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Updates in Sleep Neurology and Obstructive Sleep Apnea

Edited by Fabian H. Rossi and Nina Tsakadze

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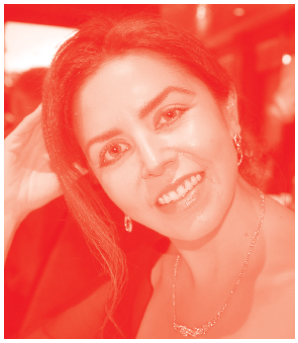

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Meet the editors

Professor Fabian H. Rossi, MD, is the head of the Clinical Neurophysiology Laboratory at the Orlando VA Medical Center and an associate professor at the Department of Neurology, University of Central Florida Medical School, Orlando, Florida. His expertise is in clinical neurophysiology and he writes extensively on the subjects of sleep neurology and polysomnography, epilepsy and electroencephalography, and neuromuscular disorders, nerve conduction studies, and electromyography. He held board certifications in each of the subspecialties of clinical neurophysiology. He has also contributed research in the field of motor neuron cultures and amyotrophic lateral sclerosis. He has given multiple national and international lectures on several topics in clinical neurology. Dr. Rossi has received Teacher of the Year awards for excellence in medical education.

Nina Tsakadze, MD, Ph.D., is a board-certified neurologist and headache specialist. She is a director of the Headache Center of Excellence at the Orlando VA Medical Center and Associate Professor of Neurology at the University of Central Florida School of Medicine, Orlando, Florida. Her expertise is in headache medicine and general neurology, and she has authored multiple publications and presented at many national and international meetings. In addition, Dr. Tsakadze has an impressive background in basic and clinical research related to molecular mechanisms of atherogenesis and thrombosis. She received an Excellence Award for her performance as a headache medicine fellow as well as several international awards, including a thrombosis fellowship at Mayo Clinic and a postdoctoral fellowship award from the American Heart Association.

Contents

Preface

The field of sleep medicine has grown and expanded over the last few decades. As a result, it has risen to great prominence and has become more complex, as technology and knowledge expanded with an improved and more comprehensive diagnosis and treatment. As sleep medicine expanded, it developed delicate links to almost every single medical discipline, especially neurological disorders, encountered at different levels from the outpatient setting to the operating room and intensive care unit.

This book provides important insight into sleep disorders and several neurological conditions such as headache and orofacial pain, epilepsy, neurodegenerative disorders, and more. It is loaded with clinical descriptions and diagnosis and treatment pearls, and provides a thoughtful, in-depth analysis of the subject of sleep neurology and obstructive sleep apnea. It is a valuable resource for clinical neurologists, general practitioners, and other medical professionals who wish to increase their knowledge and understanding of the field of sleep medicine and its relationship with general neurology. Current reference textbooks provide a deep and detailed compendium of sleep medicine but are often lengthy and not practical for the busy practitioner. Thus there is a need for a comprehensive yet concise review of the ever-developing changes in sleep neurology and obstructive sleep apnea. We are privileged to offer readers a user-friendly reference that summarizes essential pearls of sleep medicine and highlights its relationship with different neurological disorders as well as provides insight into the evolving field of obstructive sleep apnea.

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Section 1

Sleep Neurology

Chapter 1

Sleep Physiology and Polysomnogram, Physiopathology and Symptomatology in Sleep Medicine

Murat Kayabekir

Abstract

Over recent years, the importance of sleep physiology and pathology has been better understood in terms of correct diagnosis, treatment, prognosis and innovative research of diseases. Sleep disorders are often confused with clinical symptoms of adult and pediatric medical conditions. In medicine, electrophysiological signal recording methods are very important for establishing a correct diagnosis especially in neurological sciences. Polysomnography (PSG) is a golden standard diagnostic method that records electrophysiological signals used for sleep physiology and diseases. When the medical disciplines and diseases that make use of this diagnostic method are considered, its significance becomes clearer. For example, medical disciplines benefiting from PSG are as follows: "Clinical Physiology, Neurology, Ear Nose and Throat, Dentistry, Psychiatry, Pulmonology, Cardiology, Pediatric Neurology, Pediatric Cardiology, Internal Medicine, Neurosurgery, Endocrinology, etc." The patient groups diagnosed with PSG are as follows: "Sleep Disordered Breathing (Central Sleep Apnea Syndrome, Obstructive Sleep Apnea Syndrome), Obesity, Morbid Obesity, REM Behavior Disorder, Restless Leg Syndrome, Rhythm Disorders, Epileptic Disorders, Insomnia, Insomnia and Headache, Hypersomnia, Narcolepsy, Secondary Hypertension, etc." Interpretation and understanding electrophysiological signals correctly show us interactions of body systems with sleep physiology and integrated therapeutic approaches to sleep disorders. In conclusion; new approaches to sleep pathophysiology depend on a better understanding and further advancement of polysomnography.

Keywords: electrophysiology, awake, sleep, mechanism, PSG, correct diagnosis, innovation

1. Introduction

Electrophysiological signal recordings are used in medicine for research, clinical diagnosis and follow-up of diseases as well as for providing guidance to their treatment. For example; "Electrocardiogram (ECG)" is used daily as inpatient

and as outpatient, it is the most basic electrophysiological signal recording in which five waves (P, Q, R, S, and T) are interpreted. When all monitorization activities performed at the bedside of the patient are taken into consideration, recording electrophysiological signals with well-calibrated equipment and correct interpretation of the obtained results by doctors and healthcare staff seems to be at the crossroads of correct diagnosis, follow-up and treatment. In sleep monitorization, electrophysiological signal recordings are performed by multiple electrodes and provide us with important clinical information. In fact, monitoring wakefulness as much as sleep is quite important in clinical practice; it helps to establish a correct diagnosis in clinical practice and sometimes provides the opportunity to have access to unsuspected information. If PSG could be used as frequently as ECG by well-trained medical doctors and healthcare personnel in sleep medicine, sleep health and sleep disorders of the individuals in the society could be understood much better. Therefore, health could be evaluated not only in wakefulness but also in sleep leading to a continuum. During its preliminary years, sleep related studies attracted the attention of physiologists and as time passed clinical information regarding sleep disorders increased significantly and the possibility to treat all these diseases brought the attention of clinicians into this field. For human physiology and especially for the central nervous system to continue its functioning; there needs to be a healthy interaction and an organism specific balance between wakefulness and sleep cycles. Sleep is a physiological need; a state where the response of the brain to environmental stimuli has stopped reversibly. The insufficiency or absence of this need negatively influences the interactions in the neuronal circuits and pathways that are responsible for the wakefulness of the brain. It is very well known that many functions of the organism change during sleep and different physiological mechanisms come into play during NREM and REM sleep. Diseases also show changes during sleep and during NREM and REM phases. Electrophysiological studies could assist in the understanding of basic mechanisms in neurological sciences. Electrophysiological methods and PSG that are geared to understand the nights as well as the days aim at not only establishing correct diagnosis and delineating pathophysiological mechanisms but also engaging in innovation and developing novel diagnostic and therapeutic methods.

2. Sleep physiology and polysomnogram, physiopathology and symptomatology in sleep medicine

2.1 Sleep physiology and polysomnogram in sleep medicine

Sleep is a physiological and behavioral process that an individual requires to carry out his daily functions. This process is completed in a regular and continuous manner every night. As a part of biological rhythm, human brain has a healthy functioning by differentiating dark and day hours of the day. From controlling hormone levels to muscle tone, from regulating pace of breathing to contents of our thought; sleep influences all bodily and mental functions. It is not surprising that sleep can make these changes happen in the body because sleep causes significant changes in the electrical activity of the brain as a whole [1]. Sleep characterizes itself by not responding to one's surroundings and by drifting away from perception; yet it is a reversible behavior. During 1940–1950, physiologists believed that sleep was initiated as a result of tiredness that developed during the day and by a slowing down in the activation of the fore brain from

weakening in the activation of the reticular activating system. Later, based on transection studies, brain stem was shown to be responsible for generating sleep especially studies in cats; where total sections performed on pontine tegmentum induce sleeplessness. Physiologist Nathaniel Kleitman was working at Chicago University and he discovered REM sleep together with his colleague Dement in 1959 leading to a revolution in the field of sleep medicine. Two colleagues demonstrated the nature of sleep and the relation of eye movements with sleep by recording spontaneous whole night sleep. During their observations, it was understood for the first time that sleep consisted of 90–120 minutes cycles, it first got deep and then became superficial, and that during this superficial stage rapid eye movements appeared and then sleep deepened once again. Through the same series of observations it was found that, during the first half of the night deep sleep was more frequent and that REM sleep constituted 20–25% of the total length of the sleep [2, 3]. Sleep has an important function in an individual and sleep deprivation for a couple of days can hinder an individual's cognitive and physical performance, general productivity and health. The vital role of sleep on homeostasis can be clearly demonstrated by the possible death of rats who suffer from sleep deprivation for 2–3 weeks. Despite the obvious importance of sleep, we still have limited information about why it is an obligatory part of life. Sleep has two main types of physiological effects: First, its effect on the nervous system itself and second its effects on other functional systems of the body. There is no doubt that the effects on the nervous system are important. Long lasting wakefulness generally leads to progressive impairments of thought processes and even to abnormal behavioral activities (thoughts are blurred, as the duration of wakefulness lengthens irritability and psychosis ensues). Therefore, sleep is considered to protect the normal order of brain activity by different means and to preserve the normal "balance" between the different functions of the central nervous system [4, 14].

2.1.1 Mechanisms of wakefulness and sleep

In the regulation of wakefulness and sleep brain stem, hypothalamus, basal fore brain and their neurotransmitters all play a role. When we analyze *the neuroanatomy of wakefulness and sleep*, we mainly see that neurons activating wakefulness and sleep are located at pontis oralis, mesencephalic central tegmentum, posterior hypothalamus and midline brain stem, dorsolateral medulla reticular formation and anterior hypothalamic-preoptic fields at different concentrations and different localizations. *Brain stem and reticular formation* are important anatomic localizations. Wakefulness is managed by reticular activating system (RAS). RAS is localized in the pons and midbrain. RAS stimulates the cortex by ventral and dorsal tracts. Ventral tract stimulates the frontal parts of the brain through hypothalamus and subthalamus, dorsal tract stimulates the cortex through the nucleus groups in the thalamus. During wakefulness transmission of sensory information from thalamus is permitted through RAS control managed by thalamus. During sleep, the activity of RAS stops and the transmission of sensory information through thalamus is blocked and the stimulation of cortex is prevented. *Anatomic structures responsible for the hypothalamic control of sleep and wakefulness*: for wakefulness, stimuli originating from rostral pons and caudal midbrain regions reach paramedian midbrain in diencephalon and here the signals divide into two paths aiming to reach thalamus and hypothalamus. Main structures projecting to thalamus are PedunculoPontine Tegmental (PPT) and LateroDorsal Tegmental (LDT) nuclei

that are of cholinergic nature. The structure that initiates sleep is thought to be the ventrolateral preoptic nucleus (VLPO) located on the anterior part of the hypothalamus. VLPO nucleus suppresses the activities of brain stem, pons and locus coeruleus, dorsal raphe nucleus, laterodorsal tegmental pedunculopontine tegmental nucleus via GABA and galanin neurotransmitters. *Suprachiasmatic Nucleus (SCN)* is known as the light sensitive circadian pacemaker. Throughout daytime light stimulus is transmitted from retina to hypothalamus through neural pathways and results in secretion of melatonin from the pineal gland. It is an anatomical structure that has a central role in maintaining the day-night rhythm [3–5, 10]. Neurotransmitters controlling sleep and wakefulness can be listed as: "Glutamate, Acetylcholine, Histamine, Norepinephrine and GABA". Reticular activating system stimulates the cortex by using glutamate while ponto-mesencephalic tegmental neurons do the same job by using acetylcholine. Neurons at locus coeruleus use mostly norepinephrine, these extend from the brain stem to the cerebral cortex by including the fore brain, and they activate the stimulation of the cortex and contribute to maintaining sleep. Cholinergic neuronal network results in wakefulness in two types of cortexes: (1) It projects to laterodorsal tegmental and pedunculopontine tegmental nuclei, midline and intralaminar thalamic nuclei and to a lesser degree to lateral hypothalamus and basal for brain. (2) Cholinergic neuron group starts from the basal for brain and has a widespread projection to cortex. This pontomesencephalic neuron group is part of the ascending reticular activating system; they not only play a part in the activation during wakefulness but also are actively involved in paradoxical sleep. Glutamate is another excitatory neurotransmitter; it acts as the primary neurotransmitter of the ascending reticular activating system. Glutamate is found at a very high concentration at the brain stem reticular formation. This neurotransmitter plays an active role in the wakeful brain and is secreted from the cortical cells to a significant degree throughout wakefulness. During slow wave sleep "burst discharges" appear due to the activation of special glutamate receptors. Histamine also plays an important role in wakefulness. Neurons containing histamine are found in tuberomammillary nuclei and in posterior hypothalamus. Noradrenergic neurons (locus coeruleus), have diffuse projections in the brain that extend to the cortex. Histaminergic neurons are associated with cortical activation during wakefulness whereas they are shut down during REM sleep. To sleep there needs to be a shift from sympathetic regulation to parasympathetic regulation. Parasympathetic centers of significance are found in "solitary tract nucleus neurons, anterior hypothalamus and preoptic fields". Serotonergic raphe neurons facilitate the initiation of sleep while GABA-ergic neurons inhibit the activating system. These GABA-ergic neurons are selectively activated during slow wave sleep. As a result of this inhibition, brain stem, hypothalamus and nasal fore brain are suppressed and disfacilitation (inhibition) and hyperpolarization of thalamocortical system takes place. Thereby from the wakeful state where we see rapid, tonic discharges on EEG, the system shifts to sleep state we start recording sleep spindles and slow wave activity. Initiation and continuation of slow wave sleep is made possible by lengthening and strengthening the inhibition of the activating system with GABA-ergic system [1, 4–11].

2.1.2 Normal sleep

Sleep is a complex mix of physiological and behavioral processes. Typically, sleep takes place while the individual is in a horizontal position, immobile with closed eyes and when all other indicators point out to sleep. There are two

distinct stages of sleep: The one with non-rapid eye movements (NREM) and the one with rapid eye movements (REM). These stages are differentiated from one another and from wakefulness with clear margins. NREM sleep is classically divided into three stages based on EEG. EEG patterns usually consist of a mixture of synchronous sleep spindles, regular waves like K-complexes and high voltage slow waves. Based on the depth of sleep, there are three NREM stages, during the first two stages, wake-up thresholds are generally low and during the third stage it is at its highest or a body that can move and for a brain that can regulate, NREM sleep is a relatively inactive state going together with minimal and fragmental activity. On the other hand, during REM stage, the body is immobile because of muscular atonia, in EEG shows activation and episodic rapid eye movements can be observed. Sleep cycle starts with NREM (calm, synchronized sleep, deep wave sleep); nearly every 90 minutes NREM and REM (mobile, desynchronized, paradoxical sleep) follow one another. Slow wave sleep dominates the first one third of the night and is related to the duration of wakefulness before sleep. REM sleep dominates the last one-third portion of the night and is related to the circadian rhythm. First stage of sleep, namely NREM-1 lasts only for a couple of minutes after the initiation of sleep and it goes together with low wake-up threshold and provides the transition from wakefulness to sleep. NREM-2 stage of sleep is identified by the presence of sleep spindles and K-complexes on EEG. To wake-up, there needs to be a more intense stimulus during NREM-2 compared to NREM-1. If stimuli given during NREM-1 are administered during NREM-2, there is no arousal; but K-complexes will appear. NREM-2 gradually progresses to high voltage slow activity and transforms into NREM-3 stage. In a young healthy individual, the percentage of slow waves in sleep pattern should be 20–50%. NREM-REM cycles of sleep follow throughout the night by repetitions. First NREM-REM cycle lasts about 70–100 minutes, the second and further cycles last around 90–120 minutes. In young adults, during the first one third of the night deep sleep is predominantly seen during NREM stage, whereas during the last one-third portion of the night REM sleep dominates. Short wake-up periods usually happen when shifting to REM sleep [10, 11].

2.1.3 Electrophysiological signal recordings of wakefulness and sleep

During wakefulness electroencephalogram (EEG) reflects an active cerebral cortex engaged in perception and cognitive functions that shows relatively low voltage, high frequency and rapid activity. The discharge by a single neuron or a single nerve fiber can never be recorded from the scalp surface. Only when thousands even millions of neurons or fibers are simultaneously fired, electrical potentials pertaining to a single neuron or a single fiber can be recorded as this much of an electrical potential would suffice to make such a measurement from scalp surface [1]. When eyes are closed, several neurons show synchronous discharges at a frequency of 12 per second constituting alpha waves. When the eyes are opened afterwards, the activity of the brain increases to a greater degree; but the synchronicity of the signals decrease which leads to the canceling out of the brain waves. As a result of this, weak waves of higher but irregular frequency which are called beta waves appear. If the cortex does not have any connection with the thalamus, then alpha waves are not generated. Stimulation of non-specific reticular nuclei that surround thalamus and stimulation of diffuse nuclei that are located inside the thalamus result in the generation of waves in the thalamocortical system with a frequency of 8–13 per second which is the natural frequency for

alpha waves. That is why it is possible that alpha waves appear from the spontaneous negative feedback impulses in the diffuse thalamocortical system that also includes brain stem activating system. Delta waves include all the waves in EEG that have a frequency of less than 3–5 per second. They appear during very deep sleep, they also appear in the experimental animal studies where cortex has been separated from the thalamus with a subcortical section. Therefore, delta waves can appear in the cortex independent of the activities in the lower parts of the brain. Sleep spindles are produced by the thalamus. They appear as 12–15 Hz oscillations in between slow waves during NREM sleep in human EEGs. The production mechanism of these oscillations is related to the degree of hyperpolarization in thalamocortical cells. While shifting from wakefulness to sleep, the membrane potentials of thalamocortical cells are exposed to a progressive hyperpolarization, thus synaptic responsiveness decreases and sensory information transfer is prevented. When a sufficient level of hyperpolarization is achieved, we start seeing rhythmic bursting in nucleus reticularis neurons belonging to thalamus at a frequency interval which is in correlation with sleep spindle. Furthermore, slow wave oscillations due to membrane hyperpolarization also take place. It is accepted that sleep homeostasis is significantly affected by the size and characteristics of the sleep spindles that are formed [11–14].

2.1.4 Polysomnogram and polysomnography

"Polysomnography" "PSG" is the recording of sleep via electrophysiological signals. Sleep recordings that appear on a sheet of paper or on a computer screen are called "Polysomnogram". Throughout one night electrophysiological signals recorded during wakefulness and sleep are as follows: "Electroencephalogram (EEG), electromyogram (EMG; jaw, arm and leg), electrooculogram (EOG), electrocardiogram (ECG), snoring, oro-nasal air flow (L/s) (liter/second) chest and abdomen movements (respiratory effort recordings), O_2 saturation, and body position and real time-video-image recordings". "Penile tumescence, gastroesophageal reflux and blood pressure" are other electrophysiological signals that are recorded, despite not being performed for all patients. Polysomnography is the procedure where different physiological or pathophysiological parameters are recorded during sleep for six or more hours, evaluation of these by a medical doctor and generation of a report (**Figure 1**).

Polysomnography is performed for two main purposes: (1) Understanding physiological (normal) sleep and meanwhile demonstrating the changes that take place in the organism (for example heart rate changes can be analyzed)

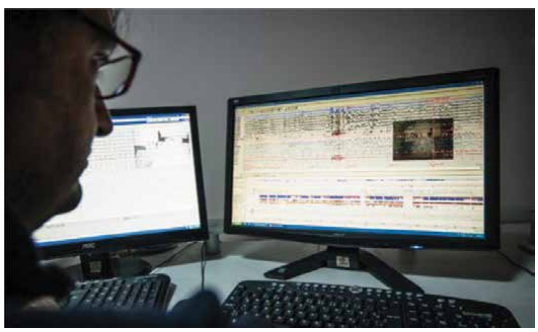

Figure 1.
Examination of a polysomnogram by a medical doctor.

(2) Identification of abnormal events that take place during sleep; diagnosis of different sleep disturbances, guide in their treatments. PSG starts by explaining the procedure to the patient in great detail. The patient should understand that there would not be any pain involved with the procedure, that no medications would be used. The patients are informed that their natural sleep will be recorded through superficial electrodes to be placed on their bodies. The patients should be reminded that they would not be spending the night by themselves, and that a technician would be present to follow the process from a monitor. After the patient puts on his sleepwear, electrodes are placed for an overnight sleep test and calibration process is initiated. First, the calibration of PSG equipment is made. This is performed before the electrodes are placed. Afterwards the electrodes are calibrated. This is done after the electrodes are placed in the electrode box. Lastly, physiological calibration is performed. This calibration is performed via the electrodes that transmit physiological changes through EEG, EOG, and EMG, leg movements, chest and abdomen movements. The PSG records of electrophysiological signals features are as follows (**Figure 2**): *EEG recordings during PSG*: Gold and silver electrodes are used for sleep EEG. It is important to clean the skin where the electrodes are to be placed. This is performed to decrease the resistance between the skin and the electrodes. Another important issue is to use substances that would increase the conductivity of the electrodes and to make sure that electrodes stay in place

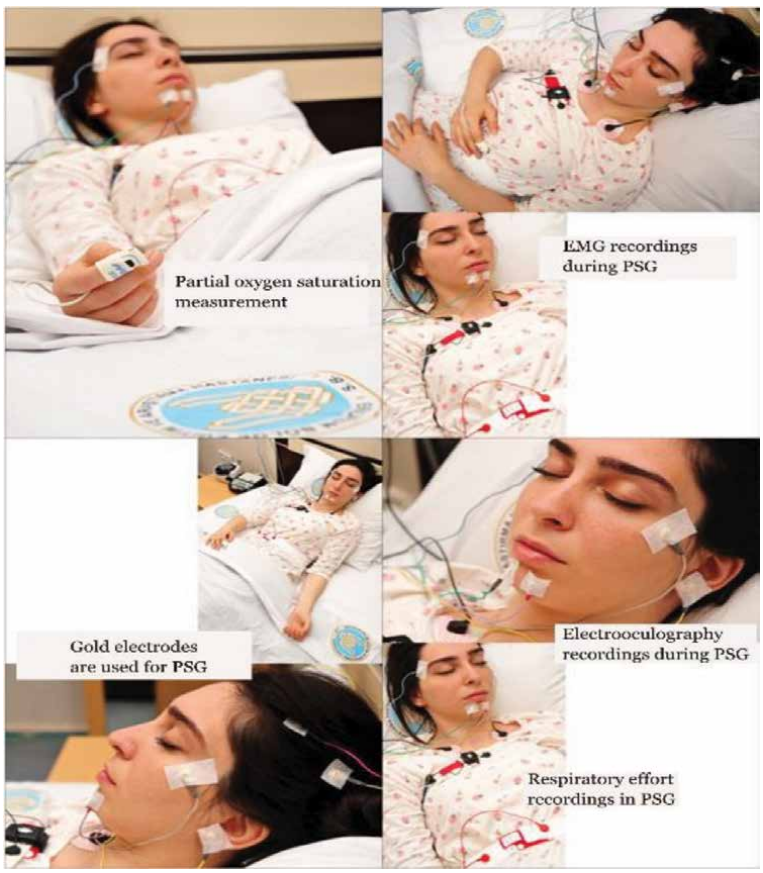

Figure 2.
The PSG records of electrophysiological signals.

throughout the night. Most commonly used fixer is "collodium". For PSG, it is recommended to have recordings from at least three channels. These channels are F4-M1, C4-M1 and O2-M1. M1 is placed on the left mastoid process. To these electrodes, F3, C3, O1 and M2 electrodes are attached as back up. If one of the electrodes mentioned above gets bad during the night, then F3-M2, C3-M2 and O1-M2 derivations are used. Here, M2 corresponds to the right mastoid process. Additionally, Fz-Cz, Cz-Oz and C4-M1 derivations can be used for EEG recordings. For this spare electrodes Fpz, C3, O1 and M2 need to be placed. *EOG recordings during PSG*: The objective of having electrooculography recordings during polysomnography is to identify the eye movements. This recording is in fact the recording of the voltage difference between cornea and retina. With the movement of the eye, the distance from the retina and cornea to the electrodes changes and creates a dipole. This change is recorded with EEG. Two EOG electrodes are used in PSG recordings. E1 is located 1 cm below the left lateral canthus E2 is placed 1 cm above the right lateral canthus. Both electrodes are referred to the electrode (M2) placed on the left mastoid process. That means EOG is recorded from two channels as E1-M2 and E2-M2. Alternatively, E1-Fpz and E2-Fpz can be used. *EMG recordings during PSG*: In polysomnography, electromyography (EMG) is of importance in detecting R stage (REM sleep). This recording is different than a classical EMG. It is performed to assess striated muscle tone. Using three electrodes is recommended for this recording; only two of these are used to do the recording. Superficial electrode is placed on the mandible and is referred to either of the electrodes placed below this. In polysomnography it is sufficient to have only one channel for EMG recording. *Respiratory Effort Recordings in PSG*: In polysomnography, there needs to be at least three respiratory parameters recorded: "oro-nasal air flow (L/s) chest and abdomen movements and O_2 saturation". Recording of stopping air flow (apnea) is performed by oronasal thermal sensors. For the recording of respiratory effort, inductance plethysmography method is used. For the measurement of O_2 saturation, pulse oximetry that identifies the O_2 saturation of hemoglobin in the capillary blood would be the most appropriate method. *Recording of Periodical Leg Movements (PLM) during Sleep in PSG*: Superficial electrodes are placed on the anterior tibial muscle. Two electrodes should be placed to each leg (active, passive) and one channel should be recorded from each leg adding up to two channels. Peak to peak amplitude of the EMG activity that is generated in the absence of movement should be 4–6 microvolts, at least four movements should take place with 5–90 seconds intervals and each of these movements should take 0.5–5 seconds to fulfill the criteria for PSG diagnosis of periodic limb movement disorder. *Multiple Sleep Latency Test-MSLT*: This is the electrophysiological signal recording method used to objectively evaluate daytime sleepiness. This is a polysomnographic recording obtained during daytime and a half to 3 hours after waking up from a nocturnal polysomnogram. It should consist of five tests of 20 minutes duration, which are 2 hours apart from each other. Two basic data for evaluation: (1) Time of sleep onset (2) Appearance of REM sleep throughout the recording process. REM of short duration that appears during recording is defined as SOREM (Sleep Onset REM). MSLT; is part of the clinical evaluation for narcolepsy and idiopathic hypersomnia.

