per hour is considered normal, a value of 5-14.9 is considered mild, 15-29.9 is considered moderate and AHI more than 30 events per hour characterizes severe sleep apnea [12,16]. The gold standard in the diagnosis of OSA is polysomnography (PSG). There is also a home sleep apnea test (HSAT), but it is not as accurate as PSG. PSG is a monitored 8-hour sleep study in controlled conditions, during which sleep and breathing parameters are assessed. The test allows to evaluate: air flow through the nose, respiratory effort using bands on the chest and abdomen, oxygen saturation, snoring using a microphone, sleep phases with electroencephalogram (EEG), electromyography (EMG), electrocardiography (ECG), body and legs position [16,17]. The interpretation is done in conjunction with medical history, a list of drugs the patient is taking, sleeping routine and polysomnography test record.

Central sleep apnea

Central sleep apnea (CSA) is a disease caused by the dysfunction of the breathing generator in the pontomedullary breathing pacemaker [18]. It occurs between 0,6% and 20,3% in patients who have difficulty breathing during sleep [19]. Risk factors for CSA include: male gender, low body mass index (BMI), drugs - mainly opiates, heart diseases such as atrial fibrillation, coronary artery disease and stroke [19,20,21].

If the cause of CSA is not established, the disease is defined as idiopathic [18]. In patients with CSA with cardiovascular diseases, the main cause of the disease is low cardiac output, which subsequently leads to hypoxemia, which results in activation of the sympathetic system and results in hyperventilation [20,21]. During sleep apneic threshold decreases which results

in hyperventilation resulting in hypocapnia which leads to apnea which results in hypercapnia and the cycle repeats [20,21]. In CSA with heart failure, Cheyne-Stokes respiration often occurs, which is characterized by sequential waxing and waning changes in tidal volume all while prolonging apnea and cycle time (from 45 to 75 seconds) [21].

Another mechanism that causes CSA is that the patient is above 3000 meters above sea level in a so-called hypoxemic environment [22].

Opiate use is one of the mechanisms of CSA. These drugs inhibit the action of the rhythm-generating medullary neurons in the pre-Bötzinger and RTN/pFRG, resulting in arrest of hypoxemic and hypercapnic respiration [22].

In addition, patients with CSA have a higher number of NREM sleep phases relative to REM than healthy people, which is conducive to the occurrence of episodes of apnea [22].

Symptoms of the disease are insomnia, night-time sleep fragmentation, decreased quality of life and excessive daytime sleepiness [18,19]. Polysomnography is the method of choice for diagnosing CSA [18,20]. It consists of 5 or more central apnea index (CAI) and an increased apnea-hypopnea index (AHI) during the study. These symptoms usually occur during the NREM sleep phase [19].

Therapeutic possibilities of central and obstructive sleep apnea

In the case of central therapy, treatment methods include: positive airway pressure (PAP) therapy, oxygen therapy and pharmacological therapy [19,22,23].

For PAP, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) and adaptive support ventilation (ASV) are used. In the cohort study Sadeghi et al. 42. 2% responded to CPAP therapy, 20. 3% to CPAP and oxygen therapy, and 28. 1% to BIPAP of patients [24]. CPAP can be used as a method to treat CSA. According to Zhang et al. Treatment with CPAP may reduce the symptoms of the disease [19]. BIPAP is used in patients who do not respond to CPAP. It may be effective in patients with obstructive events [19,24]. ASV shall be used when other methods of aiding ventilation have been exhausted. ASV is a dynamic adjustment of inspiratory pressure support and a back-up respiratory rate [19]. In a study by Roder et al. In addition, ASV has been shown to prolong REM sleep in CSA patients to levels observed in healthy people [25].

Nocturnal supplemental oxygen is mainly used for CSA caused by heart failure. There are insufficient data to support the efficacy of this method as a self-treatment [26].

For pharmacological treatment in CSA, acetazolamide is mainly used [23,27]. In the case of

acetazolamide, it can be used at doses of 36-1000 mg/d, with the meta-analysis of Schmickl et al. Higher doses give better results – there is a reduction in the amount of AHI and an increase in the quality of sleep [27]. Buspirone, triazolam and theophylline can also be used for pharmacological treatment, but there is insufficient scientific evidence to support their efficacy [23].