2.1.5 Recording and scoring of sleep

Scoring of sleep corresponds to staging of sleep. For the staging of sleep polysomnography recordings are separated into 30 second-long intervals (epoch); each epoch

is scored with a sleep stage. Sleep stages are as follows: "Stage N1 (or NREM1), Stage N2 (or nREM2), Stage N3 (or NREM3), Stage R (REM), Stage W (wakefulness)". Each 30 second interval needs to match with one of these stages. Three main electrophysiological signals are used when sleep stages are identified: "EEG, EMG, EOG". There three parameters are evaluated for each epoch and one sleep stage is matched with each 30 second interval. There are certain rules to be respected when staging of sleep is performed: *Stage N1*: it is generally regarded as the stage where the shift from wakefulness to sleep happens (sleep initiation stage). If more than one half of an epoch consists of low amplitude and mixed frequency EEG activity that replaces alpha rhythm, this part is staged as Stage N1. In an individual who does not have any alpha activity during wakefulness, seeing only one of the following three features in EEG is sufficient to categorize that part as Stage N1: (1) Baseline activity in EEG should be at least 1 Hz lower than that is seen during wakefulness. (2) Observing sharp vertex waves on EEG (in central regions with duration of shorter than 500 ms, waves with sharp edges). (3) Slow eye movements should appear in EOG (lasting longer than 500 ms, conjugated, regular, and sinusoidal) (**Figure 3**). *Stage N2*: it is the longest portion of sleep both in terms of duration and proportion. In EEG, the presence of either a sleep spindle or K-complex results in naming that stage as Stage N2 (**Figure 4**). Stage N2 sleep starts in this manner and despite the absence of K complex and/or sleep spindles, the stage continues being N2 until further changes take place in the epoch (Stage W, N3, R or arousals). Only when there is a progress to Stage W, Stage 3 or Stage R or when an arousal appears, Stage N2 is concluded. *Stage N3*: It is called as slow wave sleep. In EEG, it is seen as delta activity with a frequency of 0.5–2 Hz and with amplitude that is more than 75 microvolts. During this stage there can be sleep spindles and K complexes. The only criterion for Stage N3 is the presence of slow waves (delta wave oscillations) in more than 20% of this part (**Figure 5**). *Stage R*: indicates REM sleep. In terms of central nervous system functioning this is a completely different stage of sleep. Three features are required in the epoch to be called Stage R (1). In EEG the wave activity is of low amplitude

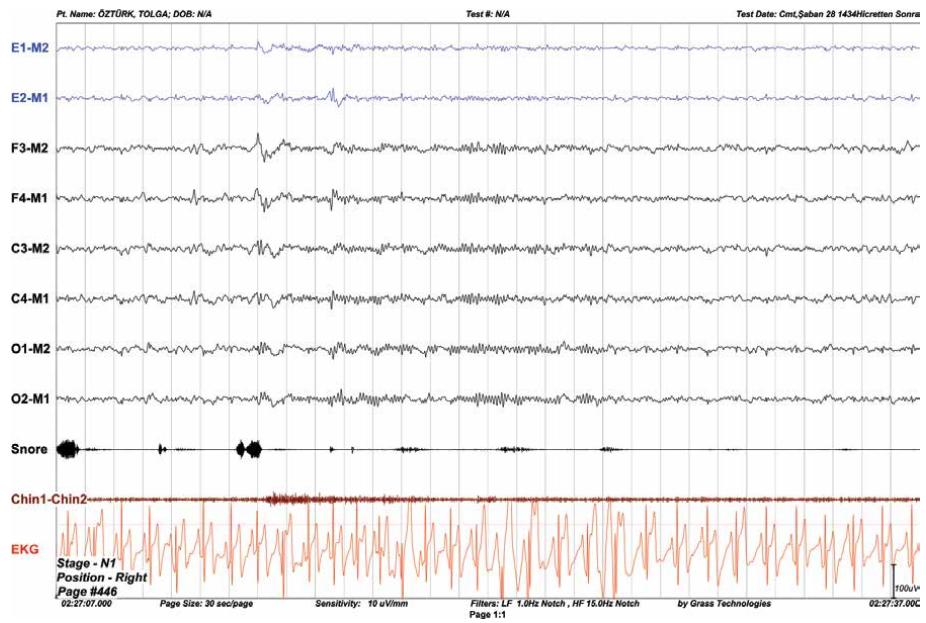

Figure 3.
Stage-N1.

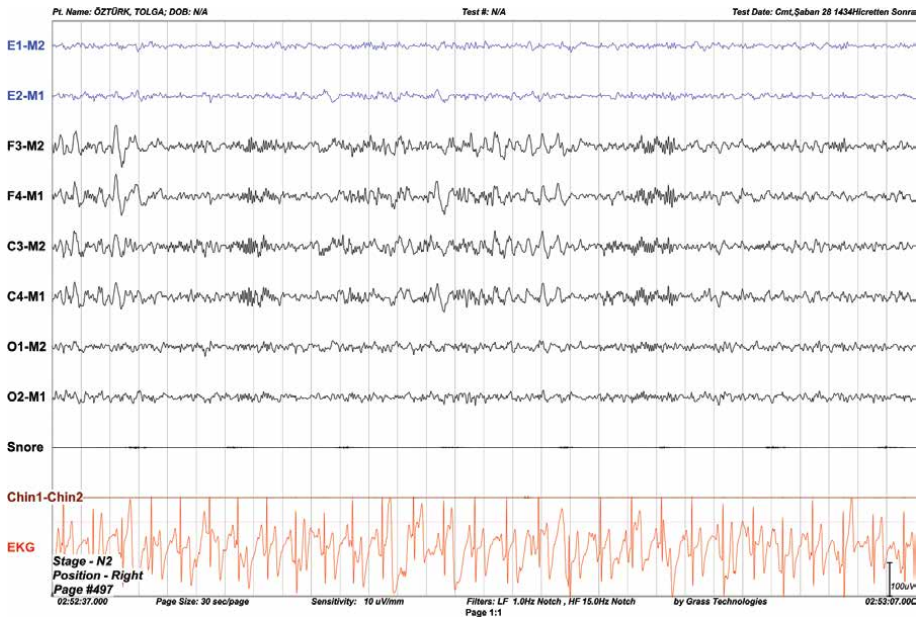

Figure 4.
Stage-N2.

and mixed frequency (2). In jaw EMG, there is a low basal EMG activity which is the lowest of all stages (3) In EOG rapid eye movements are observed (rapid eye movements—REM; these are eye movement shorter than 500 ms in duration, when are conjugate, irregular, sharp spike eye movements). In epochs that follow Stage R, even in the absence of rapid eye movements, if the other two rules remains, it continues to be classified as Stage R (**Figure 6**).

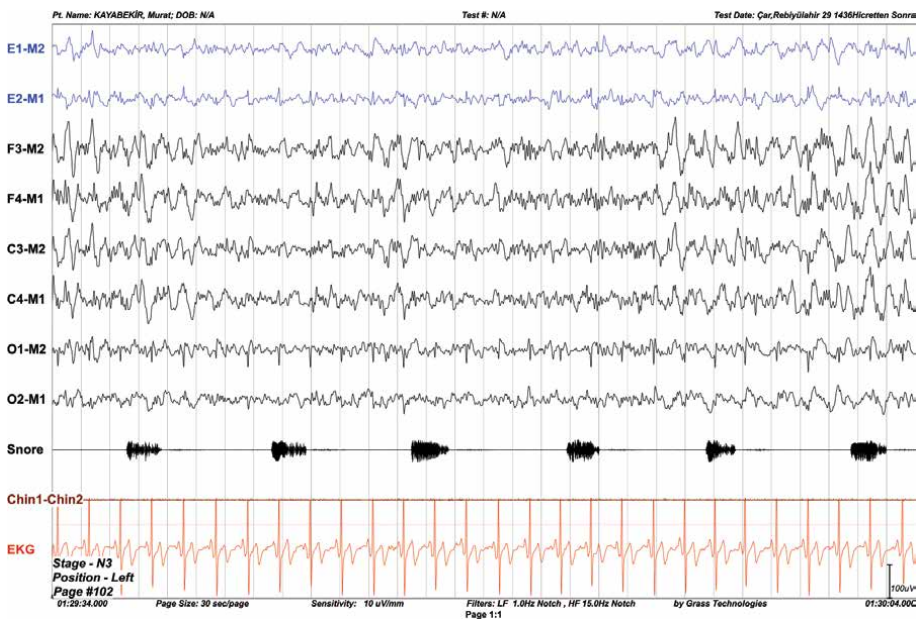

Figure 5.
Stage-N3.

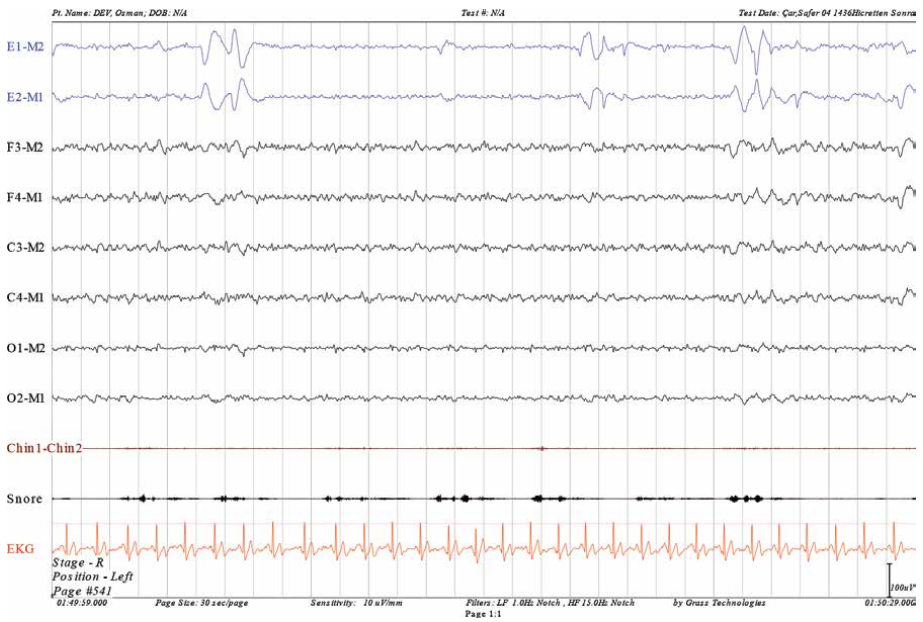

Figure 6.
REM sleep.

2.1.6 Recording and scoring of breathing during sleep

American Academy of Sleep Medicine (AASM) has published the rules for scoring sleep, sleep associated events as well as respiratory events. Based on these rules, abnormal respiratory occurrences that are observed during sleep are "apnea, hypopnea, arousal associated with respiratory effort, hypoventilation and Cheyne-Stokes breathing". Electrophysiological signal recordings that are required for interpreting respiratory problems in PSG are: "O_2 saturation, nasal/oronasal air flow (nasal cannula, thermistor), thoracic, abdominal respiratory effort, EEG recordings (absolutely required to identify arousal), body position, tracheal microphone, ECG, leg EMG recordings". To detect respiratory effort the following methods are used: (1) *Measurement of thoracic and abdominal movements*, this is the most widespread method used in the sleep laboratories to detect the respiratory effort. (2) *Respiratory muscle EMG*, standard electrodes are placed into intercostal spaces. These can be mixed with ECG recordings. This is the oldest method available. (3) *Pleural pressure*, esophageal pressure is measured to measure the inspiratory effort. Patients cannot tolerate esophageal balloons. Newer, thin, piezoelectric transducers with catheter tips are better tolerated. Esophageal pressure measurements are very helpful in two instances: (a) Identification of central apnea and hypopnea with a high sensitivity (b) The diagnosis of upper respiratory tract resistance syndrome. However this method is uncomfortable.

Apnea scoring: Apnea starts with a net loss of breathing amplitude when signals coming from nasal cannula as an alternative to oronasal thermistor stops and it ends with the start of the first breath that comes close to the basal value. Apnea is scored based on the following criteria: (1) 90% or more of a decrease in the peak signal of the thermal sensor compared to the basal amplitude. (2) Having an incident of at least 10 seconds duration. (3) At least 90% of the incident fulfilling the amplitude decrease criteria required for apnea scoring.

Based on respiratory effort, there are three types of apnea: (1) Obstructive apnea: apnea during a respiratory effort. (2) Central apnea: apnea criteria and the absence of respiratory effort during the period where air flow stops. (3) Mixed apnea: apnea criteria that start with an absence of respiratory effort and follows with a continuing increase in respiratory effort. *Hypopnea scoring*: It is performed based on following criteria: (1) More than 30% of a decrease in the signal amplitude of the nasal cannula compared to the baseline. (2) The episode lasting for at least 10 seconds. (3) 4% or more of a decrease in the O_2 saturation compared to the baseline saturation. (4) At least 90% of the incident should satisfy the amplitude decrease parameters accepted for hypopnea. *Apnea index (AI)*: defines the number of apneas that occur within an hour while sleeping. *Apnea-hypopnea index (AHI)*: defines the total number of apneas and hypopneas combined during an hour while sleeping. *Respiratory effort related arousal (RERA) scoring*: arousal resulting from 10 seconds or longer of flattening of the inspiratory portion of nasal pressure which does not fulfill the criteria for hypopnea or apnea. *Respiratory disturbance index (RDI)*: it defines the summation of apnea, hypopnea and RERA incidents that appear in an hour during sleep. *Hypoventilation scoring*: if $PaCO_2$ increases more than 10 mmHg during sleep compared to levels obtained in supine position during wakefulness this is scored as hypoventilation. *Cheyne-Stokes breathing is score*: when there are at least three consecutive crescendo and decrescendo breathing changes, with at least one of the following criteria: (1) five or more central apnea or hypopnea during an hour of sleep (2) breathing amplitude changes in crescendo-decrescendo style in a consecutive manner lasting at least 10 minutes (3) Cheyne-Stokes breathing cycle lasting for 60 seconds in general, but variable. *O_2 saturation measurement*: measurement of O_2 saturation is generally performed with pulse oximetry. It detects the O_2 saturation of hemoglobin in the capillary blood through the emission and absorption of light generated from a source. *O_2 desaturation index (ODI)*: it defines the number of oxyhemoglobin desaturation incidents per hour seen during sleep [15–18].

2.2 Physiopathology and symptomatology in sleep medicine

2.2.1 Relationship of sleep with body systems and diseases

Cardiovascular system: known hemodynamic measurements "heart rate, heart rate variations, blood pressure, cardiac output, baroreflex activity and peripheral vascular resistance" provides us important information as to how the cardiovascular system functions in sleep as well as in wakefulness. In NREM and REM stages of sleep, due to parasympathetic system activation heart rate, blood pressure, cardiac output and peripheral vascular resistance decreases. Lowest levels of arterial blood pressure are seen during Stage N3. The decrease in the heart rate is related to the decrease in the sympathetic motor tone. During NREM sleep; blood pressure, respiratory rate and basal metabolic rate decrease by 10–30%, this is the most comforting and most restful period of deep sleep. In the hemodynamic changes in sleep, arterial baroreflex mechanism is thought to play a regulating role. Baroreflex arch consists of peripheral receptors (sinus caroticus and arcus aorta), central neurons (tractus solitorius and medulla oblongata) and afferent and efferent (sympathetic, parasympathetic) neurons. The decrease in blood pressure is compensated with an increase in the heart rate centrally through this reflex arch, or vice versa. From a cardiovascular perspective, during NREM sleep, there is relative autonomic stability, sympathetic inhibition, and increase of vagal (parasympathetic) tone. It is also the stage where bradycardia

and respiratory sinus arrhythmia is seen. Despite the fact that there is parasympathetic predominance during REM sleep, due to bursting in sympathetic nervous system, blood pressure increases and variations are observed in the heart rate. During this stage, first degree or Wenckebach type second degree AV blocks, and sinus blockage can take place due to increased vagal tone. During Stage N3 blood pressure decreases by 10–20% and heart rate by 5–10% (dipper). The absence of the expected nocturnal decrease in blood pressure is called non-dipper, while a decrease of extreme scale is called extreme dipper and both can lead to cardiovascular events. Compared to NREM, blood pressure is higher during REM sleep; myocardial infarction, unstable angina, cardiac death, ventricular tachyarrhythmias, pulmonary embolism, cerebrovascular incidents and sudden cardiac death can take place during REM stage of sleep that intensifies during early hours of the day during which there is autonomic instability (sudden sympathetic discharge) triggering platelet aggregation, plaque rupture and coronary spasm [19–25]. *Respiratory system*: control mechanisms for respiration during sleep: (1) homeostatic and metabolic control; O_2 and CO_2 sensitivity mechanisms on carotid bodies through chemoreceptors provide for the regularity of breathing. (2) Behavioral (cortical) control; during activities like speaking or swallowing breathing is controlled voluntarily. (3) Wakefulness warning; during wakefulness reticular activating system sends non-tonic stimuli to the respiratory center in the brain stem resulting in an increase in breathing. NREM and REM stages are controlled with metabolic stimuli. It is shown that respiratory response by chemoreceptors decreases during NREM and this decrease gets more significant during REM. The main stimulus for respiration is $PaCO_2$, the effector organ is the lungs, and the chemoreceptors that regulate the response to stimuli are located on carotid bodies and brain stem. The system operates with stimuli and feedback mechanisms. For example, during heart failure the response to stimulus is delayed as a result of lengthened circulatory time. Likewise, a minor change in ventilation can result in a significant change in CO_2 and can cause impairment in respiratory balance. Instances where the tendency to central apnea increases in the organism are: (1) During transition to sleep; when CO_2 is at a level that is lower than that is required to stimulate respiration and the number of respiration becomes insufficient. (2) When the ratio between respiratory response and respiratory stimuli is high; idiopathic sleep apnea is an example for this. (3) Lengthened circulatory time; for example during cardiac failure typically Cheyne-Stokes breathing develops. (4) Instances where respiratory control gets out of order; in conditions pertaining to the brain, in patients with decreased or disappeared chemosensitivity, hypercapnia is seen during wakefulness. These patients experience hypoventilation especially during REM stage. That is why in patients having central alveolar hypoventilation and obesity hypoventilation syndrome, the ventilation is further hindered during sleep; so hypoxia, hypercapnia, both central and obstructive apneas are observed [26–30]. *Upper respiratory tract*: it is a multipurpose conduit. As it allows for the passage of liquids and food, it is where activities like talking, swallowing and breathing take place. It contains the following structures: "Extrathoracic trachea, larynx, pharynx and nose". The segment with the highest tendency to collapse in the respiratory system is the pharynx. The pharynx consists of three parts: (1) Nasopharynx is the part that extends from the nasal passage to the hard palate. (2) Oropharynx is divided into two parts as retropalatal and retroglossal fields. (3) Hypopharynx starts from the root of the tongue and extends to the larynx. In most of the patients with Obstructive Sleep Apnea Syndrome (OSAS), narrowing or closure of the airways that happen throughout the sleep takes place in the retropalatal and retroglossal region. For the preservation of the patency of the upper airways,

two important physiological mechanisms need to be in balance: (a) Forces that cause the collapse of the pharyngeal airways (the amount of soft tissue that covers the airways and the size of the airways). (b) Forces that dilate the pharyngeal airways (the activity of a muscle group that work in a coordinated manner to keep the airways open). Predisposing factors that would impair this balance are: "Mainly age and gender and then race, obesity, neck circumference, cigarette-alcohol-sedative use, genetic factors, co-morbid diseases (acromegaly, hypothyroidism, Down Syndrome, storage diseases like amyloidosis and mucopolysaccharidosis), body posture and gravity, anatomic factors, genetic factors and hormones influence the patency of upper airways and constitute the risk factors for OSAS [31–35]. *Sleep and immune system*: among the substances that are both sleep inducing and immunologically active we can list; Interleukin-1 (IL-1), IL-2, alpha interferon, Factor-S, muramyl peptides, tumor necrosis factor (TNF) and prostaglandin D2 (PGD2). We know that people who are sleep deprived can get sick more easily and when they pay attention to sleeping properly and resting, they heal faster. Several factors play a role in sleep regulation. TNF-alpha, IL-1-beta, growth hormone releasing hormone (GHRH), PGD2 and adenosine affect NREM sleep, whereas vasoactive intestinal peptide (VIP), nitric oxide (NO) and prolactin exert their effects on REM sleep. In the regulation of sleep-wakefulness, elements of immune system that are of significant value are; IL-1, IL-6 and TNF. When the endogenous production of IL-1-beta and TNF-alpha increases (overnutrition, infectious disease states) NREM sleep increases. The effects of certain cytokines on sleep can be summarized as follows: *Prosomnogenic cytokines*: IL-1-beta, IL-1-alpha, TNF-alpha, IL-2, IL-6, IL-15, IL-18, epidermal growth factor, nerve growth factor, interferon-gamma, neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3, and 4 have been observed in elevated concentrations in allergic diseases, and they cause swelling and tenderness in the joints, and increase the tendency for autoimmune diseases like rheumatoid arthritis. The secretion of such factors by the immune system peaks during the early hours of the night and with gradual decreases they reach their lowest levels during morning hours. Short term sleep deprivation lead to decreases in natural killer (NK) cell activity, when this deprivation lasts longer there is an increase in NK cell activity. Experimental studies on laboratory animals have shown that, in instances of lengthened sleep deprivation fatal bacterial infections stemming from the gastrointestinal system can turn fatal within 3 days. In narcolepsy cases increases have been observed in TNF-alpha levels. In OSAS patients the circadian rhythm of secretion for TNF-alpha deteriorates significantly [36–40]. *Endocrine Physiology during Sleep*: Circadian rhythm and homeostatic balance provide for the control of hormonal and metabolic changes during sleep. Sleep deprivation studies analyze the effects of sleep and circadian rhythm on hormones. Based on these studies, growth hormone (GH) and prolactin (PRL) secretion increases during normal sleep, cortisol and thyroid stimulating hormone (TSH) secretions decrease. If sleep is interrupted by wakefulness, GH and PRL decrease while TSH and cortisol increase. Physiologically cortisol decreases starting from early hours of the morning towards the evening by reaching its lowest levels during the late hours of the day and initial hours of sleep. A couple of hours before waking up, there are reactivation of cortisol secretion. Low levels of cortisol is associated with slow wave sleep. During sleep deprivation the amplitude of cortisol rhythm decreases 15% compared to normal. Especially in elderly individuals who have fragmented sleep patterns, as deep sleep decreases as well, there is an increase in cortisol levels during night time and this is associated with decreased memory and increases in insulin resistance. In Cushing syndrome patients, due to bad

sleep quality decreases have been shown in REM latency, increases in first REM intensity and decreases of deep sleep. There are three basic processes coming into play in sleep regulation: (1) Homeostatic process: it tells us the relationship between last sleep and wakefulness periods. Sleep deprivation in the organism increases the duration and depth of sleep as a compensatory mechanism. (2) Circadian process: it is also defined as the biological clock. (3) Ultradian process: it defines the duration of REM—NREM sleep cycles and the interactions between them. Melatonin is the neuroendocrine modulator of day-night rhythm. Melatonin receptors are densely located at the suprachiasmatic nucleus (SCN). The endogenous circadian rhythm of melatonin secretion is in parallel to the endogenous rhythm of sleep tendency. Secretion of melatonin from the pineal gland is under the control of SCN. This pathway is multisynaptic and has contributions from the sympathetic nervous system. Melatonin has three important physiological features: (1) Hypnotic effect: the ability to initiate sleep when homeostatic effect is inadequate to initiate or to maintain sleep. (2) Chronohypnotic effect: it is the ability to inhibit the time of waking-up that is normally regulated by the circadian center. (3) Chronobiotic effect: concerning the regulation of the circadian rhythm, it is the ability to initiate phase shifts and to do this during desired hours. The light that an individual is exposed to during night hours causes sudden decreases in melatonin levels. Beta blockers used for the prophylaxis of hypertension, cardiac arrhythmias and headaches block the sympathetic activity both at the heart and at the pineal gland. On the other hand, antidepressant drug fluvoxamine prevents the degradation of melatonin and increases its plasma concentrations. Neurotransmitter imbalance has been shown to be present in SCN of essential hypertension patients and there is a decrease in the secretion of melatonin in coronary artery disease that follows. These findings bring forward the possibility of using melatonin in hypertensive patients. At the beginning of sleep norepinephrine and epinephrine levels decrease and they reach their lowest levels within an hour. In patients with OSAS there is an increase in the levels of nocturnal catecholamines. Despite long hours of fasting during sleep, blood glucose levels have been shown to remain stable. Leptin that plays an important role in energy balance by suppressing appetite (produced by adipose tissue), increases significantly during sleep at night and thus increases slow wave sleep. In lengthened sleep deprivation, there is suppression of the night increases of leptin [41–45]. *Gastrointestinal System*: Gastric acid secretion has a circadian rhythm. Basal acid secretion is at its lowest during the hours of the day where there is no food intake, while it is at its highest during midnight. In healthy individuals, there is no relationship between gastric acid secretion and the stages of sleep. Together with the inhibition of acid secretion throughout the night (with H_2 receptor blockers and proton pump inhibitors) the healing of duodenum ulcers could be shown. Small bowel and colon motility decrease during sleep. In studies conducted on patients with irritable bowel syndrome, significant lengthening of REM sleep was identified [46].

2.2.2 Basic signs in sleep disorders and pathophysiological causes (semiology, propedeutics, preliminary instruction, introduction to further study)

The first step in the evaluation of a patient with a sleep disorder is to identify the main symptom. A detailed history of the sleep and wakefulness cycle constitutes the second step. This is followed by the medical history of the patient, a list of previously used medications, family history, detailed information about school, work, family and social life and a physical exam of bodily systems. Relevant laboratory tests are performed for differential diagnosis.

PSG establishes the definitive diagnosis. Despite developments in the field of sleep medicine, we see that neither the society nor the physicians are adequately informed about sleep and sleep disturbances. However, diseases associated with sleep are frequent in the population and can have significant consequences: they can negatively influence the individual's "work or school success, social life, marriage and other relationships as well as leading to occupational and traffic accidents. Sleep disturbances can hinder the cognitive functions of an individual and can increase the risk of having psychiatric and other system related diseases. Sleep apnea syndrome has a role in the etiology of severe diseases namely hypertension, myocardial infarction, heart failure, stroke and diabetes. Sleep deprivation can result in an increase in the number of seizures in a patient with epilepsy. Complaints of patients with diseases of other systems can be related to sleep disorders: in a patient having a follow-up with a Holter recording for hypertension, the reason behind an increase in blood pressure during sleep can be sleep apnea syndrome. Frequent arousals during the night, chest pain, not being able to climb the stairs during the day, tiredness, complaints about sleepiness are evaluated as angina by cardiologists and angiograms are performed. However, a PSG to be performed on this patient can establish the correct diagnosis of central apnea syndrome. In a patient with goiter disease, during an overnight sleep test, it is possible to diagnose sinusal bradycardia. Likewise, patients having severe OSAS can have predominant depression symptoms and can therefore admit to psychiatry outpatient departments. Children admitting to pediatric neurology outpatient departments with sleep episodes are valuated multidimensionally and then treated for epilepsy. However, if these children were to undergo PSG and MSLT (multiple sleep latency test), correct diagnoses of underlying sleep apnea syndrome, central hypersomnia and narcolepsy could have been established.

Insomnia: it is described as "difficulty falling asleep or staying asleep"; short, inadequate, superficial, easily disruptable and non-restorative sleep. The amount of sleep an individual needs changes from one person to the other based on genetic traits. Some people carry out their daily functions with 5 hours of sleep a day, whereas others who do not sleep nine to 10 hours can feel bad the next day. Sleeplessness can be related to a primary disturbance related to mechanisms of sleep or can develop due to an underlying disease. Acute insomnia develops due to an abrupt change in environmental, physical or cognitive factors that initiate sleeplessness. Sleep complaints only disappear when the individual gets used to this new condition. There are different diseases underlying primary insomnia; circadian rhythm disturbances, drug-substance use or sudden discontinuation of their use. Acquisition of behavior that hinders sleep hygiene can result in chronic insomnia. Psychophysiological insomnia is learned insomnia; the patient starts getting tense as the time for going bed approaches. This effort to get asleep and tension cause a performance anxiety and ends up being the main reason of insomnia. As the patient searches for behavioral changes to relieve herself of this anxiety, insomnia becomes inextricable: inadequate sleep hygiene, night eating (drinking) syndrome, alcohol-hypnotic-stimulant related insomnia are examples to insomnia for which such behavioral changes and habits lay the foundation. Causes of pain that increase during the night that negatively affect sleep and trigger insomnia are: "entrapment neuropathies, cluster headaches, arthritis, rheumatic pain, pain and paresthesia of the legs that are seen before falling asleep in restless leg syndrome. Most of the psychiatric diseases have a relationship with sleep: "In depression and anxiety disorder, insomnia might have started years ahead and likewise insomnia might

foreshadow psychosis or manic episodes." Examinations of physical neurological and cognitive functioning of the patient might reveal important clues about insomnia. In anxiety, tachycardia, rapid breathing and cold hands; in sleep apnea syndrome, short and thick neck, obesity and narrow upper respiratory tract; in endocrine system pathologies hyperthyroidism characterized by excessive sweating and tachycardia, round face and buffalo hump in Cushing syndrome and neurological examination might reveal causes of insomnia like neuropathy and parkinsonism. It should be kept in mind that women with iron deficiency anemia may complain of insomnia. *Excessive sleepiness*: having somnolence at inappropriate times and in inappropriate environments and being unable to prevent it. Although somnolence might be related to the nature of the individual, to the wearisomeness of his daily life or to depression, it is an important symptom that forecasts sleep disorders. In its mild forms it is seen during rest, in advanced cases the patient might fall asleep during a conversation, while doing work, during eating or while driving. Hypersomnia leads to important work and traffic accidents. In differential diagnosis, daytime excessive sleepiness due to chronic sleep deprivation should be kept in mind; additionally, excessive sleepiness can be seen during heart, kidney and liver failure, rheumatic, endocrinological and neurological diseases. Slowing down of responses, frequent yawning, closing of the eye lids, hesitance during speech or movements are the physical signs for excessive sleepiness. In people with chronic hypersomnia, round dark circles underneath the eyes attract one's attention. Sleep disturbances where one can see hypersomnolence are: "sleep apnea syndrome, narcolepsy, idiopathic hypersomnia, parasomnias"; however, certain complaints that are obtained during history help in the differential diagnosis of these disease states. Such complaints are; "snoring, apnea episodes observed by close ones, morning headaches, nocturia, sleep paralysis, hypnogogic hallucinations, cataplexy and confusion while waking up from sleep". Idiopathic hypersomnia is characterized by increased sleep time and despite there is nothing that would hinder the quality of sleep, the individual feels himself sleepy which differentiates this condition from insomnia associated with sleep deprivation. *Tiredness*: patients who have excessive sleepiness also complain about tiredness and lack of energy. However, tiredness is not associated with tendency to fall asleep. Tiredness is an important symptom for many diseases. Especially in women, tiredness due to iron deficiency anemia is usually ignored and mostly confused with sleepiness and that is why women come to sleep laboratories. Endocrine and metabolic diseases, heart, kidney and liver failures and psychiatric conditions like depression can as well lead to tiredness and fatigue. *Snoring*: it is the sound generated during sleep due to the resonance of the tissues of the upper respiratory tract which is mostly heard during inspiration, rarely during expiration and sometimes during both phases. Due to narrowed upper respiratory tract the speed of the flowing air increases, this creates turbulence and increases the intensity of the sound. Patients are usually not aware of this and they are guided to a doctor by close ones who are bothered by the noise. Sometimes the patient wakes up with his own snoring or his own effort to breathe. Characteristic features of the snoring sound give clues as to whether the patient has sleep apnea or not. In patients who had undergone surgery for upper respiratory airways, apnea episodes might as well be seen in the absence of snoring. *Sleep apnea*: it is the stopping of respiration for 10 seconds or longer during sleep. The patient's partner or close ones describe it as an interruption of snoring, as patient holding his/her breath during sleep. During apnea the snoring stops, while the apnea ends the patient has a deep inhalation,

and the snoring restarts with a loud sound like roaring or snorting. These episodes can repeat hundreds of times through the night depending on the severity of the disease. The ending of apnea goes together with wakefulness reactions. This divides the sleep and hinders its quality. It might result in hypersomnia or insomnia. There are two main types of apnea: In central apnea air flow stops together with the effort of respiration. In obstructive apnea, air flow stops because of a narrowing in the upper respiratory tract but the effort of respiration still continues. Obstructive apnea is mainly accompanied by snoring and other complaints like night sweats, feeling of suffocation, nocturia, morning headaches, irritability, forgetfulness and depression and hypertension might follow. The patients are generally obese with short and thick necks; they also have narrow upper respiratory tracts. This body composition is not a rule though; people from all age groups including children might have obstructive apnea. Central apnea might be due to lesions of the brain stem and regions associated with the regulation of breathing. Furthermore, heart failure, metabolic and toxic encephalopathies might lead to central apnea. Central apnea might happen both in sleep and during wakefulness. *Night and morning headaches*: their relationship with sleep disturbances and neurological diseases is important. In the presence of morning headaches, one should consider problems related to sleep and respiration. This headache is diffuse and blunt in nature and is related to a decrease in O_2 saturation. Cluster headaches typically appear during REM sleep. *Cataplexy*: It is the sudden loss of muscular tonus triggered by intense emotional stimuli and physical exercise. It is described as muscular atonia or hypotonia ranging from couple of seconds to couple of minutes in duration. If this symptom is together with sleepiness during the day, then it is always related to narcolepsy. The fact that consciousness and memory are preserved during the incident differentiates cataplexy from syncope and epileptic seizures. *Sleep paralysis*: it is the carrying over of REM sleep related atonia to wakefulness. The duration of the incident is limited to seconds or minutes. When the episodes become more frequent and they last longer, this disturbs the patient significantly and even be frightening. Despite the patient is awake, visual and auditory hallucinations might be present. In order not to experience this situation during sleep, the individual avoids to sleep and develops insomnia. Narcolepsy, depression, alcohol use, sleep deprivation and shift changes are instances where this symptom might be seen. *Hypnagogic and hypnopompic hallucinations*: hallucinations taking place during the beginning of sleep are called hypnagogic, those appearing while the individual is about to wake up are called hypnopompic. These hallucinations might have visual, auditory and tactile components; they can either be pleasing or frightening. Other than being seen during narcolepsy, they can happen in instances of sleep deprivation or when there are changes in sleep patterns as well as following alcohol consumption. *Parasomnias and movement during sleep*: parasomnias are involuntary physical events that take place when an individual is about to fall asleep, during sleeping and when he/she is about to wake up. the activation of the central nervous system during parasomnias results in features caused by activation of autonomic nervous system and motor activity. NREM parasomnias are disturbances in waking up from NREM sleep and the most common are confusional arousals, sleep terror, and sleepwalking. They mainly appear during deep slow wave sleep especially during the first 1/3 of the night. Familial characteristics are prominent. Despite the patient might seem like awake during the incident, arousal is not complete and he does not interact with his surroundings, does not respond to external stimuli, is not easily arousable, resists to

efforts of waking him up and can show agitation. Patients are difficult to arouse during the event but if awaken they are confused; when episode ends, he can easily fall asleep after going to bed and does not remember the episode the next day. *Movements associated with sleep*: during REM sleep, muscle tonus disappears. REM sleep behavioral disturbance (RBD) is a parasomnia associated with REM sleep during which muscle tonus does not disappear but increases. As a result of this, the patient starts playing her/his dreams. It is characterized by aggressive behavior like speaking, shouting, kicking, punching or slapping, jumping, running which include violence and might harm the patient herself and her bed partners. The most important difference of arousal disturbances from NREM parasomnias is the development of episodes towards morning hours when REM sleep intensifies, when the patient wakes up after the episode, he is not confused and can remember a dream that can explain her/him behavior during which s/he has frequently felt threatened. Most of the patients are in the advanced age group and are idiopathic cases. Associated neurological diseases are "Parkinson's, Multisystem Atrophies and Dementia with Levy Bodies". The condition can also be seen in individuals using tricyclic antidepressants, monoamine oxidase inhibitors and serotonin reuptake inhibitors and in those who have recently stopped consuming alcohol. *Talking during sleep*: these are vocalizations ranging from murmuring to meaningful conversation during superficial NREM sleep. They can rarely be seen during REM stage as well. Stress, febrile diseases and frequent sleep deprivation can result in this. There is no need for treatment if there is not any underlying sleep disturbance. *Bruxism*: it is a movement disorder characterized by repetitive rhythmical jaw clenching and ensuing teeth grinding. It increases with stress and can result in face pain, jaw pain, teeth pain and damage to the teeth and even breaking of teeth as well as jaw dislocation. *Rhythmical movement disorder*: these are stereotypical movements that start immediately before falling asleep and continue during superficial sleep. The most known one is to rhythmically knock the head on the pillow or the headboard. It is a phenomenon usually encountered during infancy or early childhood and it disappears with increasing age by decreasing in intensity. *Restless leg syndrome (RLS) and periodical leg movements (PLM) during sleep*: RLS usually appears during evening hours and mostly after going to bed. These are unpleasant leg symptoms that cannot be well expressed by the patients. The disturbing sensation leading to an irresistible need to move the legs is the most important feature. As symptoms disappear with movement, patients constantly move their legs while in bed and they can even stand up and start walking around after a while. When patients come to see a physician with the complaint of insomnia, antidepressants that might be prescribed for treatment can increase the severity of RLS. Other causes that can increase the severity of the symptoms can be listed as: "Iron deficiency anemia, B_{12} and folate deficiencies, uremia, spinal cord lesions, diabetes mellitus, peripheral neuropathies, excessive exercise and caffeinated beverages". *Signs in children*: although they might be non-specific, the physician should definitely take sleep disturbances into consideration in children coming with the following complaints: "Developmental delay, decrease in school performance, distractibility, hyperactivity, moodiness, stubbornness and aggression". School-age children can admit to doctors with complaints of feeling themselves not rested throughout the day, not having slept enough, difficulty in concentrating, adenoid hypertrophy, lack of attention and sleepiness during classes. In the presence of such symptoms, diagnoses of sleep apnea, insomnia, RLS, hypersomnia and narcolepsy should be considered [47–54].

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Chapter 2

Comorbid Sleep Disorders and Headache Disorders

Fabian Rossi, Carlyn Rodriguez-Nazario, Umesh Sharma, Lourdes Benes Lima, Joshua Rossi, Mays Alani, Michelle Nunes, Aqsa Ullah, Elisa Marie Rossi and Nina Tsakadze

Abstract

Sleep disorders are closely intertwined with different kinds of headache disorders. In some forms of headaches, this association is profound, such as in hypnic headache, where headaches only occur during sleep, or in cluster headache, which has connection to the REM sleep. In other headaches, the association with sleep is more subtle, but nevertheless, very relevant–for instance in migraine, where sleep deprivation or excessive sleep may act as a trigger for migraine, while sleep has a curative effect on the migraine attack. This chapter focuses in the relationship between sleep disorders and headaches focusing on the five primary forms of headaches: migraine, tension-type headache, paroxysmal hemicrania, hypnic headache, and secondary form of headaches such as obstructive-sleep-apnea-related headaches and medication overuse headaches (MOH).

Keywords: sleep, headaches, migraines, insomnia, sleep deprivation

1. Introduction

The association between headaches and sleep is well known for more than 100 years [1]. Some headaches emerge from specific sleep stages, other headaches originate from nonspecific sleep stages, and finally some are triggered by insufficient sleep or over-sleeping and are relieved by sleep. Changes in sleep pattern is a known factor that predisposes and perpetuates headaches in an acute or chronic fashion. Sleep disorders are associated with both, primary headache syndromes such as migraines, tension-type headaches, cluster headaches, hypnic headaches, and secondary headache disorders such as headaches-on-awakening, and MOH [2]. Primary headaches are headaches where pain and associated features such as nausea or light sensitivity are the illness, and secondary headaches are headaches that result from an underlying medical disorder. The number of sleep disorders associated with headaches is also vast, such as OSA, insomnia, RLS, etc. [3]. In general, at times, more than one type of sleep disorder may coexist in a single patient, and the same applies to headache disorders.

2. Pathophysiology

Headaches and sleep disorders share similar neurochemistry and neuroanatomy. The ascending reticular activating system (ARAS) is a multi-neuronal polysynaptic system, which promotes wakefulness. The ARAS has two main ascending activating pathways: first one is located in the brainstem, and projects to the thalamus, and the second is a thalamocortical pathway with its glutamate-containing neurons. The second pathway is a mono-aminergic with several brainstem nuclei including periaqueductal gray (dopamine), locus coeruleus (noradrenaline), dorsal raphe nuclei (serotonin), and tuberomammillary (histamine). These nuclei containing neurochemical neurons project through the hypothalamus to the basal forebrain (cholinergic system) and to the cerebral cortex, to promote wakefulness. Finally, hypocretin-containing neurons (excitatory neuropeptide) that via lateral hypothalamus project to the cerebral cortex to awake it [4].

Sleep is divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep. Non-REM sleep is subdivided in three sleep stages: stage N1, stage N2, and stage N3. Stage N1 is a bridge between wakefulness and sleep (light sleep stage) where individual can be easily aroused. As sleep deepens, it moves into stage N2 defined by the presence of spindles and K-complex on the EEG, and Stage N3 a deep sleep stage where people are hard to arouse. The neurons that induce non-REM sleep are located in the anterior hypothalamus and inhibit the ARAS and the main neurochemicals are serotonin and gamma-aminobutyric acid (GABA). REM-sleep is defined by electroencephalographic features of wakefulness, loss of muscle tone (atonia), and rapid eye movements. The neurons that induce REM sleep are located in the upper pons and the main neurochemical is acetylcholine [4].

The rhythmicity of awake and sleep stages, also known as circadian rhythm, is regulated by an internal biological "clock" located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. Neurons of the SCN are capable of almost constant self-sustained cycle. This rhythmicity is accomplished through a precisely timed and highly regulated negative feedback between specific gene expressions and their resulting proteins. Light exposure, social activities, physical activity, and melatonin (a pineal gland hormone) assist this synchronized, also called entrained, internal clock. The wake and sleep time is also controlled by the homeostatic drive that results from extracellular accumulation of adenosine (ATP byproduct) that increases during wakefulness and the longer is the sleep deprivation period - the more intense is the drive to sleep. The dynamic balance between the circadian and homeostatic drive promotes either wakefulness or sleep [4].

Migraine is associated with the inappropriate central activation of painful neuronal pathways. These pathways involve brainstem, thalamus, hypothalamus, and cortex—the same structures which are involved in the regulation of wakefulness and sleep, [5–7] especially locus coeruleus, dorsal raphe nuclei, periaqueductal gray, and hypothalamus. Brainstem nuclei, locus coeruleus and dorsal raphe nucleus are implicated in the nociceptive control and modification of the cerebral blood flow [5–8]. Periaqueductal gray stimulation with electrodes may trigger migraine-like headache [9]. DBP of the PAG for other painful disorders was associated with induction of migraine in prior nonmigraines [10] and increase in iron content in the PAG of migraine patients [11, 12]. In migraine, there is an increment in the regional cerebral blood flow (rCBF) of the dorsal PAG and raphe nuclei [13]. Hypothalamus is implicated in the pathogenesis of migraine and cluster headache. The suprachiasmatic nucleus is localized in the hypothalamus, which connects with the periaqueductal gray, spinal nociceptive, and ARAS, all of which are implicated in mechanisms of pain and headache. Hypothalamus plays a

role in the early phase of migraine—premonitory phase, which precedes headache phase by up to 72 hours and presents with fatigue, yawning, food cravings, and is associated with an increase in the hypothalamic blood flow [14]. Hypothalamic activation during cluster headache (CH), increase in the hypothalamus gray matter, and DBS efficacy in treating the refractory CH, supports the theory that hypothallus is implicated in the genesis of CH [15, 16].

3. Clinical diagnosis

The appropriate diagnosis of headaches and sleep disorders, relays on history, physical examination and corroborated by additional tests such as polysomnography, and at times mean sleep latency test (MSLT). Detailed history of headache characteristics is essential, since diagnosis of headache disorders relays solely on history, while the diagnosis of sleep disorders can be approximated by history, but often requires a sleep study for confirmation, for instance for the diagnosis of sleep apnea. Several questionnaires have been designed for the diagnosis of headache and sleep disorders. Headache questionnaire and headache diary may assist in assessment and quantification of the headache's frequency, severity, associated features, and response to the specific therapy. Sleep questionnaire may also assist in determination of the levels of drowsiness as in the Epworth sleepiness scale, which attempts to assess the levels of drowsiness in different scenarios of daily life, with score of 10 or higher being associated with the significant impairment in the activities of daily leaving. Other questionnaires as STOP-BANG are more specific for determination of the probability of having the sleep apnea. Other questionnaires may determine the severity of the restless leg syndrome. Polysomnography is the gold standard for the diagnosis of sleep disorders, especially obstructive sleep apnea, periodic leg movement of the sleep, and is less likely to diagnose parasomnias and narcolepsy.

4. Headache types and sleep

4.1 Primary headaches associated with sleep disorders

Migraine with and without aura. Migraine is defined as uni- or bilateral, moderate to severe headache associated with photophobia, phonophobia, and nausea and/or vomiting, and aggravated by activity. Migraine is reciprocally intertwined with sleep patterns. Too much or too little sleep at night or irregular sleeping pattern (circadian rhythm disorders or sleep fragmentation) are all common migraine triggers. Meanwhile, sleep may have a curative effect on the migraine headaches—the so-called "healing naps" (2). Nearly 90% of episodic migraineurs who complain of poor sleep quality and poor night sleep, have more severe migraine and increased daily burden [17]. Sleep hygiene could be a trigger or relieving factor for migraine chronicity, depending on whether it is poor or good, respectively [18]. Poor sleep quality and/or duration is a trigger for migraine [19] and causes increase in migraine frequency [20]. Similarly, Korean study showed increase in frequency of migraine in patients with poor sleep [21]. Migraine is related to several sleep disorders, such as insomnia, OSA, parasomnias, sleep-related movement disorders, REM-sleep related disorders [22]. Half to two-thirds of migraineurs suffer from insomnia [23]—the most common sleep disorder, and migraineurs have a 3-fold increase in daytime sleepiness [24]. Insomnia is more common in patients with chronic

migraine (with at least 15 headaches per month) than in patients with episodic migraine [25]. Migraine is closely linked to insomnia as they trigger or aggravate each other [26, 27]. CBT for insomnia improves headache frequency [28]. One third of patients with the refractory chronic daily headache is diagnosed with OSA [29]. There is strong comorbidity between migraine and OSA [2] and patient with migraine who are compliant with CPAP have lower incidence of headaches. The use of opioids for management of headaches is not recommended, but they are still often used, and are also associated with central sleep apnea [30] with increase in nocturnal hypoxemia [31]. Patient with more nocturnal migraines are usually older, have longer history of migraine and shorter sleep time, probably related to more sleep fragmentation often seen in older individuals [32]. There is also connection between migraine and RLS with an increase in frequency of RLS in migraines, and also RLS is more severe in patients with migraine [33], REM sleep behavior disorder (RBD) is more frequent in migraine patients [34] and these patients have severe headache-related disability and insomnia. Migraines is also associated with bruxism and somnambulism in children [35].

Cluster headaches: are severe to very severe unilateral headaches, periorbital and temporal in distribution, lasting between 30 and 180 min, frequency of 1–8 headaches per day, and associated with conjunctival injection (red eye), increased lacrimation, rhinorrhea, and restlessness. Circadian and circannual periodicity is a hallmark of cluster headache. Two thirds of headaches occur at night between 9 PM and 10 AM. Cluster headaches are linked to REM sleep and to sleeping late in the morning—which has more REM sleep. The fact that individuals with cluster headaches have lucid recall of dreams 2 hours into sleep support the REM sleep association with CH. Patient with cluster headaches have a high incidence of OSA. A study showed over 8-fold increased risk for OSA in patients with cluster headache, and that risk increases further up to 24-fold in patients with an elevated body mass index of greater than 25 kg/m2 [36].

Paroxysmal hemicrania (PH) is unilateral headache, side-locked (occurring on the same side), short-lasting, average duration of 30 minutes, occurring multiple times a day (up to 40 attacks a day), associated with autonomic features (conjunctival injection, lacrimation, rhinorrhea, ptosis, etc.) which primarily affects women. PH often occurs at night and is associated with REM sleep and occurs only during REM sleep [37].

Hypnic headaches (HH) mainly affects elderly male patients, and presents with mild to moderate bilateral headache, which awake patients from sleep, usually between 1 and 3 AM. It was believed to be related REM sleep, but recent studies revealed that its occurrence is more common during NREM sleep [37].

Exploding head syndrome (EHS) was originally classified as a sleep disorder, which occurs during transition from wakefulness to sleep. Patients report hearing extremely loud or explosive noise, which is nonpainful, but is often associated with significant apprehension [37]. Recently, EHS was reported as an aura of migraine with brainstem aura while patient was fully awake [38]. Previously, EHS was reported as an aura of other type of migraine [39].

Tension-type headache is the most common type of headaches, which are known as "featureless" headache, in contradistinction to migraine TTH are not usually associated with photophobia, phonophobia, or nausea. Insomnia often triggers or aggravates TTH, whereas sleep may relieve them [40]. Insufficient sleep or oversleeping may trigger TTH [41, 42]. Headaches, sleep disorders and depression may share common brain mechanisms, e.g. dysregulation of serotonin, melatonin and hypothalamic dysfunction and management of sleep disorders and depression is essential for the adequate control of the TTH.

4.2 Secondary headaches associated with sleep disorders

Sleep-apnea-syndrome related headaches; presents with awakening headaches (headaches on awakening rather than headaches that awaken patients from sleep). These headaches start in the morning and resolve 30 min after awakening. They are bilateral frontal headaches, squeezing in character, and daily or almost daily. There is no associated photophobia, phonophobia, or nausea. These headaches are most commonly caused by obstructive sleep apnea (occur in 18–60% of patient with OSA) but also central sleep apnea and hypoventilation. Awakening headaches affects 4–6% of the general population and 18% of patients with insomnia. OSA-related headaches may also present with migraines features, chronic daily headache, or be similar to TTH [40–42]. The pathogenesis of the awakening headaches related to the OSA, is probably associated with hypercapnia, vasodilatation, elevated intracranial pressure, and poor sleep quality [43–45].

Medication overuse headaches (MOH) is also associated with sleep disorders: MOH is a secondary form of headache triggered by the frequent use of acute pain medication for management headaches. MOH is associated with poor sleep quality [2, 3, 9].

5. Treatment

The treatment is mainly targeted to relieve pain and associated features of headache. In case of migraine, the treatment has undergone major advances with the development of new specific anti-migraine therapies and more treatments are in development. If not a migraine- specific medication, treatment should be selected based on patient comorbidities, in order to address more than one problem at the same time. Medication should be initiated at the lowest dose with gradual increase of the dose to an effective range, while monitoring the response and potential adverse effects. Treatment, if well tolerated, should be continued for at least 2–3 months, with re-evaluation after that.