In the case of OSA, the main non-surgical treatment is PAP, mostly CPAP [28,16]. This method is effective in about 75% of patients [28]. The problem with PAP therapy is that not all patients tolerate it, in which case the patient should implement other methods of treatment [29]. In addition, the reduction of body weight by the patient brings great results [16]. The patient should also pay attention to the body position in which he sleeps, he should not sleep on his back [28,29]. You can also use braces yet different braces, especially in patients with mandibular retrusion, short anterior face height [28,16]. Pharmacotherapy in the treatment of OSA, does not bring particular effects [29].

A surgical approach can also be used to treat OSA. Treatment methods include uvulopalatopharyngoplasty, tracheostomy, maxillomandibular advancement surgery and staged or phasic surgical protocol for OSA [28,29]. Uvulopalatopharyngoplasty involves the plasticization of the soft palate [28,29]. Tracheostomy is one of the oldest surgical procedures. It is currently used in patients who have failed other methods of surgical treatment [28,29]. Maxillomandibular advancement surgery is considered by some to be the gold standard of OSA treatment. It involves performing an osteotomy and extending the maxilla and mandible, which reduces the risk of collapse of the soft palate [28,29]. The Staged or Phasic surgical protocol for OSA involves several stages of surgical treatment in patients, phase II is used only in patients in whom phase I treatment has failed. The effectiveness of the protocols is estimated at about 95% [28,29]. An interesting method is the use of hypoglossal nerve stimulation. It was approved for use by the US Food and Drug Administration in 2014 year. It is used in patients with a BMI index of <32, an AHI index of <50, older than 22-years-old, who cannot tolerate PAP therapy. The device causes a decrease of symptoms by about 70%, as well as a reduction of the amount of snoring from 96% to 35% [28,29,30]

When choosing a method of treatment of a patient in CSA and OSA, it is necessary to remember the quality of life of the patient, as well as the tolerance of the given method by the patient.

Conclusions

Sleep is an essential state of human body that dictates its circadian rhythm. Sleep disturbances are becoming more common and diversified and that should be considered a serious challenge in maintaining a good health of a person. One of the activities that is intertwined with sleep is breathing. It was discovered that is it regulated by the breathing central pattern generator and the loss of neurons in that area may result in complications such as sleep apnea which can be classified as obstructive sleep apnea (OSA) and central sleep apnea (CSA). Obstructive sleep apnea affects about 7-11% of middle-aged adults, however, those numbers may be underreported, as symptoms of OSA are unspecific and may be overlooked. The etiology is associated with obstruction of upper airways. Sometimes it takes many years for patient to associate certain symptoms with OSA. The most common of them is excessive sleepiness but the list is very long so there have been certain questionnaires (Berlin Questionnaire, STOP-Bang questionnaire, Epworth Sleepiness Scale) developed to help diagnose this condition. Untreated OSA leads to various cardiovascular diseases, e.g. the risk of stroke is two times higher in patients with OSA in comparison to people without it. The treatment of OSA can be surgical or non-surgical. Surgeries vary from uvulopalatopharyngoplasty, tracheostomy to maxillomandibular advancement surgery and staged or phasic surgical protocol. Non-surgical treatment of OSA include: CPAP, reducing body weight, changing sleep position and braces. On the other hand, central sleep apnea appears in 0,6 to 20,3% people with breathing difficulties during sleep and is caused by malfunction of breathing generator in brainstem. Documented treating options include: CPAP and acetazolamide. Other proposed therapies for OSA and CSA need further investigation, as there is not enough evidence to recommend them for new protocols.

Author's contribution

Conceptualization, Iwona Welian-Polus, Karolina Gendek; methodology, Kamila Babkiewicz-Jahn, Justyna Matuszewska ; software, Karolina Gendek; check, Iwona Welian-Polus,; formal analysis, Izabela Oleksak, Kamila Babkiewicz-Jahn; investigation, Iwona Welian-Polus, Justyna Matuszewska; resources, Karolina Maliszewska, Kamila Babkiewicz-Jahn; data curation, Izabela Oleksak, Wiktoria Wilanowska, Karolina Gendek;writing – rough preparation, Wiktoria Wilanowska; writing – review and editing, Iwona Welian-Polus, Karolina Gendek; visualization, Karolina Maliszewska, Justyna Matuszewska, supervision,

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