Migraine treatment algorithm is mainly divided into pharmacological interventions and nonpharmacological interventions. Among the pharmacological interventions the paradigm of treatment is based on preventative and acute/rescue therapy. Options included on the preventative armamentarium are oral antihypertensive (beta blockers, calcium blockers, ACEI/ARB), anti-depressants (SNRI/TCA), anticonvulsants (valproate, topiramate), Botox injections, CGRP mAB. Options for the acute treatment of migraine include triptans, Dihydroergotamine, Ergotamine, Neuroleptics, NSAIDs, and newer categories of recently FDA-approved gepants (ubrogepants) and ditans (lasmiditan). Among nonpharmacological interventions there are psychological interventions, including cognitive behavioral therapy (CBT), relaxation therapy and biofeedback. Neuromodulation including transcranial magnetic stimulation (TMS), Cefaly device, noninvasive vagus nerve stimulator GammaCore, remote electrical neuromodulation (REM), and acupuncture. Lifestyle modifications, including regular sleep and healthy diet, good hydration, management of triggers and stress management and use of supplements/vitamins, such as magnesium oxide and vitamin B2 (riboflavin) [46].

Acute treatment for cluster headache is mainly based on high flow oxygen and fast acting triptans, such as Sumatriptan and Zolmitriptan, available in injectable form and/or nasal spray. Inhalation of 100% oxygen by nonrebreather mask at a rate of 12–15 L/m for 10–15 minutes is used as a first line therapy. Acute therapy for cluster headaches requires fast acting routes of administration with subcutaneous triptans as

the most effective, followed by nasal and then oral formulations. Neuromodulation with GammaCore—a noninvasive vagus nerve stimulator, which was approved for both acute and preventive treatment of cluster headaches can be used safely multiple times per day, alongside with high flow oxygen. Other approaches for acute symptomatic management include occipital nerve blocks with local anesthetics and/or steroids, sphenopalatine ganglion block, intranasal 4% lidocaine spray or oral steroid taper as a transitional approach. As for prevention of cluster headaches, the drug of choice is verapamil with a total daily maintenance dose between 480–720 mg divided in 3 daily doses with immediate release formulation generally preferred. Lengthening of the PR interval is a feared adverse effect of Verapamil, with doses mainly above 240 mg a day, therefore ECG monitoring is recommended initiation of the therapy, after each dose adjustment, and every 6 months thereafter while on the medication. Other preventive regimens for cluster headache includes topiramate, lithium, melatonin, baclofen and valproic acid [46].

Among the paroxysmal headaches such as paroxysmal hemicrania, SUNCT (Short-Lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing), SUNA (Short-Lasting Unilateral Neuralgiform Headache Attacks with Autonomic Symptoms), response to indomethacin is crucial and even included in diagnostic criteria for paroxysmal hemicrania and hemicrania continua. For patients, who cannot tolerate indomethacin other medications have been proposed, including cyclooxygenase type 2 inhibitors, verapamil, and topiramate. For the prophylaxis of SUNCT and SUNA the first line treatment is lamotrigine, followed by topiramate or gabapentin [46–48].

Treatment alternatives for hypnic headache include caffeine, melatonin, clonazepam, acetazolamide, indomethacin sustained release and lithium carbonate.

Treatment for TTH include pharmacological and nonpharmacological approaches. Simple analgesics, such as aspirin or other NSAIDs, acetaminophen, may be effective if only for a short period of time or if used infrequently. Preventive alternatives for TTH include tricyclic antidepressants (Amitriptyline) or SSRI's. Some patients respond to nonpharmacological approaches, such as massage, meditation, and biofeedback.

Continuous positive airway pressure (CPAP) is the mainstay of treatment for sleep apnea syndrome-related headaches, which appears to improve headache frequency and intensity [46–48].

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Chapter 3

Sleep Disorders and Epilepsy

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Abstract

Complex interplay and reciprocal interactions between sleep and epilepsy have been known for centuries. However, newer technologies and in-depth studies have provided us with better understanding of this relationship. Nocturnal seizures can interrupt sleep, while a number of factors, including antiepileptic drugs and sleep disorders, can aggravate seizures. Interestingly, different epileptic syndromes may trigger increase in seizure frequency at a certain phases of the sleep-wake cycle, while others may not show any correlation with these phases. We aim to provide an overview of the interactions between sleep and epilepsy, and provide better understanding how knowledge of the relationship between these two conditions can help more effective management of both disorders.

Keywords: sleep, epilepsy, seizures, antiepileptics, sleep deprivation

1. Introduction

For centuries, the intimate and reciprocal interaction between epilepsy and sleep was well recognized. In the late 1800s, Gowers investigated the relationship between grand mal epilepsy and the sleep-awake cycle [1]. In 1929, Langdon-Down and Brain found that nocturnal seizure occurrence had two peaks, approximately 2 h after bedtime and between 4 and 5 am, and daytime seizures occurred predominantly in the first 2 hours of awakening [2]. These conclusions were at first based solely on clinical observations. However, the advent of the electroencephalogram (EEG) revealed that sleep not only activated clinical seizures, but also interictal epileptiform discharges (IEDs), thus sleep and sleep deprivation becoming the standard laboratory activating techniques during the EEG recording. Epilepsy may also affect sleep architecture.

This chapter is an overview of the relationship between sleep and epilepsy.

2. Electrophysiology of sleep

The human states are divided into wakefulness, Non-REM (NREM) sleep, and REM sleep, REM being rapid eye movements. Sleep non-REM are subdivided in N1, N2, and N3. N1 and N2 are superficial sleep stages, where patient may be easily aroused and N3 is a deep sleep, where arousal is difficult. The characterization of each of those three stages is based on the EEG recording, in conjunction with eye and muscle activity recording. N2 is characterized by the presence of spindles and K-complexes and N3 - by the presence of high voltage slow delta waves.

The existence of two antagonistic systems promoting wakefulness and sleep was assumed in 1930 by von Economo [3]. In the 1940s, the "ascending arousal system" concept in the brainstem of animal and human brain, maintaining wakefulness, became clearer and more accepted. Now this system is called activating reticular arousal system (ARAS) [4]. The ARAS consist of neuronal network, containing several neurotransmitters, including acetylcholine, noradrenalin, serotonin, catecholamine, histamine, and orexin that play a role in the arousal system [5, 6]. Saper discovered that the ventrolateral preoptic area (VPLO) was involved in inducing NREM sleep [7]. It contains GABA-ergic and galanin-ergic neurons which inhibit the activating brainstem ARAS harboring and keep it from firing throughout the entire NREM sleep, providing the substrate of the "sleep system" with opposite function to the "wake system" When VLPO neurons fire during sleep, they inhibit the arousal system cell groups, thus disinhibiting and reinforcing their own firing. Similarly, when arousal neurons fire at high rate during wakefulness, they inhibit the VLPO, thereby disinhibiting their own firing [7]. This concept is nowadays accepted as the basics of the hypothalamic "sleep switch" module underlying alternations of sleep and awake cycle.

The brainstem cholinergic system provokes fast rhythms on the EEG, while abolishing thalamic spindle generation and delta oscillations [8]. Cortical neurons are depolarized by glutamate release, mainly from the thalamocortical fibers, but also by cortico-cortical axons once the activation has started and/or from reduction of K^+ conductance by acetylcholine, norepinephrine, and other neuromodulators [9].

3. Effect of sleep on epilepsy

Seizures and epilepsy syndromes are classified based on the time of occurrence of seizures regarding the sleep-wake cycle. Pure sleep epilepsies, arousal epilepsy, wakefulness epilepsy, and epilepsy occurring irrespective of time are the four main types of seizures [1, 2, 10]. Sleep accentuated epilepsy includes epilepsies with seizures occurring during both awake and asleep state, but epileptiform activity becomes accentuated during sleep.

Gowers noted that seizures happening during daytime cluster at certain times of the day, specifically upon awakening and late afternoon; and seizures occurring at night tend to occur mainly at bedtime and early morning hours before awakening [2] Janz observed that up to 45% of patients with primarily generalized tonic–clonic seizures had nocturnal seizures [10].

In general, NREM sleep facilitates interictal epileptiform activity (IEA) and REM inhibits IEA and is protective against seizures. NREM sleep is a synchronized state that allows better conduction of electrical impulses rather than REM sleep that is an asynchronous state [11–14]. The hypothesis is that during NREM sleep more neurons are in a resting state making them more recruitable into discharges. Whereas during REM sleep there is more neuronal firing that makes neurons less available to generate IEA. Despite the fact that the generators of different sleep and arousal states exert some common effects on seizure disorders, the distinct pathways, seizure manifestations, and mechanisms involved also depend on the pathophysiology of the specific epileptic syndrome. This section will briefly discuss the effect of sleep on specific epilepsy syndromes.

4. Adult epilepsies, associated with sleep

Seizures are divided in generalized and focal. In generalized seizures, the epileptic activity starts in multiple brain regions simultaneously, while in focal

seizures, the epileptic discharges originate in one area of brain that may or may not spread to other regions of the brain. Seizures occurring with loss of consciousness are known as focal dyscognitive seizure or focal seizure with loss of consciousness, formerly known as complex partial seizures. Seizures occurring without change in awareness are called focal simple seizures where there is no loss of consciousness.

4.1 Generalized seizures

4.1.1 Primary generalized tonic-clonic seizures

Gowers first noted that patients with primary generalized tonic-clonic seizures have their seizures in two peaks during sleep: the first - two hours after sleep onset and at the end of the sleep cycle [1]. There are two peaks of sleep-related seizures occurred between 9-11 pm and 3-5 am respectively [10]. Further studies showed that generalized tonic-clonic epilepsy occurs mainly during NREM sleep [15, 16]. Generalized interictal epileptiform activity (IEA) increases in NREM sleep [17]. In arousal epilepsies or epilepsies occurring during awake and sleep states, IEA can occur at any time. Meanwhile, in pure sleep epilepsy, IEA have been described during REM sleep and/or on awakening in 9% of the patients and restricted to NREM sleep in 41% [10].

4.1.2 Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy [JME] is a syndrome characterized by the combination of myoclonic, absence, and generalized tonic-clonic seizures that especially occur in the morning in the first one to two hours after awakening, that is a hallmark of this syndrome. Seizures are often triggered by externally provoked arousals in the morning after a sleepless night associated with alcohol consumption. JME is an age-related, genetic, and generalized epilepsy syndrome that typically begins in early adolescence [10, 18]. Seizures can also occur on awakening from a nap, but rarely at other times during the day [18]. The classic EEG shows generalized spike-wave complexes at 4-6 Hz as well as polypiles. The discharges increase markedly at sleep onset and awakening, but are less frequent in NREM sleep, REM sleep, and wakefulness. The arousal period is apparently a hyper-synchronous state that makes more permissible the conduction of epileptic discharges.

Valproic acid or other newer broad-spectrum antiepileptics [AEDs] such as levetiracetam, lamotrigine, topiramate, zonisamide and perampanel may lead to excellent seizure control in patients who adhere to rigid compliance and avoid seizure precipitant such as sleep deprivation and alcohol binges. Medication requirement typically endures throughout life, with seldom patients being successfully weaned from therapy long-term in later adulthood.

A closely related primary generalized epilepsy syndrome called generalized tonic-clonic seizures upon awakening (GTCOA) has a similar pattern of occurrence of convulsions, but without myoclonic seizures.

4.2 Focal seizures

4.2.1 Temporal lobe epilepsy

Sleep related complex partial seizures originating in the temporal lobe are frequent and represent around 33% of all temporal lobe seizures [19]. Nocturnal temporal lobe epilepsy (NTLE) is a subtype of medically refractory temporal lobe epilepsy, usually presenting during adolescence with seizures nearly exclusively

confined to nighttime sleep [18]. In most cases, seizures are characterized by sudden awakening from sleep with a sensory aura, which then progresses to a focal seizure with impaired awareness. The latter is often associated with amnestic automatisms that mimic a NREM parasomnia called confusional arousal. Most patients (around 70%) also have secondary generalized tonic-clonic seizures [18].

Regarding IEA, most studies have found an increase in interictal epileptiform activity during NREM sleep with decrement during REM sleep. The spike frequency was 85% in NREM and 12.5% in REM sleep [20]. Sammaritano found that the extent of the electrical field increased in more than 75% of the spikes in NREM compared with the wake state. Meanwhile, there was a restriction of the electrical field of the epileptiform activity during REM sleep. Desynchronization of EEG pattern during REM sleep reduces the likelihood of spatial and temporal summation of aberrant depolarizations [21]. One third of patients have bilateral IEDs that occur independently on both sides, especially during NREM. However, localization of the primary epileptogenic area is more reliable in REM sleep than in wakefulness, and in wakefulness more than in slow-wave sleep. Therefore, REM sleep provides an opportunity to better localized the epileptic focus. When seizures occur during daytime they are common in the afternoon or are bimodal, and peak in the morning and afternoon [22].

5. Pediatric epilepsy associated with sleep

5.1 Generalized epilepsies

5.1.1 Absence epilepsy

Absence seizures clinically present as a brief transitory behavioral arrest lasting a few seconds that is detectable while patient is awake and typically triggered by hyperventilation, and less often by photic stimulation [23]. Typical EEG shows a generalized 3-Hz spike-wave complexes. The activation of the IEA is most marked in the first sleep cycle [24]. Absence seizures are often inhibited by full wakefulness and REM sleep. During NREM slow-wave sleep the cell activity is more synchronous and allows the activation of spike-wave responses, whereas during REM, a traditional desynchronization state, spike and wave are uncommon [25]. The spike and waves present during NREM state differ also from wakefulness IEDs because they are briefer, more fragmented, more irregular, and slower than during wakefulness [20].

5.1.2 West syndrome

West Syndrome is characterized by the triad of infantile spasms, psychomotor retardation, and hypsarrhythmia in the EEG. Hypsarrhythmia is characterized by chaotic and disorganized background of high voltage, asynchronous spike and slow-wave activity [26]. Only 2-5% of the spams occurred during sleep despite increase in EEG abnormalities during NREM sleep [27]. The hypsarrhythmia pattern may become more apparent during sleep. During REM sleep, a marked attenuation or disappearance of the hypsarrhythmia pattern is noted [28]. Treatment of Infantile spasms includes ACTH, prednisone, and vigabatrin. Vigabatrin [gamma vinyl, gamma-aminobutyric acid (GABA)] is a specific, irreversible inhibitor of GABA-transaminase. Other treatment includes Zonisamide, Topiramate, Valproic acid, Nitrazepam, Pyridoxine, and Ketogenic diet. Surgery

should be considered in cases with asymmetric spasm, focal neurologic abnormalities on examination, EEG with focal or lateralizing features, and radiologic evidence of structural abnormality.

5.1.3 Lennox – Gastaut syndrome

Lennox-Gastaut's syndrome [LGS] usually begins in the first decade of life and is characterized by multiple types of primary generalized seizures, including prominent nocturnal tonic, astatic/atonic, atypical absence, myoclonic, and generalized tonic-clonic seizures with associated psychomotor and cognitive delay. It is often preceded by a history of infantile spasms with hypsarrhythmia in the EEG. Typical EEG shows slow spike-wave [SSW] complexes at 1.5-2.5 Hz, multifocal epileptiform abnormalities, paroxysmal fast activity, and diffuse background slowing. The quantity of the bursts of SSW complexes increases during NREM sleep [29]. Paroxysmal fast activity is a typical pattern of LGS characterized by diffuse bursts activity with a frequency of 15-20 Hz, mainly during NREM with an occurrence up to hundred times per night, but absent during REM sleep [23].

5.2 Focal epilepsies

5.2.1 Frontal lobe epilepsy

Frontal lobe epilepsy [FLE] is the second most common focal epilepsy. Seizures with origin in the frontal lobe tend to occur preferentially during sleep and have prominent motor features, often recognized by family members or friends, **Table 1**. There are two very distinct epileptic syndromes that characterized frontal lobe seizure. They are known as nocturnal frontal lobe epilepsy and supplementary sensorimotor area epilepsy.

Nocturnal frontal lobe epilepsy (NFLE) predominates in male, typically with onset in infancy through adolescence, and is familial in 6-40% of the cases [30–32]. It is characterized by paroxysmal arousals with brief hypermotor features, motor attacks with complex dystonic and dyskinetic movements, and/or episodic nocturnal wandering that mimics the NREM parasomnia called sleepwalking. NFLE usually presents with multiple attacks per night. Video-EEG polysomnography is necessary for definitive diagnosis. Approximately 50% of the cases have normal ictal or interictal EEGs. NFLE usually respond to carbamazepine, but cases of medically intractable NFLE have been well established [30–33].

Supplementary sensorimotor area (SSMA) epilepsy is another unique subtype of frontal lobe epilepsy. Seizures characteristically begin with somatosensory auras progressing to a "fencing" posture with the arm contralateral to seizure

Early hyper-motor activity
Short duration
Minimal or no post-ictal period
Presence in clusters
Often secondarily generalized
Occurrence at night

Table 1.
General features of frontal lobe seizures.

focus relatively extended and ipsilateral arm abducted and flexed; speech arrest or vocalization and flailing or trashing limb movements.

5.2.2 Autosomal dominant nocturnal frontal lobe epilepsy

The autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) shares the same characteristics as NFLE described above, but is associated with genetically heterogenous mutations in the nicotinic acetylcholine receptor complex, which is inherited in an autosomal dominant pattern [33]. There are four known loci for ADNFLE, three with known causative agents. These genes, CHRNA4, CHRNB2, and CHRNA2, encode various nicotinic acetylcholine receptor α and β subunits [34].

ADNFLE is often misdiagnosed as nightmares. Attacks often occur in clusters and typically first manifest in childhood.

5.2.3 Benign focal epilepsy of childhood

This is the most common type of epilepsy within the pediatric sleep-related epilepsy spectrum and accounts for 15-25% of all childhood epilepsies [35]. Benign Rolandic' s epilepsy or benign focal epilepsy of childhood with centrotemporal spikes is a simple partial seizure disorder with hypersalivation, hemifacial and/or hand focal motor-clonic activity that might secondarily spread with generalized tonic-clonic seizures. Seizures often occur exclusively during sleep in three-quarters of patients [36, 37]. The mean age of onset is 7 (3 to 13 years), with recovery by mid-adolescence. Normally, the children affected have normal development with infrequent seizure, but occasionally treatment is necessary. EEG shows high voltage spike and wave discharges over the ipsilateral centrotemporal regions but may occur bilaterally. The discharges increase in frequency, voltage, field, and complexity during sleep. Sleep usually enhances central-midtemporal epileptic discharges, especially in first third of the night, during N3, but also during REM sleep [38]. Treatment is usually successful with AEDs that are effective in partial epilepsy such as carbamazepine, oxcarbazepine, or levetiracetam.

5.2.4 Laundau – Kleffner syndrome electrical status epilepticus of sleep

Laundau-Kleffner syndrome (LKS) is a rare childhood disorder characterized by loss of language comprehension and verbal expression in association with electro-encephalographic finding of status epilepticus during sleep [ESES]. This syndrome is associated with subacute progressive language regression. At some point during this syndrome, there is a dramatic activation of IEA during sleep called ESES that consist of generalized spike-wave complexes at 2-2.5 Hz occurring for >85% of slow wave-sleep with or without clinical seizures. There is marked attenuation of the spikes during REM sleep and wakefulness EEG. With the onset of ESES, there is usually an associated cognitive decline with a speech disorder [39]. Seizures may manifest as nocturnal focal motor or generalized tonic-clonic seizures. LKS most commonly presents in children 2-10 years of age. There is usually remission of the seizures and epileptiform discharges by age of 15, however some patients can develop an autistic regression [40]. Corticosteroid and IVIG are effective and can be considered for treatment of both clinical and EEG changes [41–43]. AEDs including valproate, ethosuximide, clonazepam, clobazam, vigabatrin and felbamate are also effective. In refractory cases, epilepsy surgery including temporal lobectomy in lesional and non-lesional cases have been associated with improvement in language and refractory seizures [44, 45].

6. Comorbid sleep disorders in epilepsy

Many patients with epilepsy complain of excessive daytime sleepiness (EDS), with reported prevalence as high as 16.9%–28% [46–48]. In fact, EDS is the most common complaint of subjects referred to sleep disorder centers. EDS in epileptic patients may result from nocturnal seizures, sedative effects of antiepileptic drugs, poor sleep hygiene, and co-morbid primary sleep disorders [49]. EDS in these patients is often mistakenly attributed to AED adverse effect rather than to an underlying primary sleep disorder.

More than 50% of the epileptics suffer from insomnia up to certain extent, as a result of adverse effects of AEDs, substance abuse, nocturnal seizures, and comorbid anxiety and depression. and out of these 43% has poor seizure control and significant impact on quality of life [50].

Co-morbid primary sleep disorder should be sought and treated, but the exact incidence of primary sleep disorders in patients with epilepsy remains uncertain.

Obstructive sleep apnea (OSA) is the most common cause of sleep-disordered breathing and may exacerbate seizure burden in as many as 33% of patients with medically intractable epilepsy undergoing pre-surgical planning [51, 52]. Predisposing factors for OSA are older age, male, obesity, dental mal-occlusion and Crowded upper airways [53].

Polytherapy AEDs in patients with drug-resistant epilepsy are at increased risk of obesity as compared to monotherapy. Anti-seizure drugs including valproic acid, pregabalin, perampanel, gabapentin and vigabatrin are associated with weight gain, therefore, can potentially worsen or increase the risk of OSA [54]. Adults who developed epilepsy later in life or had worsening seizure control, had a higher apnea–hypopnea index (AHI) and Epworth Sleepiness Scale (ESS) score compared with those who were seizure-free or had an improvement in seizure control [52]. Nasal continuous positive airway pressure (CPAP) therapy demonstrated seizure reduction in patients with OSA and refractory epilepsy in several observational studies [55–59].

Restless legs syndrome (RLS), which is defined as the urge to move the legs that improve or partially relieves with activity, worsen with inactivity and is worse at night, is common feature in epileptics with a prevalence of 10.2%–28.2% [48, 60].

7. Sleep deprivation

Sleep deprivation is one of the most potent triggers of epileptic seizures and epileptiform discharges in patients with generalized epilepsy, triggering seizures in up to 25% of patients suffering from epilepsy [61].

Back in the 1960s and 1970s a series of articles suggested that sleep deprivation was a facilitator of interictal epileptiform discharges, and therefore a promoter of seizures. Lack of adequate sleep causes dysregulation of the hypothalamic pituitary function with release of stress hormones such a cortisol and noradrenaline, which leads to worsening of seizure control [62]. In a recent study, more than 97% of patients with epilepsy reported at least one factor that provokes seizures, and the top three were sleep deprivation, stress, and fatigue [61]. In many cases alcohol consumption was also a common trigger.

Sleep deprivation is often used in epilepsy monitoring units to increase the frequency of seizures. In addition, interictal epileptiform discharges are also more apparent after sleep deprivation.

Environmental factors and sleep hygiene are also crucial in the control of seizures. Appropriate noise level, light intensity, surrounding temperature, humidity, and type of bed are needed for a comfortable sleep. Another important issue is sleep hygiene. Certain behaviors and practices interfere with normal nocturnal sleep. They include time of going to sleep, consumption of food and drinks before sleep, watching TV, working on the computer, using the phone, reading, or physical activity before sleep.

Sleep deprivation is the most common trigger for awakening seizures seen in juvenile myoclonic epilepsy.

8. Effect of epilepsy on sleep

The effect of epilepsy on sleep was first described in 1890 by Fere, based on clinical findings of difficulty falling asleep and impairing sleep efficiency. About two-third of patients suffering from epilepsy have sleep dysfunction [63]. Three main mechanisms that need to be considered regarding this topic are: 1. the epilepsy itself may be associated with sleep disturbance due to mechanisms intrinsic to the syndrome; 2. the effect of seizures on sleep architecture; and 3. the effect of AEDs on sleep.

Experimental amygdala kindling, an animal epilepsy model involving temporal structures, showed disturbed sleep patterns with sleep fragmentation and a shift toward lighter sleep [64]. In humans, patients with epilepsy have reduced NREM N2 and N3 sleep and REM sleep [65]. Sleep abnormalities seem to be more marked in patients with temporal lobe epilepsy compared to generalized epilepsies [15]. The limbic system participates in the neural networks underlying sleep organization, sleep induction, and arousal. **Table 2** shows the effects of epilepsy on seizures.

Patients suffering from nocturnal seizures show reduced sleep efficiency, increased time into REM period, and increased drowsiness [65]. The effects of AEDs on sleep will be discussed separately in the next section.

Increased sleep onset latency
Increased awakening after sleep onset
Increased NREM N1 and N2
Decreased frequency of spindles during N2
REM sleep suppression
Increased sleep fragmentation

Table 2.
Common effect of epilepsy on sleep.

9. Effect of antiepileptic drugs on sleep

Anti-epileptic drugs [AEDs] may reduce sleep fragmentation, while improving nocturnal seizures control. However, AEDs have differential effects on sleep architecture [66]. Several studies identified that gabapentin, tiagabine, pregabalin, clobazam, and carbamazepine reduce sleep latency and/or improve sleep efficiency. Phenobarbital, carbamazepine, phenytoin, valproic acid, and higher doses of levetiracetam may have an effect or aggravate daytime sleepiness. Felbamate, zonisamide, and lamotrigine at high doses may causes insomnia. Some AEDs

Drug	Sleep effect
Phenobarbital	Decreases SOL, decreases WASO, decreases REM, increases EDS
Gabapentin	Decreases SOL, decreases WASO, increases NREM N3, increases REM, improve insomnia
Carbamazepine	Increases NREM N3, increases sleep fragmentation
Phenytoin	Decreases SOL, decreases REM, increases sleep fragmentation
Pregabalin	Increases NREM N3, improve insomnia
Levetiracetam	Decreases NREM N3 increases EDS
Ethoxizimide	Decreases NREM N3, increases REM
Valproic acid	Increases sleep fragmentation, increases WASO, increased daytime sleepiness
Benzodiazepines	Decreases NREM N3 and SOL

SOL: sleep onset latency, WASO: wake after sleep onset, EDS: excessive daytime sleepiness.

Table 3.
Common antiepileptic drug effect on sleep architecture.

have no effect or have minimal effect on sleep architecture such as topiramate, zonisamide, lamotrigine, vagabatril, lacosamide, and low doses of levetiracetam [66]. Dose-dependent sleep effects of antiepileptic drugs and nondrug treatments independent of the improvement of epilepsy have not been studies and may help to identify if these changes are clinically significant.

Table 3 shows the most common antiepileptic drugs effect on sleep architecture.

10. Effect of ketogenic diet

Ketogenic diet improves total sleep time and NREM slow-wave sleep [67].

11. Effect of vagal nerve stimulator on sleep

Vagus nerve stimulation [VNS] is used in some form of refractory epilepsy. VNS increases NREM N3 stage and reduces daytime sleepiness. VNS may worsen or increase risk for sleep-disordered breathing [67].

12. Effect of epilepsy surgery on sleep

Epilepsy surgery has a positive effect on sleep. It improves total sleep time, decreases wake after sleep onset, increases REM sleep, and improves the subjective sleep quality. No changes were seen in the subjects who continued to have frequent seizures after surgery [67].

13. Seizures and parasomnia

Parasomnias are disorders with undesirable physical and mental events that occur mainly or exclusively during NREM and REM sleep, often accompanied by skeletal muscle activity and autonomic arousal. Mental phenomena may also occur, including emotions, thoughts, and images.

The NREM parasomnias are associated with central nervous system activation, skeletal muscle activity, and signs of autonomic arousal. Common examples of NREM parasomnias in children are confusion arousals, sleepwalking, and nocturnal terrors that present with different degree of motor and autonomic activation. The distinction between NREM parasomnias and seizures might requires the need for polysomnography with video recording and extended EEG leads.

REM sleep involves a highly energized state of brain activity with increased motor activation during REM where patients can enact the dreams. Patient scream, throw punches and kicks, show exploratory behaviors, involving staring, head rising, head turning, grasping, and searching; stalking imaginary prey, as well as episodic attack behavior; and locomotion. The mechanisms responsible for the oneiric behaviors are postulated to result from the disruption of brain neuronal organization during REM sleep. There is presumably disinhibition of motor pattern generators in the mesencephalic locomotor region, which results in phasic motor over-activation with behavioral release during REM sleep.

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Chapter 4

The Relationship between Amyotrophic Lateral Sclerosis and Parkinson's Disease and Sleep Disorders: Pathophysiological and Clinical Approach

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Abstract

This chapter focuses in the interrelationship between sleep and two neurodegenerative disorders: Amyotrophic Lateral Sclerosis [ALS] and Parkinson's disease [PD]. Sleep disorders have deleterious effect on the quality of life and survival in these neurodegenerative disorders, while the reverse is also true where neurodegenerative disorders significantly impair the sleep, leading to a vast sleep complains that worsen the clinical course of these conditions. Other neurodegenerative disorders such as dementias, spinocerebellar ataxias, atypical parkinsonism, etc. will not be cover in this chapter.

Keywords: sleep, amyotrophic lateral sclerosis, hypoventilation, Parkinson's disease, parkinsonism

1. Introduction

Given the effect of neuromuscular disease on respiratory muscle strength (including the diaphragm, upper airway and accessory muscles), it is an undeniable fact, that neuromuscular disease can cause disruption of sleep. In general, sleep disorders are underrecognized in this population, as their secondary effects can mimic symptoms of the underlying disease. Recognizing sleep-related disorders in patients with neuromuscular disease such as Amyotrophic Lateral Sclerosis (ALS) is of utmost importance, as they are potentially treatable problems and their correction can improve quality of life and even increase survival time [1].

ALS is an incurable neurodegenerative disorder of upper and lower motor neurons, which is characterized by degeneration of the corticospinal tracts, resulting in loss of motor neurons in the brain, brainstem and anterior horn cells of the spinal cord. Age of onset of disease is in the sixth decade of life and is usually

sporadic, though a minority of patients have familial disease. Numerous abnormalities exist in cellular and molecular function in ALS, including protein aggregation, mitochondrial dysfunction, DNA and RNA processing and central nervous system inflammation [2].

The hallmark of clinical disease is the presence of both upper and lower motor neuron signs. Weakness in ALS starts as asymmetrical or focal, and then progresses to generalized weakness, ultimately affecting all skeletal muscles. Loss of motor neurons in the brainstem and spinal cord causes weakness of the pharyngeal, laryngeal, intercostal and diaphragmatic muscles. This predisposes patients with ALS to respiratory dysfunction (the physiology behind this to be detailed below). When respiratory dysfunction becomes severe, tracheostomy and permanent ventilation are required. From the time of the diagnosis the median survival time is 3 to 5 years. The most common cause of death in ALS is respiratory failure [3, 4].

There are two FDA approved medications for ALS. Riluzole was approved in 1997 and provides a modest survival benefit of 3 months. A second medication, Edaravone, a free radical scavenger, was approved in 2017, but is only approved for use in ALS patients without respiratory insufficiency, and is controversial for clinical use due to its burdensome administration schedule and questionable clinical efficacy [5]. Numerous clinical drug trials have failed to demonstrate marked clinical benefit in ALS. However, provision of non-invasive ventilation has shown survival benefit in some ALS patients [6]. The dearth of effective treatment options for ALS underscores the importance of modifying those factors that optimize quality of life and extension of survival, particularly sleep and respiration.

2. Pathophysiology

Adequate involuntary ventilation is essential for effective sleep. The pathway by which voluntary ventilation occurs involves the cerebral cortex, brainstem and corticospinal tracts to motor neurons in the C3-C5 spinal segments which supply the phrenic nerve. The phrenic nerve innervates the diaphragm. In the state of wakefulness (in which both voluntary and involuntary ventilation persists), the diaphragm is the major inspiratory muscle and is assisted by accessory muscles. The accessory inspiratory muscles include the intercostals, trapezius, scalenes, sternocleidomastoid and pectoralis major muscles. Involuntary or automatic breathing involves the respiratory centers in the brainstem (pons and medulla). This is the central respiratory drive. Oxygen and carbon dioxide levels sensed by chemoreceptors (peripheral and central) directly influence automatic breathing (which is then carried out through the spinal segments formerly mentioned innervating the diaphragm through the phrenic nerve). During non-REM sleep, muscle tone is decreased and during REM sleep muscle tone is almost completely lost. Automatic ventilation during sleep is almost completely dependent on the diaphragm (particularly in REM sleep) therefore diaphragmatic dysfunction (such as that seen in ALS) can predispose to hypoventilation and nocturnal hypoxemia. The sensitivity of chemoreceptors is also reduced during sleep [1].

Effective sleep also depends on maintaining a patent upper airway. Patency of the upper airway is dependent on secondary muscles of respiration, which include the muscles of the pharynx. Pharyngeal muscle tone is maintained by trigeminal sensory afferents during inspiration, when negative pressure is generated. This prevents upper airway collapse. Weakness of pharyngeal muscles (such as in ALS) leaves one susceptible to airway collapse and the upper airway resistance seen in obstructive sleep apnea [1].

3. Clinical features of sleep disturbances in amyotrophic lateral sclerosis

Sleep disorders are quite prevalent in patients with ALS, but often underreported, misdiagnosed, and undertreated. It has been shown that the onset of nocturnal breathing abnormalities often precedes the onset of overt daytime respiratory dysfunction [3]. A recent study showed that sleep disorders occur in 70 percent of patients with ALS, where 65 percent have insomnia, 50 percent have sleep-breathing disorders including hypoventilation, and 85 percent suffer from night-time awakening related to ALS symptoms [7].

The most common form of sleep disturbance encountered in ALS is due to hypoventilation, rather than obstructive nocturnal events [8]. As ALS progresses, the involvement of the respiratory muscles is unavoidable; this results in nocturnal hypoventilation [9, 10]. Hypoventilation is the primary etiology of nocturnal oxygen desaturation (hypoxemia) in patients with ALS. This is due to bilateral phrenic nerve dysfunction resulting in diaphragmatic weakness or paralysis [11]. Nocturnal hypoventilation is first present when supine, as this is where the diaphragm is put at its worst mechanical disadvantage resulting in a drop in lung volumes [3, 12]. Diaphragmatic dysfunction in ALS is of particular concern in regard to sleep-disordered breathing as the diaphragm is the sole active respiratory muscle during REM sleep (where accessory and intercostal muscles are naturally inhibited) [13]. For this reason, nocturnal hypoventilation is especially worse during REM sleep [12, 14].

Quality of sleep in those without advanced disease can be normal (although quality of life is impacted by respiratory muscle weakness) [11]. As the disease progresses fragmentation of stage N3 of sleep occurs due to loss of circadian rhythms [13]. All stages of sleep are eventually affected resulting in daytime hypercapnia which is defined as an elevated CO2 > 45 mm Hg. Hypoxemia and hypercapnia result from respiratory failure and the hypoventilation syndrome caused by restrictive thoracic disease from weakness of respiratory muscles. This hypoventilation syndrome results in a decrease in sensitivity of chemoreceptors due to chronic hypercapnia [15]. Hypoventilation is further complicated with the co-existence of sleep-breathing disorders.

Sleep-breathing disorders are common in ALS. Oropharyngeal weakness affecting dilatory muscles leads to obstructive sleep apnea that presents like in non-ALS OSA patients with snoring, snorting, apneas, and frequent nocturnal arousals [16]. In a study of 18 patients with ALS, it was found on polysomnography that total sleep time was decreased, and frequency of sleep-disordered breathing and arousals were higher than in age-matched controls. Eight of these patients were found to have periods of hypoventilation (most often during REM sleep). There were no recorded apneas. Bulbar involvement did not show a significant association with degree of sleep-disordered breathing [2]. Bulbar weakness does however predispose to obstructive sleep apnea due to weakness of tongue protrusion and palatal control. Bulbar weakness is also associated with increased secretions and weak cough [13]. That being said, since patients with bulbar ALS have tongue atrophy, they have less prevalence of OSA [17, 18]. Central sleep apneas in ALS patients may result from central motor neuron impairment, though they are less frequent than OSA [15].

Particular importance should be placed on addressing respiratory muscle weakness (hypoventilation) rather than the number of apneas or hypopneas on polysomnography in ALS patients [11]. OSA is common in ALS and if untreated shortens the survival of ALS patients [3, 12]. Non-invasive positive pressure ventilation can prolong time to tracheostomy and provide benefit in regard to quality of life in the setting of respiratory muscle weakness and sleep-disordered

breathing [11]. Therefore, when OSA is suspected a polysomnogram should be requested to confirm its diagnosis.

In regard to the effects of sleep-disordered breathing on quality of life, ALS patients often complain of excessive daytime sleepiness resulting from nocturnal sleep fragmentation and insomnia. Nocturnal hypoventilation results in orthopnea, morning headaches, excessive daytime sleepiness, and cognitive dysfunction [12, 17]. A study showed the most common nocturnal complaints in ALS patients were nocturia, sleep fragmentation, and cramps (each seen in about half of the patients) [19]. **Table 1** shows the common sleep disturbances seen in ALS.

Nocturnal restlessness, sleep fragmentation with multiple awakening, snoring, and apneas leads to excessive daytime sleepiness, difficulties to arouse in the morning, difficulties to arouse from sleep, cognitive problems and poor work performance. In severe cases when insomnia and sleep continuity is severely impaired patients develop lethargy, cyanosis, early morning headaches, nausea and vomiting and leg edema. **Table 2** shows the most common sleep features in ALS patients.

Patients with ALS suffer from other conditions that also affect the sleep such as restless leg syndrome (RLS), REM-sleep behavior disorder (RBD), cramps, immobility-associated discomfort, pain, depression-related sleep disorders and dementia-related sleep disorders which may affect the sleep continuity. Even patients newly diagnosed with ALS have shown poor sleep quality related to depression and poor nocturnal mobility [12, 17, 19].

There are important secondary cardiopulmonary effects of chronic nocturnal hypoxemia that should not be overlooked. These include pulmonary hypertension, right heart failure and arrhythmia. There is also an increased risk of stroke, myocardial infarction and lethal cardiac arrhythmias. This highlights the critical

Insomnia
Excessive daytime sleepiness
Sleep fragmentation
Sleep related hypoventilation
Sleep breathing disorders

Table 1.
Sleep disturbances in ALS.

Nocturnal features	**Daytime features**
Nocturnal restlessness	Excessive daytime sleepiness
Sleep fragmentation	Increase daytime napping
Increase WASO	Fatigue
Insomnia	Poor concentration
Apneas/hypopneas	Poor work performance
Snoring/snorting	Morning lethargy
Orthopnea	Morning headaches
Respiratory interruptions	Cognitive dysfunction
Difficulty to aroused in the morning	
Nocturnal cyanosis	
Choking	
Nocturia	
Nocturnal cramps	
Nightmares	

WASO: wake after sleep onset.

Table 2.
Sleep-related features in ALS.

need to diagnose and treat sleep-disordered breathing early particular in ALS where lifespan is devastatingly shortened [20].

4. Diagnosis

Essential to the identification of ALS patients with sleep abnormalities is maintaining a high index of suspicion and taking a detailed sleep history. This ideally takes place with a family member or caregiver present (or anyone who may share a bed with the patient). This second party can provide history regarding the patient's behaviors during sleep and functioning in the daytime (some of which the patient himself/herself may not be aware of). Specific questions regarding the presence of excessive daytime sleepiness, cognitive dysfunction, orthopnea, apneas and snoring are essential. Frequent awakenings, snoring and choking are clues for suspecting obstructive sleep apnea. Nocturnal orthopnea is often an early sign of respiratory dysfunction causing hypoventilation. Commonly used screening tools for sleep disorders include STOP-BANG, Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index Scale [3]. All patients with respiratory dysfunction or bulbar weakness should be screened for sleep disorders. Close attention should be placed on examining for signs of respiratory dysfunction such as accessory muscle use (particularly when supine). Increased work of breathing can result in weight loss and cachexia. Patients with bulbar dysfunction progressively develop changes in their voice, difficulty clearing secretions, weak cough and difficulty swallowing [21].

There are multiple modalities that can be utilized in the diagnostic evaluation of respiratory muscle weakness and sleep disorders in ALS. The use of more than one modality increases the precision and accuracy of the diagnosis and prevents over- or underestimation of respiratory muscle strength [20]. **Table 3** outlines the different laboratory investigations used to diagnose sleep disorders in ALS.

If hypoventilation is suspected, then spirometry should be requested. Clinical indicators include excessive daytime sleepiness, morning headaches, frequent nocturnal waking, and vivid dreams [22]. Forced vital capacity (FVC) has long been used to predict survival and disease progression in ALS patients. Faster progression of disease has been associated with FVC < 75 percent of predicted value. A more accurate measure of weakness of the diaphragm is supine FVC however this can be difficult to evaluate [21, 22]. The difference between standing and supine FVC correlates with orthopnea and a fall from sitting to supine >20 percent has a sensitivity of 90 percent for identifying diaphragmatic weakness [12], whereas sitting FVC < 50 percent has only a sensitivity of 58 percent. Despite wide availability in obtaining FVC it is not as sensitive for early respiratory dysfunction and values may be inaccurate in patients with bulbar dysfunction who cannot maintain a tight seal on the mouth piece [21].

Arterial Blood Gas (ABG)
Pulmonary Function Tests
• Sitting and supine forced vital capacity (FVC)
• Maximal inspiratory pressure (MIP)
• Maximal expiratory pressure (MEP)
Sniff Nasal Pressure (SNP)
Overnight Pulse Oximetry
Polysomnography (PSG)

Table 3.
Investigations commonly used to detect sleep disorders in amyotrophic lateral sclerosis.

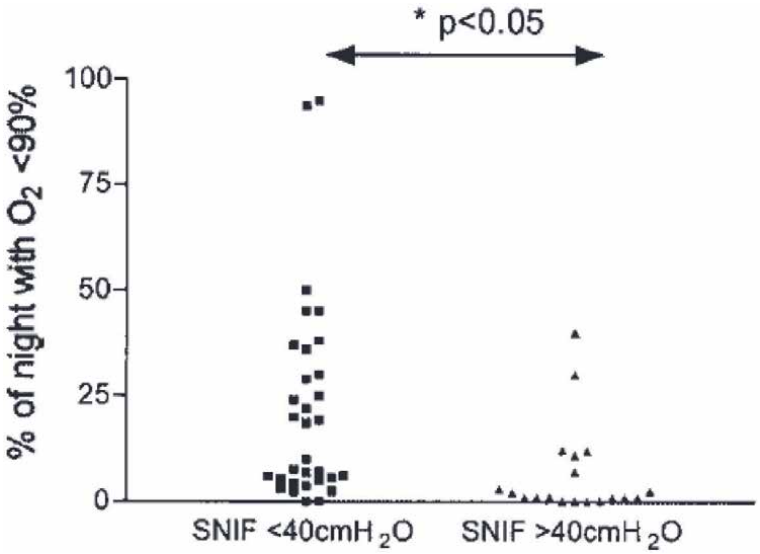

Figure 1.
Scatterplot of the proportion of the night spent with nocturnal hypoxemia (defined as oxygen saturation < 90 percent) in ALS patients with SNIF <40 cm H2O compared to those with SNIF >40 cmH2O [24].

The sniff nasal transdiaphragmatic pressure (SNIP) is a strong predictor of diaphragmatic muscle strength. It is a non-invasive inspiratory volitional test. It can also be used to monitor progression of disease [21]. In addition, SNIP testing is not limited by the requirement of securing an adequate seal over the instrument's mouthpiece, rendering it advantageous for evaluation of patients with prominent cranio-bulbar weakness. The sniff test has a sensitivity of 97 percent for a sniff value <40 cm H2O for predicting six-month mortality, compared to 58 percent sensitivity of VC < 50 percent [23, 24]. SNIP value <40 cm H2O is strongly correlated with nocturnal hypoxemia in ALS patients [24] (see **Figure 1**). This predictive value for nocturnal hypoxemia was not seen with other measures of respiratory sufficiency such as MIP and FVC [24].

Maximal inspiratory pressure (MIP) and maximal expiratory pressures (MEP) are useful for predicting early respiratory muscle weakness. MIP is done by inspiring from residual lung volume. MEP is done by having the patient maximally expire against a closed airway. MIP > 80 cm H2O or MEP > 90 cm H2O excludes significant respiratory muscle weakness [21]. MIP < 40 cmH2O also identifies people at risk of hypoventilation. This test may underestimate the degree of respiratory muscle weakness as it involves a mouthpiece and those with facial or bulbar weakness may not form a tight seal around it. This test does require effort on the part of the patient [21].

Nocturnal pulse oximetry and capnography can also be used for screening for hypoventilation. Nocturnal pulse oximetry is often the first test ordered when sleep disturbance is suspected as it is inexpensive and non-invasive [20]. Nocturnal desaturation <90 percent for >5–10 percent of the time may suggest hypoventilation [23]. A nocturnal desaturation to less than 90 percent for one minute is also helpful to diagnose hypoventilation [22]. Patterns seen in early disease suggestive of hypoventilation are cyclical desaturations with low baseline oxygen saturation. This pattern is also seen in COPD or interstitial lung disease and nocturnal pulse oximetry cannot distinguish between these conditions. There are also some technical problems with nocturnal pulse oximetry as the oximeter can become dislodged or readings can be inaccurate in the setting of anemia. [20] Capnography is utilized

in diagnosing hypoventilation by measuring a nocturnal transcutaneous carbon dioxide [PtcC02] increment of >10 mm Hg above 50 mm Hg for >10 min. This is performed with simultaneous pulse oximetry recording to compensate for possible aberrant valuates seen at times with PtCO2 [25].

Nocturnal and daytime arterial blood gases (ABG) is another tool that can be used to predict nocturnal hypoventilation resulting in hypoxia (PaO2 < 60 mm Hg) and hypercapnia (PaCO2 > 45 mm Hg). Nocturnal hypoventilation is suggested by an increase of PaCO2 by 10 mm Hg when comparing nocturnal to daytime values. This method is more invasive, and disparities can sometimes only be seen late in the disease [20]. Hypoventilation can also be diagnosed by ABG with hypercapnia defined as a cut off of PCO2 > 45 mm Hg while resting in a seated position for 15 min [26].

In-laboratory overnight polysomnography is the gold standard for the diagnosis of hypoventilation and OSA. At home tests are not recommended for patients with neuromuscular disease as these are limited studies. The standard polysomnogram consists of at least 3 electroencephalography (EEG) channels, chin and leg electromyography (EMG), 2 eye (electrooculogram) leads, effort channels, flow channels, electrocardiography and SaO2. This allows for tracking and monitoring the stages of sleep, SaO2 abnormalities and any abnormal movements [20]. Polysomnography [PSG] with capnography [transcutaneous PCO2] detects sleep-related hypoventilation [PCO2 increment more than 10 mmHg during sleep versus wakefulness, especially during REM] and is more sensitive than oximetry. One third of the patients with confirmed sleep hypoventilation have normal oxygenation [12, 19]. Using PSG, the etiologies of sleep disturbances can be distinguished using analysis of this multimodal test and patterns of SaO2 abnormalities. This allows for recognition of hypoxemia that is event related (obstructive sleep apnea) or due to hypoventilation (or a combination of both) [20].

The measurement of diaphragmatic thickening using ultrasound is a new developing technique that predicts hypoventilation, though no cut off value has been established [19].

5. Treatment

Basic sleep hygiene should always be emphasized with the patient and family as the usefulness of these interventions is often overlooked. Treatment of comorbid conditions that may be contributing to sleep disorders or fatigue such as hypothyroidism, depression or obesity should also be addressed.

The mainstay of treatment of sleep-disordered breathing in ALS is through assistance of the weakened respiratory muscles with positive upper airway pressurization [20]. Non-invasive positive pressure upper airway ventilation [NIV] should be considered when hypoventilation is clinically suspected and confirmed with spirometry [19]. Practice parameters recommend initiation of NIV when SNIP falls below 40 cm H2O, FVC < 50%, or in the setting of abnormal nocturnal oximetry [22].

It is well established, that NIV improves symptoms of sleep disturbance, quality of life and cognitive function and is primarily indicated in sleep-disordered breathing and inspiratory muscle dysfunction. NIV may also prolong tracheostomy -free survival [19]. Studies have shown a slower rate of decline of FVC and pulmonary function with use of NIV in ALS patients. Benefit in survival correlated with at least 4 hours of NIV use at night [20]. Most patients with ALS will need NIV at first while sleeping, but later as symptoms progress with more dyspnea and hypercapnia/hypoxemia-related-symptoms NIV will be required for longer periods of ventilation and then continuously [12, 19]. They are at first treated with NIV and

finally with tracheostomy with total ventilator support, if elected by the patient, or with supportive measures in hospice until death.

The aim of NIV is normalization of hypercapnia, hypoxia, and the apnea-hypopnea index. This results in improvement of the sleep architecture and prolonged survival up to one year [19]. NIV is divided in pressure-assisted control where partial pressure is provided and volume-assisted control where the patient receives a predefined gas volume. Volume-assisted control has the advantage of overcoming airflow obstruction and being effective in obstructive events, but it has the disadvantage of an uncomfortable feeling caused by the ventilation and no compensation for leaks [27]. The pressure assisted control is more comfortable and it compensates for leaks. One study showed greater survival with pressure-assisted over volume-assisted ventilation [28]. NIV using nasal ventilation is preferred because it allows speech and induces a lower rate of OSA. Patients require close surveillance in the first few days of use to determine proper the settings and then monthly or quarterly evaluations thereafter. NIV failure is most commonly caused by leaks [29] and the coexistence of untreated OSA that increases mortality.

Bronchial congestion caused by weak coughing and excessive sialorrhea may also cause failure of NIV therapy. Sialorrhea may be treated with drugs [atropine, scopolamine, belladone tincture], and if these drugs fail with salivary glands radiation; Botox injections are not recommended. Keeping the head up to avoid supine position, cervical collars, or mandibular advancement may also be helpful in addition to NIV [19].

To assist cough, mechanical insufflation-exsufflation (MI-E) devices can be prescribed to patients in order to clear airway secretions and prevent development of pneumonia. These devices administer pressure (both positive and negative, as might be done in a voluntary cough) artificially and can be used via face mask or tracheostomy [30].

It is important to mention, that bulbar dysfunction poses some management challenges in regard to the use of NIV. Compliance with use of NIV in these patients is lower due to decreased tolerance. As previously mentioned, hypersalivation in these patients worsens prognosis with NIV and requires symptomatic treatment. The initial study that showed increased survival with use of NIV [31] in patients with ALS did not show benefit in patients with severe bulbar symptoms however more recent studies have contradicted this. For this reason, treating symptoms that limit NIV usage in these patients is essential. Full face masks rather than the nasal mask are necessary for patients with bulbar dysfunction due to incomplete mouth closure [32].

6. Sleep disorders in Parkinson disease

Parkinson Disease [PD] is the second most common neurodegenerative disorder after Alzheimer's disease [33]. PD occurs as a result of chronic, progressive decrease in dopamine levels of the substantia nigra, secondary to loss of dopaminergic neurons in the pars compacta and the occurrence of Lewy bodies in the cytoplasm of remaining neurons [34]. It is primarily diagnosed clinically and patients may present with the characteristic motor deficits, which include the resting tremor, bradykinesia, rigidity and postural instability. However, most will have both motor and nonmotor symptoms. The nonmotor symptoms cause disturbances, which affect sleep, mood, cognition, sensation and autonomic function. Among the nonmotor symptoms in PD, sleep disorders are second in frequency only to neuropsychiatric disorders [35].

It is estimated that between 55 to 80 percent of PD patients suffer from sleep disorders [SD] [36, 37]. Sleep can be affected in a multitude of ways with the most common SD displayed in **Table 4**. Some disturbances will precede the disease, while others are indicators of disease progression. In many cases, more than one sleep

Nocturnal sleep disorders	Diurnal sleep disorders
Insomnia	Excessive daytime sleepiness
Circadian rhythm disorders	Sleep attacks
Sleep breathing disorders	
Restless leg syndrome	
Periodic limb movements of sleep	
Rapid Eye Movement (REM) sleep behavior disorder	
Nocturia	

Table 4.
Sleep disorders in PD.

disorder may coexist in the same patient. Poor sleep, particularly if chronic, will have an impact on daily activities causing excessive daytime sleepiness [EDS] and sleep attacks [SA]. The neurodegenerative process caused by PD itself will exacerbate daily drowsiness, as well as certain medications [38]. Therefore, a detailed sleep history in a patient with PD is imperative to identify symptoms in order to treat accordingly and monitor their progression. There is evidence to suggest that improving a patient's quality of sleep not only will improve their quality of life, but can also lead in an improvement of their motor symptoms.

Another important consideration for patients with bradykinesia and rigidity, who may have trouble turning in bed at night or getting to the bathroom - is using an extended release formulations as their last dose of the day that might disrupt their sleep or, even worse, lead to falls.

Two validated scales were created to assess the severity of the impact of PD [Parkinson Disease Sleep Scale (PDSS) and Scales for Outcome in PD Sleep [SCOPA-S] [39, 40].

7. Sleep architecture changes in PD

Patients with PD often have many sleep architecture changes, the most common ones are shown in **Table 5**. The sleep architecture abnormalities include intrinsic brain changes caused by the underlying neurodegenerative disorder, co-existent sleep disorders, nocturnal motor symptoms, and dopaminergic medications.

8. Nocturnal sleep disorders

8.1 Insomnia

Insomnia affects approximately 50 to 60% of patients with PD, making it the most common sleep disorder and perhaps the most complex to treat given its multifaceted basis [42]. When it lasts for more than three months, it is considered chronic insomnia [43].

It can be further classified into the following patterns:

- Sleep-onset insomnia: when the patient has difficulty falling asleep
- Sleep-maintenance insomnia, also referred as sleep fragmentation: when the patient has difficulty staying asleep
- Terminal insomnia: when the patient awakens involuntarily earlier than usual

Decreased total sleep time
Increased sleep latency
Increased sleep fragmentation
Increase WASO
Decreased sleep efficiency
Decreased spindles
Decreased N3 stage
Decreased REM stage

WASO: wake after sleep onset. N3; NREM slow waves stage [41].

Table 5.
Sleep architecture in PD.

The most common insomnia is sleep-maintenance insomnia seen in 80 percent of patient with PD, whereas sleep onset and terminal insomnia are seen in 18 percent and 40 percent of the PD patients, respectively [36, 37, 44, 45]. Insomnia is more prevalent in women, those with longer PD duration, and those with depression or anxiety. The causes of insomnia is multifactorial and includes the neurodegenerative process of PD itself, co-morbid sleep disorders, nocturia, cramps, limitation in mobility (i.e. difficulty turning in bed), early morning leg dystonia, pain, confusion, urinary dysfunction, sleep breathing disorders [SBD], and drugs [36, 42, 45, 46, 47]. Circadian rhythm disorders and psychiatric disorders [depression, anxiety, hallucinations, etc.] may also contribute in the genesis of insomnia [45–47].

Before deciding on a treatment option for insomnia, it is important to establish the specific pattern of insomnia and other risk factors that may be contributing to the condition. For example, addressing motor symptoms and/or obstructive sleep apnea may significantly improve insomnia therefore reducing or even eliminating the need for pharmacological interventions.

Almost half of patients with PD take medications for insomnia [36, 37, 42]. The use of levodopa-carbidopa controlled release [LD-CD] at bedtime may reduce motor bradykinesia/akinesia with improvement in total sleep time [48]. Dopamine agonists [DA] such as ropinirole-24 hour prolonged release (2-24 mg/day) [49], pramipexole (up to 4.5 mg/day) and transdermal rotigotine patch (up to 16 mg/day) [50] can be used as adjuncts to LD-CD. This combination has shown to improve both nocturnal motor activity and sleep symptoms. Two trials with transdermal rotigotine patch demonstrated improvement not only nocturnal motor symptoms but also wake time after sleep onset [WASO], nocturia, pain, RLS with reduced daily sleep episodes and overall improved quality of life in PD patients [51, 52]. MAO-inhibitor rasagiline has shown to improve total sleep time and reduce sleep latency when used in combination with LD-CD compare to when LD-CD is used alone [53]. Rasagiline's beneficial effects on insomnia are likely related to an increment in melatonin levels.

After motor impairment and co-existent sleep disorders are identified and treated, insomnia can further be managed with cognitive behavioral therapy utilizing sleep hygiene techniques, stimulus control, sleep restriction, relaxation techniques, and cognitive therapy [53, 54]. Soporific drugs such as eszopiclone, zolpidem, doxepin, trazodone, ramelteon, and melatonin have been used with various success in the therapy of insomnia in PD patients [44]. Melatonin at very high doses (50 mg) at bedtime was compared with 5 mg/day at the bedtime in the treatment of insomnia in PD patients. Melatonin 50 mg dose showed a statistical significant improvement in total sleep time compared to lower doses, however melatonin at 5 mg improved subjective sleep disturbance, sleep quantity, and daytime drowsiness compared to placebo. Melatonin may be associated with morning headaches, hallucination, and daily drowsiness [55].

8.2 Nocturia

Nocturia is defined as an increase in the frequency of nocturnal urination. About one third of PD patients suffer from nocturia [56]. Nocturia in PD is most likely a result of autonomic dysfunction caused by detrusor hyperreflexia from lack of dopamine which decreases the inhibition of micturition. However, it is important to rule out secondary organic causes of nocturia (such as urinary tract infections, prostrate disorders, anxiety, congestive heart failure, etc.) before altering anti-Parkinson medication doses [45, 48].

Subcutaneous apomorphine at a dose of 3-8 mg at bedtime has been used to treat nocturia as it reduces the hyperreflexia in the detrusor muscles [57]. Rasagiline at a dose of 1 mg/day can increase bladder capacity and decreases residual volume [58]. Intranasal desmopressin and botulinum toxins in the detrusor muscles may be beneficial. Anticholinergic drugs [oxybutynin, solifenacin, darifenacin, tolterodine], can potentially help with nocturia, although the side effects of these drugs (drowsiness and cognitive impairment) might be an impediment [35].

8.3 Restless leg syndrome

Restless leg syndrome [RLS] is a sensorimotor disorder characterized by an unpleasant leg sensation associated with an urge to move the legs, relieved by leg movement, worsen by inactivity and worse at night [43]. RLS is seen in about 20% of patients with PD, which is a higher rate than in the general population [59]. Primary RLS is a genetic disorder, whereas secondary RLS results from other conditions such as renal disease, iron deficiency, co-existence of neuropathies, medications, etc. [43, 60]. PD patients who develop RLS tend to have later PD onset, poor sleep quality and more cardiovascular and anxiety disorders [45, 59]. RLS need to be differentiated from common complain seen in PD patients such as uncomfortable nocturnal motor symptoms secondary to immobility, akathisia and dystonia. The treatment of RLS in PD patients is similar to the treatment for non-PD patients. Identify and treat any underlying secondary causes of RLS first. Iron supplementation is required when ferritin levels are below 50 microg/ml. Antidepressants may worsen RLS symptoms therefore adjustment in dosage or replacement with bupropion with dopaminergic effect is warranted [60, 61]. Antidopaminergic and antihistaminic medications can also worsen RLS [45]. L-dopa-carbidopa is no longer recommended to treat RLS due to the high risk of augmentation (treatment complication from dopaminergic drug with worsening of the RLS symptoms [45, 60, 61]. Dopamine agonists (ropinirole, pramipexole, transdermal rotigotine patches) and GABAergic products (pregabalin, enacarbil, gabapentin) can be used as first line of therapy. The latter being particularly useful in patients with a coexistent neuropathic pain [60, 61]. Other drugs as clonazepam and opioids may be used to induce sleep and treat pain, respectively. New devices that apply pressure to the legs may also relieve RLS symptoms [62].

8.4 Periodic leg moment of sleep

Periodic leg moment of the sleep [PLMS] is a sleep disorder characterized by repetitive leg movements while patient is asleep that result in sleep fragmentation and daily drowsiness. Whereas the diagnosis of RLS is clinical the diagnosis of PLMS is polysomnographic. A PLMS index [leg movements per hour of sleep] of 15 or more is considerate abnormal [43]. PLMS is seen in 80% of patients with RLS [43] and the incidence of PLMS is 30–80% of patients with Parkinson disease [45, 63].

Age and dopamine loss may contribute to PLMS [64]. The mainstay treatment for PLM is the use of dopamine agonists [65].

8.5 REM behavior disorder

REM Behavior Disorder (RBD) is a REM-parasomnia characterized by the ability of the patient to reenact the content of his dreams with complex and violent motor behaviors which varies from vocalization, throwing punches, kicking, flailing, screaming, to jumping from the bed and running. This can cause injuries to the patient and/or to the bed partners [43]. RBD is commonly seen in PD [66] and is more prevalent in the second half of the night when REM sleep occurs [43]. Studies have demonstrated that RBD may manifest years prior to the development of PD symptoms with an estimated 75–90% of RBD patients developing PD after 10 to 14 years from onset [43]. RBD may precede the onset of others alpha-synucleinopathies such as Lewy Body dementia and multiple system atrophy [43]. RBD should be considered in patients presenting with history of "acting out their dreams or motor activation while sleeping" and confirm it with video polysomnography, though not require for its diagnosis. Creating a safe sleeping environment is the first step in management. This condition responds to low dose of clonazepam [0.25-2 mg qhs]. Clonazepam improves total sleep time, sleep efficiency, increase in NREM sleep, and decrease WASO [67, 68]. However, this medication was associated with sedation, cognitive deficits, and increments in falls [45]. Melatonin 3 to 12 mg at night or at higher doses is also helpful in RBD and can be used with dementia and obstructive sleep apnea where clonazepam is not recommended. Melatonin may be used as solo or co-adjuvant therapy for insomnia and at high doses may be associated with morning headaches, sedation, or delusion/hallucinations [45, 69]. Patients who failed clonazepam and melatonin may respond to rivastigmine [70] or ramelteon [71] at night.

8.6 Sleep-breathing disorders

Obstructive sleep apnea (OSA) is the most common sleep breathing disorder (SBD). Other forms of SBDs are also seen in PD such as snoring, central and mixed apneas [43]. OSA is characterized by intermittent and repetitive events of pharyngeal airway collapse with complete upper airway obstruction (apnea) or partial upper airway obstruction (hypopneas) during sleep, especially during REM sleep when the effect of the atonia is more pronounced. Patients present with nocturnal snoring, snorting, sleep fragmentation, insomnia, and daily consequences of daytime sleepiness, fatigue, poor concentration, poor memory, and mood changes. If severe, it is associated with sleep attacks [spells of sudden sleepiness] [43]. The prevalence of OSA in PD varies between 20–60% depending on the methodology used to score respiratory events [45] and according to two recent studies it is more common in PD patients than in the general population [72, 73]. An additional study showed that SBDs are also more common in other forms of parkinsonism such as vascular parkinsonism than controls [74]. From all forms of SBDs [snoring, central sleep apneas and obstructive sleep apneas] OSA is the most common form in PD [74]. This is likely related to multiple factors seen in patients with PD: most PD patients are elders [advanced age is a risk factor for OSA], PD present with autonomic dysfunction [autonomic dysfunction increases the risk for OSA], PD patients share loss of motor neurons from brainstem involved in respiration [reduced respiratory drive] and control oropharyngeal muscles [fluctuating respiratory muscle coordination increases risk for OSA], PD patients have restrictive lung disease caused by chest wall rigidity and upper airway abnormalities as shown spirometry

abnormalities in up 65% patients with PD [75]which increased the risk for upper airway obstruction [42, 74]. The diagnosis of OSA is suspected through history and specific screening questionnaires such as STOP-BANG and Berlin's questionnaire. In PD, STOP-BANG has a high sensitivity, but low specificity in the diagnosis of OSA, whereas the Berlin's Questionnaire has a higher sensitivity in the diagnose of PD, but it sensitivity declines as the severity of PD declines [76]. And it is confirmed with polysomnography at a sleep center or level III portable monitoring at home [77, 78]. OSA may worsen PD as it worsens sleep fragmentation and causes intermittent hypoxia [45, 79, 80] which is associated with worsening in the cognitive function [81, 82]. Sleep disorders are considered one of the most disabling of the non-motor symptoms of PD [83]. The treatment of OSA with PD is the same than in patients without PD: body weight loss, positional therapy, continuous positive airway pressure (CPAP), and surgery [45, 84]. The cognitive impairment often reported in patient with Parkinson disease [81, 82] also improves with positive airway pressure therapy [85].

8.7 Circadian rhythm disorder

Circadian rhythm disorders (CRD) are implicated in the pathophysiology of PD [86], but their real prevalence in PD patients remains unknown [87]. Motor and non-motor features [autonomic function, visual performance, sleep-awake cycles, and response to dopaminergic drugs] experienced a diurnal fluctuation from the circadian system [88]. Dopamine is an intermediary of light providing input to the retinal circadian clock which provides a direct input to the suprachiasmatic nuclei (SCN). Thereby, via retinal dopamine-containing amacrine cells, information is conveyed across a series of clock genes that control the circadian rhythm. Dopamine deficiency, seen in Parkinson disease, affects specific clock genes (dysregulation of Bmal gene expression) resulting in dysfunction of the central sleep–wake cycle control [86, 87]. Studies using actigraphy to record times of wrist motor activity [wakefulness] and times of motor inactivity [sleepiness] showed lower peaks of physical activity during rest time and higher levels of activity at night compared with control [89, 90]. Motor symptoms in Parkinson disease worsen in the afternoon and evening in stable patients and patients with wearing off [advanced PD] indicating that the response to dopaminergic drugs declines throughout the daytime [91]. This decrease in diurnal activity and increase in nocturnal activity observed in PD patients is influenced by dopaminergic drugs [86]. A variability in the pharmacokinetics of levodopa, i.e. faster during daytime and while standing compared with being supine at night, play the role in levodopa variability [92]. Patient with PD with hallucinations show more fragmentation of the rest activity with more unpredictability in the circadian pattern [93].

Autonomic dysfunction, a common feature in PD, also follows a circadian pattern with a nocturnal blood pressure reversal pattern i.e. blood pressure equal or higher than daytime blood pressure as demonstrated in most of the patients in one study [94]. An attenuation of sympathetic nervous system activity in PD patients was demonstrated by a heart rate variability study where power spectral analysis using a 24-hour ambulatory EKG revealed a decrease in total frequency component and low frequency/high frequency ratio [86, 94]. Studies in PD patients have shown a reduction in core body temperature. This reduction in core temperature correlated with higher rates of self-reported RBD symptoms, reduction in percentage of REM sleep, and prolonged latency compared with controls [95].

Hormonal changes are also affected by circadian rhythms in PD. PD patients have shown elevated serum cortisol levels and reduced serum melatonin levels compared with controls [96, 97]. Furthermore, melatonin diurnal fluctuations are

blunted in PD patients [98] which correlates with the self-reported symptoms of EDS [97]. The amplitude in melatonin decreases and melatonin phase advanced in PD treated patients compared with non-treated patients indicating that as PD progresses melatonin decreases with a phase advancement [99]. Dopamine drugs affect the regulation of melatonin circadian pattern and sleep onset patients in PD patients [100].

Circadian rhythm changes affect also visual performance in PD [101] most likely caused by impairment in retinal dopamine content that follows a circadian rhythm independent of light/dark cycles [102] Dopamine agonists may regulate the rhythmic expression of melanopsin in retina ganglion cells [88].

In summery the causes of CRD in PD are multifactorial and some are included below list:

- Disorders of the sleep-awake neuronal circuity controlling the circadian rhythm.
- Hypothalamic dysregulation with a decline of the SCN that lead to reduction in melatonin production and sleep-awake disruption.
- Dysregulation of the genes that control the awake-sleep cycles such as Bmal1 gene and clock genes expression [dopamine regulates the Bmal1/clock activity]
- Disconnection of SCN with neuronal circuitries and hormonal signals
- SCN degeneration associated with clock gene dysregulation
- Striatum dysregulation [dopamine controlled clock proteins Per1/Per2 gene expression]
- Decrease rhythmic expression of retinal melanopsin [regulated by dopamine] that affect the entrainment of diurnal circadian rhythm
- Animal models of PD revealed changes in the neurons firing pattern of the SCN associated with changes in the circadian rhythm amplitude [86, 87, 103]

Light therapy is a non-invasive technique proven to be safe, well tolerated, and effective on the treatment of daily drowsiness and impair alertness in PD [104–106].

9. Diurnal sleep disorders

9.1 Excessive daytime sleepiness in PD

Excessive daytime sleepiness (EDS) involves symptoms of frequent napping, feeling abnormally sleepy and sleep attacks. It is seen in 33–76% of patients with PD [100, 107] and is likely a result of damaged to the orexin-producing neurons from the posterior lateral hypothalamus involved in the wakefulness [108]. Other brainstem stimulating monoaminergic neurons are also implicated in promoting wakefulness in damaged in PD [109]. EDS is common in advanced PD and is a marker of dopamine loss [110, 111]. **Table 6** display the condition more commonly associated with EDS in PD.

Severe PD
PD-related disability
Cognitive decline
Frequent hallucinations
Dementia
Depression
Polypharmacy
Co-existence sleep disorders
High comorbid disease burden
High doses of antiparkinsonian Drugs

Table 6.
Cause of excessive daytime sleepiness in PD.

Sleep attacks, which are defined as sudden irresistible drowsiness without awareness of falling sleep, are seen in 21% of PD patients. These are particularly concerning as they can cause serious injuries or even death, for example, as a result of a car accident when the patient falls asleep while driving [45, 55]. The Inappropriate Sleep Composite Score (ISCS) have a high specificity to detect the risk of car accidents related to EDS while driving [112]. A study with drug-naïve patients with early PD showed that patient who developed EDS after 5 years of treatment had higher baseline levels of drowsiness [113].

Management of EDS includes improving sleep hygiene, daytime regular exercises, avoid strenuous exercises a few hours before bedtime, reducing sedating medications both psychiatric (i.e. antidepressants, benzodiazepines, antipsychotics, etc.) as well as anti-Parkinson medications (particularly dopaminergic medications and levodopa), especially when used in combination [45, 114]. Stimulating anti-Parkinson medication earlier into the day such as amantadine and selegeline may help with EDS and if appropriate may be used instead of DAs [115]. If above plan fails, consider starting stimulants such as:

- Caffeine at a dose of 200 mg twice a day [116]
- Modafanil at a dose of 100–400 mg/day [117, 118].
- Methylphenidate at a dose of 1 mg/kg TID [119]
- Sodium oxybate at a dose of 3–9 grams per night at bedtime and 4 hours later [120].

Treatment of co-existent sleep disorders is essential.

Increase total sleep time
Increase sleep efficiency
Reduce sleep fragmentation
Decrease WASO
Increased slow wave sleep
Increase REM sleep
Improve insomnia
Improve restless leg syndrome
Improve daytime sleepiness

Table 7.
Deep brain stimulation, sleep architecture and sleep disorders.

9.2 Deep brain stimulation

Deep brain stimulation (DBS) is the most common surgical intervention for the treatment of PD. The procedure involves the surgical placement of electrodes, either unilaterally or bilaterally, in certain target areas in the brain. Most commonly placed in the subthalamic nucleus (STN) or the internal globus pallidus (GPi). The electrodes are then connected to a pulse generator implanted in the chest. DBS is known to improve motor symptoms and overall quality of life however we have only recently established that it also improves non-motor symptoms, including sleep [121]. STN DBS especially has shown significant improvement in sleep quality, sleep efficiency and sleep duration [121].

The beneficial effect on sleep architecture and sleep disorders [45] are displayed **Table** 7.

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Chapter 5

REM-Behavior Disorder

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Abstract

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia exclusively occurring during REM sleep. Viewing this disorder through a neurologic lens can provide longitudinal context for patients and their treating physicians, given the well-known association of RBD with a specific group of neurodegenerative disorders: the alpha synucleinopathies. It is important to have a high degree of clinical suspicion, the ability to make an accurate diagnosis, manage the symptoms, and more importantly monitor the patient for evolution of possible underlying neurological pathology. This chapter will discuss aspects of the clinical history, physical examination, ancillary testing, and diagnostic criteria.

Keywords: rapid eye movement (REM), REM sleep behavior disorder (RBD), Parkinson's disease (PD), alpha synucleinopathies, dementia with Lewy bodies (LBD)

1. Introduction

There are a variety of disorders that can manifest complex movements and behaviors that happen during sleep. REM behavior disorder (RBD) is one such disorder characterized by loss of physiologic REM muscle atonia and dream enactment. Motor activity consists of highly complex, vigorous or violent dream enacting behaviors that are noticed when they result in injuries of the patient or their bed partner. Some behaviors include punching, kicking, jumping out of bed, and talking. If the patient is awoken they may recall an unpleasant dream of falling, being attacked or chased by either another person or an animal. The latter are common dream contents associated with RBD.

A disorder of the elderly, RBD onset occurs between the sixth and seventh decades [1], with an estimated prevalence of between 1 and 7.7% of the population [2]. The true extent of this disorder is largely unknown [3]. The disease is male predominant [4]. Symptoms are thought to arise from underlying dysfunction of the brainstem structures that regulate REM sleep atonia, mostly located in the dorsal mesopontine tegmentum and ventromedial medulla [4]. Injury to these areas can occur in the setting of structural lesions (such as stroke or multiple sclerosis), medication side effects (seen with certain antidepressants and beta blockers), or neuronal loss from neurodegenerative disease. There is a known association between RBD and the group of neurodegenerative conditions classified as alpha synucleinopathies. RBD is considered a prodrome of these conditions and can be present years before other neurological symptoms become apparent, thus the importance of early diagnosis and subsequent monitoring [5].

2. Diagnosis

Often RBD is a missed diagnosis, likely due to under reporting. While some patients have no recollection of their nighttime behaviors, others may simply not view these are abnormal. Obtaining an accurate clinical history then depends on corroborative information gathered from the patient's bed partner, as they may witness the dream enactment behavior. Of note, spouses may comment on the patient's night time behaviors being out of character as compared to how they behave during the daytime. For patients who do not have a regular bed partner, questions regarding vivid dreams (specifically of being attacked or engaged in combat) and unexplained night time injuries such as falling out of bed should be explored.

Differential diagnoses for complex nocturnal behaviors can be divided into several categories (see **Table 1**) including: partial arousal parasomnias, nightmare disorder, sleep related respiratory disorders, sleep related movement disorders, seizure disorders, and psychiatric disease. *Partial arousal parasomnias* occur mostly from slow wave sleep (happening during the first half of the night as noted in **Table 2**) and pathophysiology is presumed to be an incomplete transition from sleep to wakefulness [6]. These episodes consist of an arousal with associated disorientation and amnesia. Behaviors are quite primitive such as walking and eating. Episodes may be exacerbated by factors that increase the threshold for arousal (e.g. sleep deprivation, sedating medications). *Confusional arousals* are part of this category; however, these are rare in adults. As opposed to sleep walking and sleep related eating disorder,

Partial arousal parasomnias (arising from slow wave sleep):

- Sleep talking/somniloquy
- Sleep walking/somnambulism
- Night terrors
- Confusional arousals
- Sleep related eating disorder

Nightmares
Obstructive sleep apnea
Periodic limb movements of sleep
Nocturnal frontal lobe epilepsy
Nocturnal panic attacks
Sleep-related groaning (Catathrenia)

Table 1.
Differential diagnoses of RBD.

NREM parasomnias	**RBD**
Occur in the first part of the night	Occur in the second part of the night
Patient is amnestic of event	Patient recalls the event
Variable duration (minutes or longer)	Last seconds to minutes
Patient is difficult to arouse	Patient easily arousable
Male predominance	Male predominance
Provoked by sleep deprivation, stress	Unprovoked
Higher prevalence among children	Higher prevalence among older adults

Table 2.
SWS parasomnias vs RBD.

NFLE	RBD
Stereotyped asymmetric hypermotor behaviors of trunk or proximal extremities	Variable dream enacting behaviors in a self-defense manner including vocalizations
Short duration 5–60 s	Duration is seconds to 2 min
Patient is amnestic to the event	Patient recalls the event
Occurs from NREM stages	Occurs during REM sleep
May have nightly clusters	Rare, sporadic events
Age of onset first or second decade	Age of onset fifth decade

Table 3.
Nocturnal frontal lobe epilepsy vs RBD.

confusional arousals are associated with poor responsiveness and amnesia but during confusional arousals there is no ambulation. *Nightmare disorder* consists of recurrent awakenings during which the patient is able to recall a disturbing dream and experiences associated intense emotions such as fear, anxiety, or sadness. It is important to note that in nightmares there is preservation of REM atonia, therefore body movement is rare and the patient is fully alert after awakening (as opposed to a confusional arousal). *Obstructive sleep* apnea should be investigated if patient has a history notable for excessive daytime sleepiness. *Periodic limb movements of sleep* and other *sleep fragmenting conditions* may precipitate partial arousal parasomnias, which can be misinterpreted as RBD. Lastly, while parasomnias are largely a disorder of childhood, primary RBD (as described below) almost exclusively occurs in older adults.

Nocturnal frontal lobe epilepsy (NFLE) is one of the most important differential diagnosis for complex nocturnal behaviors that may mimic RBD (see **Table 3**) [7]. NFLE also presents with complex, exclusively nocturnal, bizarre behaviors; the hallmark of this disorder is that each episode is stereotyped (like with all epilepsies), where actions occurring during parasomnias or RBD are varied. The "classic" example is bicycling of the legs at night time out of sleep. Unlike RBD or parasomnias, there is no particular predilection for a time of night for these seizures to occur. Similar to parasomnias (but unlike RBD), the patient will be amnestic to the events themselves. Preferred treatment for nocturnal frontal lobe epilepsy includes anticonvulsant agents such as carbamazepine, oxcarbazepine, and lamotrigine.

Once suspicion for RBD is raised, confirmatory polysomnogram (PSG) should be pursued as this will provide a definite diagnosis. A full attended polysomnogram set up includes: abbreviated electroencephalography leads, eye movement monitoring, nasal airflow monitoring, oronasal thermistor, mental/submental EMG, snore sensor, single ECG lead, chest/abdomen respiratory effort belts, pulse oximetry, and bilateral tibialis anterior EMG monitoring. When testing for RBD additional monitoring includes surface electromyography (EMG) preferably of the upper extremities as lower extremity movements are less specific [8]. The most sensitive information is obtained from monitoring of the chin (mental/submental electrodes) and flexor digitorum superficialis. Diagnostic features on PSG include increased muscle activity on surface EMG, specifically of both the chin and upper extremities. Activity on EMG is categorized as tonic or phasic. Tonic activity lasts longer than 15 s, while phasic activity is much shorter lasting less than 5 s. Typically, tonic activity is observed in the chin, while phasic activity is observed in both the chin and upper extremity EMG. Additionally, combined chin/arm activity should be present for at least 27% of a 30 s epoch (as per the International Classification of Sleep Disorders Guidelines). This is a highly specialized test and its interpretation relies on visual quantification, therefore technical quality is of the utmost importance [9]. Performing a full

18 channel EEG montage during routine diagnostic PSG can help rule out NFLE, especially if a complex behavior is captured on the PSG study night.

Diagnostic criteria as established by the International Classification of Sleep Disorders, Third Edition include [10]:

- Repeated episodes of sleep related vocalization and/or complex motor behaviors
- Behaviors are documented by polysomnogram to occur during REM sleep or based on clinical history of dream enacting behavior, are presumed to occur during REM sleep
- Polysomnogram demonstrates REM sleep without atonia
- Disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance abuse.

3. Primary rapid eye movement sleep behavior disorder (synucleinopathies)

Once diagnosed, RBD can be classified as primary (idiopathic) or secondary. *Idiopathic RBD* can be considered an early symptom of alpha synucleinopathies which include: Parkinson's disease, Lewy Body Dementia and Multiple System Atrophy. The diagnosis of RBD can be made years before any other neurologic symptoms are identified. In 80% of cases RBD preceded the diagnosis of neurodegenerative disease (more easily recognized motor features), by a mean of 14 years [11]. There is evidence to suggest that patients with RBD and mild cognitive impairment will develop dementia in an interval of 5 years or less [9]. Other subtle potentially predictive biomarkers of RBD (see **Table 4**) include: olfactory loss/anosmia, autonomic dysfunction (ranging from sexual dysfunction to cardiovascular symptoms), color vision deficit, cognitive impairment, excessive daytime sleepiness, psychiatric disorders (such as anxiety, depression, psychosis, impulse control disorders), personality changes, dopamine dysfunction, and excessive EMG activity [11]. The pathophysiology and temporal relation between these symptoms and motor symptom onset is highly variable. Subsequent neurological examination may show subtle signs of Parkinsonism such as mild bradykinesia, while neurocognitive testing can show evidence of memory and executive dysfunction. Neuroimaging is useful if dopamine transporter scan shows evidence of decreased dopamine uptake in the putamen. Electroencephalogram can show cortical slowing as well [9]. Biopsy of the colon and submandibular gland in patients with idiopathic RBD has shown evidence of phosphorylated alpha synuclein deposits.

Anosmia
Autonomic dysfunction
Color vision deficit
Cognitive impairment
Excessive daytime sleepiness
Psychiatric disorders
Personality changes
Dopamine dysfunction
Excessive EMG activity

Table 4.
Potential biomarkers of RBD.

4. Secondary rapid eye movement sleep behavior disorder (non-synucleinopathy)

Other causes of RBD include neurologic disorders stemming from structural lesions such as pontine stroke or multiple sclerosis plaques. This can also rarely occur in the setting of progressive supranuclear palsy, Alzheimer's disease, and Huntington disease among others. RBD can coexist with narcolepsy in 50% of patients. Medications that can precipitate RBD include antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclics, and monoamine oxidase inhibitors (MAOi). Some beta blockers have also been identified as culprits.

5. Treatment

Symptomatic management of RBD should be approached from multiple angles. First, maintaining a safe sleep environment for the patient by removing objects that can inflict harm or lowering the bed closer to the floor. Bed partners may also opt for sleeping in separate bed for their own safety. Co-sleeping is an important part of intimacy, however, and this can continue by advising the patient to sleep in a sleeping bag on top of the bed shared with their loved one. Bed alarms to warn loved ones about the patient exiting the bed can also be helpful in reducing night time injuries associated with RBD.

Medical management with melatonin or low dose benzodiazepines such as clonazepam has been shown to reduce the dream enacting behaviors. Benzodiazepines are thought to work by suppressing REM sleep. Theoretically, other REM suppressant medications (including SSRIs, TCAs, selective SNRIs) may also help, given their mechanism of action. However there are no trials supporting or refuting their efficacy and some may precipitate RBD as previously mentioned. These medications do, however, have lower tolerance and abuse potential than benzodiazepines. These treatments do not modify the risk of progression to PD, MSA, or LBD. Dopaminergic agents have not been shown to reduce dream enactment behaviors but may help comorbid periodic limb movements if present. In RBD cases refractory to conventional treatment, cholinesterase inhibitors such as rivastigmine (studied in one trial) and donepezil (several cases) have been noted to reduce the number of dream enactment episodes as reported by bed partners.

6. Ethical considerations

As stated previously, development of RBD can herald a diagnosis of potentially disabling neurological disorders by over a decade. While not every patient with primary RBD will go on to develop one of these conditions, we believe that patients should be informed of the association between RBD and the alpha synucleinopathies and therefore their risk of developing one of these disorders. The discussion should be geared towards ensuring periodic follow up and reducing anxiety by answering any questions the patient may have on the subject. Serial neurologic exams, either comprehensive or focused on Parkinsonian features like tremor, rigidity, and bradykinesia should be performed. This can ensure early, effective treatment of motor and other non-motor symptoms that can positively impact patients' quality of life.

7. Conclusion

RBD is a complex night time behavior consisting of dream enactment due to the loss of physiologic REM muscle atonia. It can be classified as idiopathic, which is in many cases a non-motor symptom of the alpha synucleinopathies. This group of neurodegenerative illnesses includes Parkinson's disease, Lewy body dementia, and multiple system atrophy. The importance of understanding REM sleep behavior disorder and its implications cannot be overstated. Clinical suspicion and appropriate history taking, supports an early diagnosis and symptomatic management. More importantly, treating physicians are able to educate and monitor patients for the development motor symptoms suggestive of neurodegenerative disease. This window of opportunity allows for enrollment in clinical trials and emerging therapies. Secondary RBD related to structural lesions or medications is important to recognize in order to discontinue the offending agent and decrease the risk of night time injury. Medical management with melatonin or clonazepam can reduce the episodes of dream enactment. Non-medical interventions such as ensuring a safe sleeping environment can help prevent injury.

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Chapter 6

Sleep and Orofacial Pain: Physiological Interactions and Clinical Management

Miguel Meira E. Cruz, Bruno Sousa and Antoon De Laat

Abstract

Sleep and pain are both vital functions on which wellbeing, health, and life itself depend. These two complex states interact in several ways serving homeostasis, but they are also regulated by a well-orchestrated, multi-oscillatory mechanism characterizing the Circadian Timing System. This interaction, which benefits critical physiological challenges, is also clinically crucial, as it mutually affects sleep and pain-related disturbances. It impacts pathophysiological pathways and relevant clinical aspects of many disorders. Furthermore, therapeutic success is frequently dependent on the adequate management of this cycle. The relationship of sleep and pain is undoubtedly of major relevance for diagnosis and successful management of various health conditions and disorders.

Keywords: sleep, orofacial pain

1. Introduction: basics of sleep-pain interaction

Sleep and pain interaction occur at several levels, both in physiology and pathology, and is influenced by a circadian timing system from which almost all functions in our body partially depend. Sleep and pain are both vital functions that ultimately contribute to general body homeostasis, and therefore to life success. Experience of pain motivates an individual to run away from potential physical injury and/or to stay protected and immobilized if an injury already occurred in order to promote and optimize recovery. While the escape-related response is tied to an increased state of arousal (being more awake), the response related to protection is linked to a state of rest (and sleep). Interestingly, sufficient sleep of good quality and pain have an inverse epidemiological relationship over the lifespan: sleep reduction, either in terms of duration or quality, increases from youth to old age, and at the same time pain-related complains follow a similar pattern. This relationship is clinically important since such negative interaction disturbs the internal milieu, and therefore impacts on prognosis of many disorders co-occurring with one or both of the symptoms of disturbed sleep and pain. Some of the most common pain-related conditions occur in the oro-maxillo-facial complex and are associated with emotional, psychological, and social disturbances that seriously compromise the patient's quality of life. Thus, orofacial pain may by itself directly and indirectly interfere with sleep quality and sleep duration and consequently increases the severity of concomitant conditions and even the pain-related outcomes. On the other hand, insufficient or inadequate sleep is known to contribute

to an increased pain intensity and a reduction of pain tolerance. A vicious cycle can then be perpetuated, and therefore an adequate knowledge on the sleep-pain interaction-related mechanisms should be an important part of learning and training in the domain of clinical sleep neurology, which is in the scope of this book.

2. Pain classification: physiology and physiopathology of orofacial pain

Nociceptive impulses generated by potential or actual tissue damage are just one of the types of input that are continually assessed and evaluated throughout the various levels within the central nervous system (CNS). Nociception provides the brain a chance to interpret pains and make behavioral adjustments to avoid further potential damaging stimuli [1].

First-order nociceptive neurons, whether they synapse in the spinal trigeminal nucleus or in the dorsal horn, excite the same type of second-order neurons that respond to nociceptive signals as well as a variety of sensory stimuli and are therefore called wide-dynamic range neurons. These neurons conduct nociception and other sensations through the brainstem and display varying degrees of arborization with structures throughout the reticular formation, where baseline physiologic processes are controlled before reaching the third-order neurons in the thalamus [2–5]. *Second-order neurons*, stimulated by the faster conducting A-delta fibers, arborize less than those receiving impulses from the slower conducting C-fibers. While the A-delta fibers release glutamate during this process, the C-fibers release a wide variety of neurotransmitters [6, 7]. The available information about the conduction velocity helps us to establish a connection between A-delta fibers and acute pain and between C-fibers and chronic pain.

Third-order circuits, which start in the thalamus and connect the sensory cortex with the basal ganglia and the limbic system, interpret nociceptive input [2, 8]. However, sometimes the pain source is difficult to locate even when pain is felt. For example, the cutaneous stimuli are easier to recognize than the stimuli from visceral organs and muscles just because dermis has much more free nerve endings. In response to pain interpretation, multilevel behavioral responses are coordinated, and descending motor commands are created. Whether nociception is delivered to the CNS through the spinothalamic tract or the trigeminal thalamic tract, pain perception evokes autonomic nervous system (ANS)-modulated cranial nerve responses [2, 9, 10].

Pain in the head and face often involves activation of the trigeminal ganglion nerves and the development of peripheral and central sensitization. The symptoms could be acute-like in toothache or chronic-like in migraine or temporomandibular disorders (TMD).

More important than a single nerve pathway, the expression "trigeminal system" alludes to a really complex course of action of, interneurons, nerve transmission fibers, and synaptic connection which process approaching information from the three divisions of the trigeminal nerve. This nerve is in fact a blended nerve containing both sensory and motor fibers. While sensory fibers innervate the face, conjunctiva, mucous membranes of the oral and nasal cavities, teeth, conjunctiva, dura mater of the brain, and intracranial and extracranial blood vessels, motor fibers support mostly the masseter, temporalis, and the other mastication muscles. Primary afferent neurons carry out sensory information from the face and mouth (except nociception) through trigeminal ganglion. The trigeminal-brain stem complex is the place where a synapse with a second-order neuron occurs. This complex receives simultaneously afferent axons from the upper cervical (C2, C3), vagus, glossopharyngeal and nerves and afferent input primarily from the trigeminal nerve (facial pain and headaches may be a consequence of this connection between the upper cervical nerves and the trigeminal spinal tract nucleus).

We can separate the trigeminal-brain stem sensory nuclear complex in two different structures: the trigeminal main sensory nucleus and the trigeminal spinal tract nucleus, also known as the nucleus of the descending tract of cranial nerve V [11]. The spinal tract nucleus is structured of three separate nuclei going from a rostral (superior) to caudal (inferior) direction: subnucleus oralis, subnucleus interpolaris, and subnucleus caudalis. Subnucleus caudalis is situated in the medulla, in some cases, stretching out to the dimension of C2 or C3 and it is the most important brain relay site of nociceptive information emerging from the orofacial area. Because the nucleus caudalis is anatomically continuous with, and structurally similar to, the spinal cord dorsal horn, and because it extends into the medulla as well, it is often referred to as the medullary dorsal horn [12]. Descending nerve fibers from higher levels of the CNS or medication can change or modulate incoming nociceptive signals to the subnucleus caudalis and projecting nociceptive signals on their way to the thalamus.

Inflammation and peripheral tissue injury increase the interaction between neuronal cell bodies and satellite glial cells within the trigeminal ganglion [13]. These interactions have been shown to play an important role in the induction and maintenance of peripheral sensitization of trigeminal nociceptive neurons. Under normal conditions, neuron-glia interactions in the trigeminal ganglia are involved in information processing, neuroprotection, and regulation of neuronal activity including the basal rate of spontaneous firing and threshold of activation to maintain homeostasis. While a transient increase in neuron-glia communication is associated with an acute response to inflammatory signals, stable gap junctions are formed between trigeminal neurons and satellite glia in response to sustained inflammation that is implicated in TMD's [14].

Astrocytes, which are specialized glial cells, and the most abundantly found cells in the CNS, perform similar functions to satellite glia [15]. This means that they facilitate the regulation of neuronal development, synaptic coupling, repair, and even nutritional support. On the other hand, astrocytes can monitor and control the concentration of ions, neurotransmitters, and metabolites, as well as water movement, and thus play a key role in modulating the excitability state of neurons both in the brain and the spinal cord [16]. Microglia, other important glial cells present in the CNS, act as immune cells to remove cellular debris and dead cells; they also release inflammatory mediators to promote healing [17, 18]. Glial cells are responsible for regulating the extracellular environment around neurons and hence neuronal activities, and their importance in regard to the underlying pathology of many inflammatory diseases is gradually becoming recognized. Therefore, they have emerged as important cellular targets for therapeutic intervention given their role in promoting peripheral and central sensitization and persistent pain [19].

3. Pathophysiological aspects of sleep-pain interaction

Understanding pathophysiological mechanisms of sleep-pain interaction requires first of all to be aware that some of those influences attributed to sleep could be in fact related to circadian modulation of both pain and sleep mechanisms.

3.1 Relationship between circadian timing system, sleep, and pain: a cyclic interaction

The circadian timing system is a complex neurophysiological network comprising a central biological clock, usually called the master pacemaker and several peripheral

oscillators, also known as peripheral clocks. The human master clock corresponds to a group of neurons located in the anterior part of the hypothalamus above the optic chiasm named the suprachiasmatic nucleus (SCN). Peripheral clocks are virtually present in all cells of the body. This time-related machinery dictates what we may consider an internal time which regulates almost all body functions in a 24-h periodic fashion. The Latin term "circadian" means circa-diem, about 1 day or 24 h, and this is because our clocks are adapted to the geophysical routine of the natural day-night cycle divided in the precise 24-h period of social time [20]. Both the period of human natural circadian rhythm and the sleep-wake cycle are not exactly 24 h but a little bit longer (more or less 24.6 h) consequently, a kind of hit on the clock should occur every day in order to get our body synchronized with social time. That is one of the main functions of melatonin, an hormone which is secreted in response to the absence of light and suppressed when light is present. The basic mechanism involves the activation or inhibition of photoreceptors in the eye's retina which activate/stop taking melanopsin to the suprachiasmatic nucleus stimulating or inhibiting melatonin secretion. Although mediated by these retinal ganglionic cell-related photoreceptors, the rods and cones also have photic inputs to SCN. Peripheral clocks within each cell have a mechanism which is identical to the clocks found in the SCN-isolated neurons. However, although in isolation each cell is time-autonomous, they tend to generate a single circadian pattern dictated by SCN when these SCN neuronal population couple with other cells via humoral and non-humoral pathways [21, 22].

For biological clocks to be successful, they should accurately keep time and adjust to environmental signals. This requires adequate coupling between the SCN and peripheral clocks. In the absence of SCN signaling, peripheral clocks become desynchronized. As there is a tissue-specific time control that is in part locally controlled, loss of synchronization usually propagates and disturbs the circadian rhythm of such tissue as it was shown to occur in the liver [23–25] as well as in other tissues and organs within the human body.

3.2 The circadian regulation of pain

Some important features of pain are regulated by the circadian timing system. For instance, pain sensitivity follows a rhythmic cycle modulated by the 24 h biological clocks. However, it remains unclear whether rhythmicity is derived from daily oscillations within the underlying causes driving the pain or from rhythmic oscillatory component of the neural processing of pain. Pain-related rhythmic influences, however seem to be independent of either subjective or objective responses suggesting that its modulation occurs on a basic physiological level. Interestingly, this 24 h related pain modulatory mechanism is also dependent of pain intensity which in turn affects pain sensitivity in such a manner that the more intense the pain is, the greater the change in its sensitivity across the day. On the other hand, the particular type of pain seems relevant for the clinical impact of its circadian modulation. A recent prototype of human daily pain sensitivity curve was proposed (**Figure 1**).

3.3 Pain regulation by the homeostatic sleep drive

The sleep-wake cycle is the most conspicuous circadian rhythm in humans with a clear relationship with night (dark)-day (light) oscillation. Actually, sleep is itself regulated by a dual process comprising a circadian component and homeostatic one. This model presented by Borbely explains that we may predict a better sleep when it occurs at night and when we are tired compared to diurnal sleep and/or when we are full of energy.

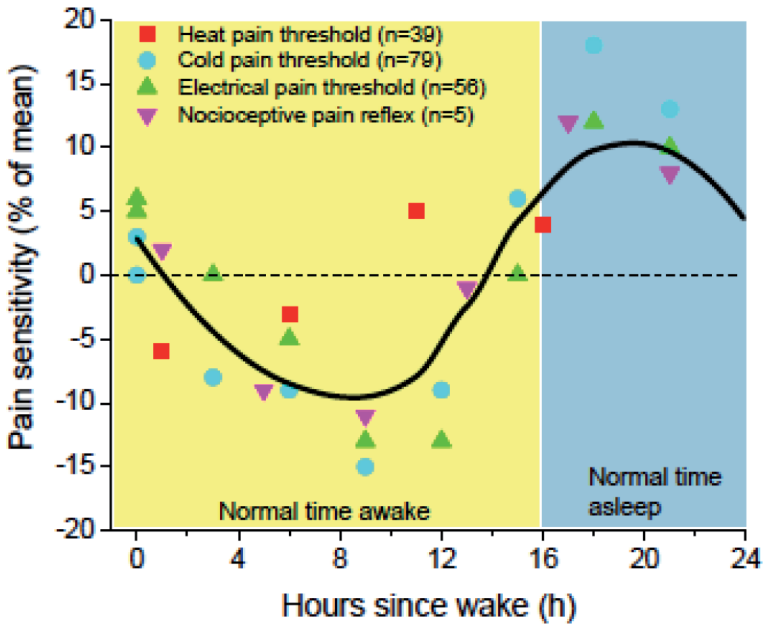

Figure 1.
Prototypical human "daily pain sensitivity" curve (adapted from [31]), the graphic illustrates the circadian profile of pain sensitivity to different pain modalities (thermic: heat and cold, electrical, and nociceptive) and their variation during the 24 h of social day.

The daily rhythm of pain sensitivity is affected not only by circadian rhythmicity, but also by sleep-related homeostatic drive. Actually, either acute and chronic pain are correlated with sleep duration and sleep quality, but while results from distinct basic studies point to a specific modulation of sleep with a wide range of results, there is a lack of human experiments to consolidate clinical knowledge. For instance, even with standardized protocols, there are significant variations in the results [26] which make interpretation sometimes difficult.

3.4 Neural pathways for pain are regulated by both circadian and homeostatic components

The dorsal root ganglia have a circadian rhythmicity since clock genes—those genes generating a near 24 h rhythm—are expressed there. The role of circadian regulation of the neural circuitry underlying pain also involves the rhythmic expression of genes that facilitate synaptic transmission as calcium channel subunits and NMDA glutamate receptor subunits [27]. On the other hand, there are some studies showing that the majority of afferents in this route are nociceptors, thus suggesting that the circadian pattern is of nociceptive origin [27, 28].

Painful stimuli and non-noxious mechanical sensitivity are differently modulated by the human circadian system since mechanical sensitivity peaks in the late afternoon (15–18 h); whereas, pain sensitivity peaks in the middle of the night (0–3 am). There is also a circadian component on inhibition of pain processing in the dorsal horn. It is however unclear what part of this inhibitory control is from the circadian machinery or dependent of the sleep homeostatic drive, since sleep deprivation is known to affect the higher levels of pain processing. Interestingly, pharmacological agents that copy that top-down inhibitory control such as morphine are ineffective after severe sleep deprivation [29, 30] and there is evidence suggesting a neutral response of fast pain processing in case of sleep deprivation. On the other

hand, cortical responses to fast pain also seem to diminish after disturbed sleep. The relative balance of circadian versus homeostatic components in pain processing may depend on the specific type of pain [31].

Although there is still a lack of knowledge on the orofacial pain-sleep interaction, basic and clinical evidence on both acute and chronic pain helps to elucidate the important role of these general components.

4. Orofacial pain diagnosis

The ability to understand and investigate the pathophysiologic processes underlying a disorder, depends on a valid, reliable classification system and common terminology to facilitate communication among clinicians, researchers, academicians, and patients.

A review of the literature regarding the classification of orofacial pain reveals a lot of classification systems with varying advantages and disadvantages [20–43]. Despite all these classifications, currently, the most accepted among the clinicians and researchers dedicated to orofacial pain is the Research and Diagnostic Criteria for temporomandibular disorders (RDC/TMD and DC/TMD).

The taxonomy of "Diagnostic criteria for temporomandibular disorders" (DC/TMD) is an evolution of the original "Research diagnostic criteria for temporomandibular disorders" (RDC/TMD). It uses a dual-axis system in which, on Axis I, the physical diagnosis is based on pathophysiology and grading of chronic pain and on Axis II depression, anxiety, and non-specific physical systems are scored, in order to determine the distribution of subtypes of TMD, psychological disorders and psychosocial dysfunction [32, 33, 44, 45]. It is important to emphasize that with the advent of the RDC TMD, it was possible to describe and compare appropriate TMD subtypes and psychosocial profiles using clearly defined and validated diagnostic criteria in groups of TMD patients, and is used in different parts of the world [34, 35, 46, 47].

An accurate orofacial pain diagnosis is obviously the first step to achieve the correct treatment for the patient. This means that the clinician must be aware of both the Axis I and Axis II of the DC/TMD. The diagnostic process involves defining the inclusion criteria that are specific to a disorder as well as ruling out specific disorders that can cause similar symptoms.

Establishing the correct diagnosis in orofacial pain is particularly difficult because of the complex inter-relationship of physical and psychological factors in the etiology of biopsychosocial chronic pain syndromes. Thus, the differential diagnosis is a critical process that—if failed—can often lead to an inappropriate treatment.

The broad categories included in the new guidelines for Assessment, Diagnosis, and Management of Orofacial Pain are as follows [36, 48]:

- Vascular and nonvascular intracranial pain disorders
- Primary headache disorders
- Neuropathic pain disorders
- Intraoral pain disorders
- Temporomandibular disorders

- Cervical pain disorders
- Extracranial and systemic causes of orofacial pain.

4.1 Vascular and nonvascular intracranial pain disorders

In this group, the differential diagnosis is essential since disorders like aneurysm, hemorrhage or hematoma, neoplasm, and edema can be life threatening and may require immediate care. The signs and symptoms include new or abrupt onset of pain, severe pain, and interruption of sleep by pain. In addition, non-pain symptoms may occur. Weight loss, ataxia, weakness, fever, changes in the neurologic examination, and neurologic deficits are common [37, 38, 49, 50].

4.2 Primary headache disorders

Migraine and tension-type headache (TTH) are considered the most prevalent among primary headaches. TTH affects 60–80% of the population while migraine has a prevalence of 15% (male 7.6%, female 18.3%) [39, 51]. Cluster headache is not very common (0.1%) [40, 41, 52, 53]; however, it is often misdiagnosed and mismanaged [42, 54]. Despite be a secondary headache disorder medication-overuse headache (MOH), it often co-exists with primary headache disorders, and consequently they are described together.

4.3 Intraoral pain disorders

Dental and other oral diseases are very prevalent conditions in the general population. Pain complaints are the primary reason why most patients seek care from dental or medical doctors. Thus, regardless of intraoral pain is not exclusively a result of dental disorders, it is essential that all complaints of pain in the mouth and face are carefully studied in order to know if there is a dental problem in its origin. There are a lot of common somatic intraoral pain disorders, which can originate from disease involving one or more broad anatomic areas: the teeth, the surrounding soft tissues (mucosa and gingiva, tongue, salivary glands), and bone.

4.4 Neuropathic pain disorders

Neuropathic pain is defined as a symptom caused by a lesion or disease of the somatosensory system, including peripheral fibers (Aβ, Aδ, and C fibers) and central neurons. Its prevalence is about 7–10% among the general population. Different causes of neuropathic pain have been described. Undoubtedly, there is a connection between neuropathic pain and population ageing as well as the increase of survival of cancer treatment and systemic diseases as diabetes mellitus. Indeed, imbalances between excitatory and inhibitory somatosensory signaling, alterations in ion channels, and variability in the way that pain messages are modulated in the central nervous system have been implicated in neuropathic pain. The challenge of chronic neuropathic pain is linked to the complexness of neuropathic symptoms, poor outcomes, and consequently difficult treatment options. The importance of the medication and other medical treatment is directly connected with the quality of life in patients suffering from

neuropathic pain. A multidisciplinary approach to the diagnosis and treatment of neuropathic pain is essential to achieve new and more efficient personalized intervention [43, 55].

4.5 Temporomandibular disorders

Temporomandibular disorder (TMD) is a general expression for pain, discomfort, and dysfunction of the masticatory muscles, the temporomandibular joints (TMJs), or both. TMD is the most common orofacial pain condition excluding dental pain. The main complaints from patients are regional pain in the face and periauricular area, limitations in jaw movement, and noise from the TMJs during jaw movements. Its prevalence is up to 15% in adults and 7% in adolescents. Long-term pain is the most important reason why patients with TMD seek treatment. Psychological disabilities are often associated with TMD. As peripheral mechanisms most likely play a role in the onset of TMD, a detailed muscle examination is recommended. The persistence of pain involves more central factors, such as sensitization of the supra spinal neurons and second-order neurons at the level of the spinal dorsal horn/trigeminal nucleus, imbalanced antinociceptive activity, and strong genetic predisposition, which also is included in DC/TMD. The etiology is multifactorial and still not clearly understood, but several biological and psychosocial risk factors for TMD have been identified. We have several treatment approaches to face temporomandibular disorders, including behavioral therapy, pharmacotherapy, physical therapy, and occlusal appliances. Evaluations indicated that the recently published Diagnostic Criteria for TMD (DC/TMD) are reliable and valid. These criteria cover the most common types of TMD and can be listed as follows.

4.5.1 Temporomandibular joint disorders

1. Joint pain
    a. Arthralgia
    b. Arthritis
2. Joint disorders
    a. Disk-condyle complex disorders
        i. Disk displacement with reduction
        ii. Disk displacement with reduction with intermittent locking
        iii. Disk displacement without reduction with limited opening
        iv. Disk displacement without reduction without limited opening
    b. Other hypomobility disorders
        i. Adhesions/adherence
        ii. Ankylosis

1. Fibrous ankylosis
2. Osseous ankylosis

c. Hypermobility disorders

i. Subluxation

ii. Luxation

1. Closed dislocation
2. Recurrent dislocation
3. Ligamentous laxity

3. Joint diseases

a. Degenerative joint diseases

i. Osteoarthrosis

ii. Osteoarthritis

b. Condylolysis

c. Osteochondritis dissecans

d. Osteonecrosis

e. Systemic arthritis

f. Neoplasm

g. Synovial chondromatosis

4. Fractures

a. Closed fracture of condylar process

b. Closed fracture of subcondylar process

c. Open fracture of condylar process

d. Open fracture of subcondylar process

5. Congenital/developmental disorders

a. Aplasia

b. Hypoplasia

c. Hyperplasia

4.5.2 Masticatory muscle disorders

1. Muscle pain limited to the orofacial region
    a. Myalgia
        i. Local myalgia
        ii. Myofascial pain
        iii. Myofascial pain with referral
    b. Tendonitis
    c. Myositis
        i. Non-infective
        ii. Infective
    d. Spasm
2. Contracture
    a. Muscle
    b. Tendon
3. Hypertrophy
4. Neoplasms
    a. Jaw
        i. Malignant
        ii. Benign
    b. Soft tissues of head, face and neck
        i. Malignant
        ii. Benign
5. Movement disorders
    a. Orofacial dyskinesia
        i. Abnormal involuntary movements
        ii. Ataxia
        iii. Subacute

b. Oromandibular dystonia

i. Acute

ii. Deformans

6. Masticatory muscle pain attributed to systemic/central disorders

a. Fibromyalgia

b. Centrally mediated myalgia

4.5.3 Masticatory muscle disorders

1. Headache attributed to TMD

4.5.4 Associated structures

1. Coronoid hyperplasia

4.6 Cervical pain disorders

Cervical pain disorders represent a very common group of musculoskeletal conditions that can greatly influence the head structures. We can divide it in two groups: those that primarily originate in the muscles and those that predominantly originate in the cervical spine. These structures very commonly refer pain to the orofacial region [44, 56].

4.7 Extracranial and systemic causes of orofacial pain

There are also some associated structures that can cause orofacial pain such as the eyes, ears, the nasal-paranasal sinus complex, the salivary glands, and the throat. In these cases, the orofacial pain is a heterotopic pain. At the same time, systemic diseases like oromandibular dystonia, multiple sclerosis, and Lyme disease, often have orofacial manifestations. The importance of an accurate differential diagnosis is obviously tremendous.

5. General considerations about clinical and epidemiological aspects of sleep-pain interaction

Clinical evidence on sleep-general pain interaction comes essentially from insomnia patients. The severity of the insomnia is associated with pain sensitivity. In a recent study, we showed that prevalence of insomnia in orofacial pain patients was almost 40%; in more than 600 clinical patients, approximately 1 in 6 suffered from relevant insomnia corroborating this important relationship between pain and sleep disturbance [57]. In a review on comorbidities of chronic facial pain and obstructive sleep apnea, Olmos also stated that sleep disturbances may impact orofacial pain in a bidirectional way [58]. Patients with obstructive sleep apnea (OSA) or with other respiratory problems during sleep, one of the most common causes of disturbed and insufficient sleep, may actually present with more pain-related complaints and we have recently showed that in a large sample of patients with temporomandibular disorders and chronic orofacial pain 22% of patients presented with snoring which

is the most common sign of sleep apnea. Furthermore, when snoring and insomnia complaints are considered together, 6% of those patients presented with both symptoms increasing the likelihood of suffering from OSA [59]. The reasons for the higher prevalence of pain in patients with sleep disturbances were discussed previously in the pathophysiological section and could be related with either peripheral (e.g., release of proinflammatory cytokines and decrease in pain tolerance) or central mechanisms. Often medication, commonly prescribed for pain management, affects breathing during sleep and can even interfere with other common sleep-related disturbances. For instance, mechanical management for pain control may affect normal respiration predisposing to sleep related breathing disorders [60].

Sleep impairment and chronic pain are also independently related with increased depressive symptoms. It has been speculated that pain, sleep, and depression could share some neurobiological matrix. Anxiety, mood changes, and depressive symptoms are however a common feature in the sleep disturbed patient, chronic pain patient, and patient with comorbidly sleep-pain-related complaints. Therefore, in patients with these complaints, it is important to adequately address these three main aspects: *Sleep*, *Pain*, and *Psychology*.

6. Assessment of sleep-pain interaction

While diagnostic aspects and evaluation of pain were discussed along this chapter and assessment of sleep was also detailed elsewhere in this book, it is important to consider some important diagnostic tools for an adequate assessment of the sleep-pain patient, such as self-reported questionnaires and polysomnography.

6.1 Self-reported measurements

An optimal use of self-report measures depends on the clinician's degree of expertise and on the specific goal. There are several screening, diagnostic, and follow up tools which can be used to properly evaluate and manage patients with sleep-pain interaction conditions.

Sleep evaluation involves several dimensions and patterns which should be differently assessed according to the main complaint and prior clinical suspicion. A sleep diary is the gold standard for subjective sleep assessment and is always a simple good way to start understanding better the usual sleep pattern of the patient. There is a consensus sleep diary (CSD) [61] that resulted for the collaborative work of both insomnia experts and potential users. This instrument is unique regarding the important related methodological issues that allow to evaluate insomnia in the research field and practical arena.

Other self-reported instruments commonly used are the Pittsburgh sleep quality index [62], to evaluate sleep quality, the Epworth Sleepiness Scale [63] to evaluate sleepiness which could be intended as an indirect measure of inadequate sleep, the Sleep Questionnaire to characterize sleep depth, and dreams and a the Sleep Disturbance Questionnaire to assess mental anxiety and physical tension. The Global Sleep Assessment Questionnaire (GSAQ) probably represents the best available screening tool for primary care practice. The chronotype as it could impact the sleep timing and the vulnerabilities for some pain sleep-wake cycle related impairments can be measured by the Morning-Evening Questionnaire [64], while states of sleepiness may be addressed by using the Stanford Sleepiness Scale [65] or the Karolinska Sleepiness Scale [66]. Visual analog scales oriented to sleep quality, sleepiness, or any other qualitative-measured dimension of sleep can also be used

and could provide important insights on the patient's status. For screening of specific high prevalent sleep disorders like sleep apnea or insomnia, there are available simple validated questionnaires as the Berlin Questionnaire [67] or the Stop-Bang [68] for sleep apnea and the Insomnia Severity Index [69], for insomnia.

6.2 Objective assessment

Polysomnography is the gold standard for sleep evaluation if movement disorders during sleep or parasomnias are suspected. In the case of disorders of central hypersomnolence, a Multiple Sleep Latency Test should be made after a PSG night in order to properly diagnose. Although PSG remains the gold option also to diagnose sleep disordered breathing, several simplified sleep studies are accepted and available. The American Academy of Sleep Medicine however recommends that PSG or home sleep apnea testing be used for diagnosis of uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA. Important to note is that if a single home testing for sleep apnea is negative, inconclusive, or technically inadequate, PSG should always be performed for diagnosis in OSA. Furthermore, if a first PSG is negative and clinical suspicion for OSA remains, a second PSG should be considered [70].

7. Treatment of sleep-pain interaction

The orofacial pain diagnosis is clinical, but sleep studies may contribute to the objective establishment of orofacial pain interference with disturbed sleep.

The patient's evaluation should include the identification of risk factors as higher levels of anxiety, alcohol consumption habits, use of long-term medication, sedentarism, stress, and a compromise in the quality of life. Patients commonly complain from non-restless sleep and higher levels of fatigue, headaches, sleepiness, and anxiety.

Differential diagnosis could be difficult because of the occurrence of multiple sleep disturbances, which may mimic some aspects of pathological interaction between sleep and pain, either clinically or in a laboratory-based evaluation.

In patients with acute conditions, the efforts should be directed to the improvement of nocturnal complaints in order to avoid chronicity. In chronic patients, symptom relief is associated to a better quality of life.

Whenever possible, identifying the primary disturbance allows an approach directed to the etiological factors and sleep hygiene as well as management of sleep disturbances should be objectives to pursue.

Pharmacological management not only should always attend to the possible interaction with pain- and sleep-related mechanisms, but also to the influences of circadian oscillations in the symptoms and in the treatment effect (chronopharmacological characteristics).

7.1 Nonpharmacological interventions

Although medications have been widely used for managing both pain and insomnia, such drugs are not free from adverse effects which many times may actually worsen one or both conditions or even be responsible for therapeutic withdrawal symptoms. Cognitive behavioral therapy is largely used for insomnia (CBT-I) and for pain (CBT-P) related conditions and is recognized as an effective first option approach to both conditions.

7.2 Cognitive behavior therapy for insomnia (CBT-I)/disturbed sleep

Regarding sleep, cognitive behavior therapy for insomnia (CBT-I) proved to be superior to pharmacotherapy in several outcome studies [71, 72]. CBT-I consists of psychoeducation about sleep and insomnia, stimulus control, sleep restriction, sleep hygiene, relaxing training, and cognitive therapy.

Stimulus control techniques pretend to associate bed with a rapid sleep onset by teaching the patient to avoid habits other than sex and sleep in bed. Naps should also be avoided and regular sleep-wake schedules must be encouraged. Another important aspect is that the patient should learn only to go to bed when feeling sleepy and get out of bed if not asleep after 20 min [73].

Sleep restriction pretends to limit the amount of time spent in bed in relation to the actual time asleep. In the first days, this will lead to a mild sleep deprivation which soon will increase the sleep drive and afterwards to a more consolidated sleep with better rest and efficiency. When the patient improves, time in bed will increase again [74].

Sleep hygiene contributes to more adequate behaviors near bedtime as avoiding caffeine or tobacco, intense exercise, or too much light, noise, and use of electronic devices [75].

Relaxation training will reduce cognitive and physical tension prior to bedtime. Techniques like hypnosis, meditation, and guided imagery can be used with more or less efficacy depending of personality and circumstances [76].

Cognitive therapy will help patient to have real beliefs regarding sleep and to adopt attitudes that will favor sleep. For instance, many patients lie in bed and think they will not sleep the whole night, making them worried about this. This technique also pretends to eliminate excessive rumination and negative thoughts, mainly in the bedtime [77].

Cognitive behavioral therapy is also available for other sleep disturbances such as sleep apnea, narcolepsy, sleep-wake circadian mismatch, and several pediatric disorders. Therefore, it could be used in several domains [78–80].

7.3 Cognitive behavioral therapy for pain (CBT-P)

Several psychological- and behavioral-related options showed to be effective for chronic pain, including CBT-P, acceptance and commitment, mindfulness, progressive muscle relaxation training, motivational interviewing, and goal setting to behavioral activation. CBT-P is effective in a manner that its principles are associated to identify and approach those negative or dysfunctional thoughts and behaviors that usually worsen patient's adjustment to chronic mechanisms of pain. It was shown to effectively reduce patient distress in patients with pain-associated conditions. Although it is expected that CBT-P also has impact on sleep in those patients, there are only few studies addressing this.

7.4 Combined cognitive behavioral therapy directed to both sleep and pain

A synergistic (CBT-I + CBT-P) approach was associated with significant greater improvements either in pain and sleep when compared with each isolated strategy. Fatigue, depression, and overall improvement in quality of live with less pain interference were observed in patients treated with this combination [81].

7.5 Pharmacological therapy

Reciprocal interaction between pain and sleep disturbance makes it important to concurrently address and treat both conditions in order to succeed. In some

patients, in which CBT is not successful or effective, pharmacological therapy is often required. Sometimes, also in the beginning of the therapeutic process, some classes of drugs are useful to optimize therapeutic adherence in both sleep and pain.

7.6 Opioids analgesics

Opioids may improve subjective sleep quality in some patients with chronic pain, but can also interfere with sleep in others, mainly if they have sleep related breathing disorders which may be aggravated by this class of analgesic drugs. Other well-known potential adverse effects are hyperalgesia, tolerance, and dependence. That is the reason to support the recommendation *against* the use of opioids for insomnia, although it could be effective in highly selected pain patients [82].

7.7 Benzodiazepine receptor agonists

This class of drugs binds to GABA (gamma aminobutyric acid)-A receptors and has sedative/hypnotic, amnestic, anxiolytic, muscle relaxant, and anticonvulsant effects. Many studies show that this GABA-mediated pharmacological activity favors sleep quality, reduces sleep latency, and wakefulness after sleep onset and improve total sleep time. Half-lives of BzRAS vary from short and intermediate to long, and therefore indications for sleep disturbance and insomnia depends of its clinical aspect (onset, maintenance, or end-stage insomnia) as well as their expected adverse effects (cognitive impairment, low attention levels, anterograde amnesia). Some controversies persist however regarding clinical improvements using these drugs on the long term. Long-term adverse reactions involve the increase in depressive symptoms, cognitive and psychomotor slowing. Its abrupt stop should not happen as rebound insomnia and seizures could appear or increase in intensity. Tolerance and dependence are also issues important to consider and in clinical practice it should be avoided to prescribe more than one benzodiazepine at the time since metabolites can combine and prolong sedation time. BzRAS should not be a first option in non-controlled patients with sleep disordered breathing as they can disturb respiratory responses and therefore increase severity of sleep-related respiratory disturbances. Finally, it is crucial to appropriately taper the BzRA in order to prevent associated deleterious effects in comparison of their probable short time advantage [83].

7.8 Non-benzodiazepine benzodiazepine receptor agonists

The agents from this pharmacological class are active at the benzodiazepine GABA complex, particularly on receptors in the ventrolateral preoptic nucleus. Due to their proven efficacy, reduced side effects and less risk for addiction, non-benzodiazepine receptor agonists (non-BzRAs) became the most commonly prescribed hypnotic agents for onset and maintenance insomnia in the recent years [84]. Zolpidem, zaleplon, and eszopiclone belong to this newest class of FDA-approved hypnotics. They improve sleep latency with fewer side effects given their shorter half-lives and receptor binding profile. While Zolpidem is currently the most prescribed drug for insomnia with no evidence of tolerance or rebound effect [85], Eszopiclone seems to have a similar safety profile but higher antidepressant and anxiolytic effects in patients with comorbid insomnia [86]. Regarding safety, behavioral effects of zolpidem, and zaleplon are much similar to triazolam and include sleep eating, sleep walking, and sleep driving. As recent data from zolpidem showed some negative cognitive impact on women, FDA recommended to lower the dose in females.

7.9 Antidepressants

Antidepressants with sedative effect as tryciclic antidepressants (TCA), mirtazapine, and trazodone are often prescribed for insomnia comorbid with pain. Such pharmacological approach showed to relieve both insomnia, depressive, and pain-related symptoms. Often they are effectively used to treat neuropathic pain. Attention should be taken however regarding their differential effects on sleep. Imipramine and desipramine are less sedating and may disrupt sleep, amitriptyline, nortriptyline, trimipramine, and doxepine lead to a reduction in sleep latency, increase of sleep efficiency, and increase in sleep duration [87]. Those properties should be taken into account either on the prescription time or in the evaluation in order to control comorbid conditions.

Doxepin is approved as a hypnotic in doses from 1 to 6 mg and as an antidepressant in doses from 150 to 300 mg. At hypnotic doses, it reduces wakefulness after sleep onset, increases sleep efficiency, and total sleep time without next day impact on diurnal excessive sleepiness [88].

The adverse effects of TCAs are mainly due to anti-adrenergic and anticholinergic effects: orthostatic hypotension, xerostomia and xeropthalmia, constipation, and cardiac electric changes (delays in conduction). The risk of those side effects are age-related and particular care should be taken when prescribing TCAs to patients with comorbid depression and suicidal ideation because they are extremely lethal in overdose [89].

Trazodone, a type 2 serotoninergic, histaminergic and alfa1-adrenergic antagonist acts by inhibition of serotonin reuptake. As other antidepressants, trazodone has a hypnotic function at low doses whereas antidepressant effects occur at higher doses. It improves sleep in elderly, depressed, and anxious patients and patients with post-traumatic stress and has shown clear benefit in several painful conditions. Side effects include sleepiness the next day, rebound insomnia, orthostatic hypotension, xerostomia, and priapism [90].

Mirtazapine, a sedative antidepressant agent, at doses of 15–30 mg, improves sleep onset, total sleep time, sleep efficiency, and wakefulness after sleep onset. Additionally, it has a positive impact on pain (recurrent headache and postherpetic neuralgia), mood, and appetite [91].

7.9.1 Selective serotonin (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI)

This class of drugs is both effective for depression and pain, but it is linked to sleep disruption. So, whenever needed, attention should be paid to avoid its use in the evening hours [92].

7.10 Antipsychotics

Despite the limited evidence, some off-label atypical antipsychotics drugs (olanzapine, quetiapine, and risperidone) are used for managing sleep disruption and insomnia. Self-reported and objectively evaluated outcomes suggest efficacy in increasing sleep duration, slow wave sleep and decreasing sleep latency. However, long-term safety and efficacy studies should be done in order to corroborate these findings. Meanwhile, even in low dose (<150 mg/day) quetiapine was associated to xerostomia and dizziness. Some cases of hepatotoxicity, restless legs, and akathisia were also reported. Risperidone was associated to somnolence and sialorrhea and olanzapine is suggested to be related to a degree of sedation which impacts morning rising time [93].

7.11 Anticonvulsants

GABA analogs Gabapentin and pregabalin are two anticonvulsants often used to treat chronic pain with comorbid insomnia and studies suggest positive effects on sleep outcomes as sleep latency and wakefulness after sleep onset as well as in deep slow wave sleep. Both are effective as adjuncts in depression and anxiety. Frequent adverse effects are dizziness, diurnal sedation, gastrointestinal problems, and peripheral edema [94].

7.12 Melatonin

Some studies show that melatonin, an hormone for regulating mammalian circadian biology exerts anti-nociception effects in animal models and humans, and a recent metanalysis strongly supports the utilization of melatonin on anti-nociception against many types of pain [95]; thus, suggesting that melatonin directed to comorbid condition should be effective without any major adverse effects.

7.13 Anti-histamines

The majority of over-the-counter agents used for sleep contain first generation anti-histamines with complementary anticholinergic effects. Those agents are associated to a fast development of tolerance and the lack of long-term studies on these agents requires some caution particularly because of the link to diurnal sedation and impaired cognitive function [96].

7.14 Placebo effect

One relevant aspect not sufficiently discussed is the placebo effect, which can be sometimes one of the most important pieces of the treatment. Conceptualization of the placebo phenomenon has significantly changed during the last decades and this armamentarium is now intended as related to the patient's perception of a treatment. Of course, this is directly related to the patient's previous experience and the patient-practitioner relationship and confidence as well as with expectations, emotions, and beliefs. However, all those factors impact on cerebral function and release of endogenous opioids. Moreover, the placebo effect has a psycho-neurobiological base, since brain image studies performed in healthy volunteers show increased cortical activity particularly in the dorsolateral prefrontal cortex and orbitofrontal cortex, possibly associated with expectations of pain relief. On the other hand, the placebo analgesia is related to decrease of the neural activity in structures like thalamus, insula, and the anterior cingulate cortex, which constitute the so-called pain matrix [97]. The endogenous opioid system is probably involved in the placebo analgesia mechanism since opioid antagonists were shown to block the placebo effect [98]. Interestingly, the placebo mechanism was shown also to interfere with insomnia, even when patients did know they were taking a pharmacologically inactive substance [99]. It is of crucial importance for clinicians to be aware of how the placebo components may affect (enhance or reduce) the outcome of active treatment in chronic pain patients in order to separate either the therapeutic effect from the placebo one and to optimize treatment outcome.

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Chapter 7

Sleep Disorder at High Altitude

Fanyi Kong

Abstract

In this chapter, we discuss the occurrence, mechanism, clinical manifestations, outcomes, and managements of a commonly encountered sleep disorder of someone traveling in high altitude for working and sight-seeing. Humans ascending to altitudes above 2500 m usually suffer from substantial disturbances in sleep quality as difficulty in sleep onset, frequent awakenings, respiratory disturbance, and a feeling of drowsiness on the next day. Data obtained from polysomnographic studies demonstrated several variations of sleep architecture in those healthy subjects ascending to high altitude during sleep, including periodic breathing and decreased non-rapid eye movement deep sleep stage 3 and 4 (in new nomenclature N3), which were usually accompanied by and the lowered arterial O_2 and restricted ventilation. Hypoxia is most severe during sleep and in correspondence to periodic breathing and sleep disturbance at high altitude. Poor sleep quality impairs cognition and executive abilities at high altitude though it may largely be improved after full time of acclimatization. Evidence-based choices for clinicians to treat sleep disorder at high altitude are relatively scarce at present. Supplemental oxygen and dietary nitrate are effective in alleviating nocturnal hypoxia. There is strong evidence supporting the efficacy and safety of acetazolamide and nonbenzodiazepines in minimizing periodic breathing and improving sleep quality at high altitude.

Keywords: sleep architecture, sleep disorder, sleep quality, periodic breathing, high altitude, treatment

1. Introduction

Every year, thousands of people come from the lowlands to high altitude such as the Qinghai-Tibetan plateau, the Andes, and the Alps, for sight-seeing and mountaineering. Although identification on high altitude is controversial [1, 2] (see **Table 1**), altitude illnesses do not generally occur until 2500 m altitude or greater [2]. Currently, there are hundreds of thousands of non-native people working and living in these areas at altitudes ranging from 4000 to 5072 m including mountaineers, search and rescue personnel, and military personnel.

Poor sleep quality is a common experience for new arrivals at high altitude in the days to weeks following acute ascent. They often encounter with increased awakenings, frequent brief arousals, a sense of suffocation relieved by a few deep breaths, and resumption of sleep, which is now known as periodic breathing (PB). Upon arising from sleep, the impression is one of greatly restless sleep. Poor sleep quality at high altitude is one of the serious complaints in people with mountain sickness and influences physical and mental well-being, which can manifest as impaired cognitive abilities [3, 4] and poor daytime performance [5]. Up to now,

	Davis et al. [1]	Rolan [2]
High altitude	Beyond 2400 m	2500 m–3500 m
Very high altitude	Beyond 4000 m	3500 m–5800 m
Extremely high altitude	Beyond 5500 m	Beyond 5800 m

Table 1.
Identification of high altitude.

there are no acceptable diagnostic criteria for sleep disorder at high altitude. It is recognized as a symptom of mountain sickness rather than an altitude disease.

Here we discuss the features of sleep at high altitude with focus on the role and causes of PB in altitude sleep disturbance, subjective changes in sleep quality, objective variations in sleep architecture, and management of sleep disorder at high altitude. We also discuss whether it is appropriate to name it high-altitude sleep disorder (HASD) as one of the altitude-related illness in accordance with the nomenclature of other high-altitude diseases.

2. Breathing disturbance during sleep at high altitude

One of the most important characteristics of sleep disorder at high altitude is PB, which usually occurs at altitudes above 2000 m [6]. PB during sleep was first recorded in 1886 by Mosso [7] and further observed by Douglas and Haldane in 1909 [8]. It is considered that under high altitude hypoxic circumstances, breathing was stimulated by hypoxia, leading to hypocapnia and lessening of hypoxia, which triggers apnea during sleep. Apnea, in turn, restores ventilatory by raising PCO_2 and increasing hypoxia, generating the periodic respiratory cycle. This cyclical crescendo-decrescendo pattern periodicity usually consists of 2–4 breaths, separated by an apnea of 5–15 s in duration from the next burst of 2–4 breaths. Therefore, unstable breathing is the main characteristic of PB.

The extent of PB increased progressively as the altitude increased [9]. There is a strong positive correlation between PB and severity of acute mountain sickness (AMS) as assessed by Lake Louise (LL) score. With the increasing of altitude, normal values for partial pressure of arterial (PaO_2) decreased compared to sea level, pH changing to respiratory alkalosis with concomitant hypocapnia [10]. Above 4000 m altitude, PB exists in most people, but this phenomenon may be beneficial, because with the worsening of PB, a higher arterial oxygen saturation (SaO_2) was observed during sleep [10, 11]. After 3 months of acclimatization at 3800 altitude, PB could also be observed in lowlanders. Although acclimatized lowlanders experienced PB more frequently than native Tibetans at 89–85% of SaO_2 stage, there is no significant difference in total PB events occurring either in non-rapid eye movement (NREM) or rapid eye movement (REM) stage [12]. See details in **Figure 1**, periodic breathing during sleep between native Tibetans and acclimatized Han lowlanders at 3800 m altitude. Even for a longer time (13 months) of camp in the Antarctic base Concordia (3800 m), PB prevailed for the major part of sleeping time [13]. These findings from a cross-sectional and a longitudinal study support our current understanding which assumes PB would not be largely relieved after acclimatization.

The mechanism underlying this respiratory pattern for apnea and PB during sleep in hypoxic environments is believed to be a reduction in the PaO_2 and acid-base adjustments. The procedure of PB may be summarized as conflicting dynamics between hypoxic stimulation of ventilation and suppression of respiratory output

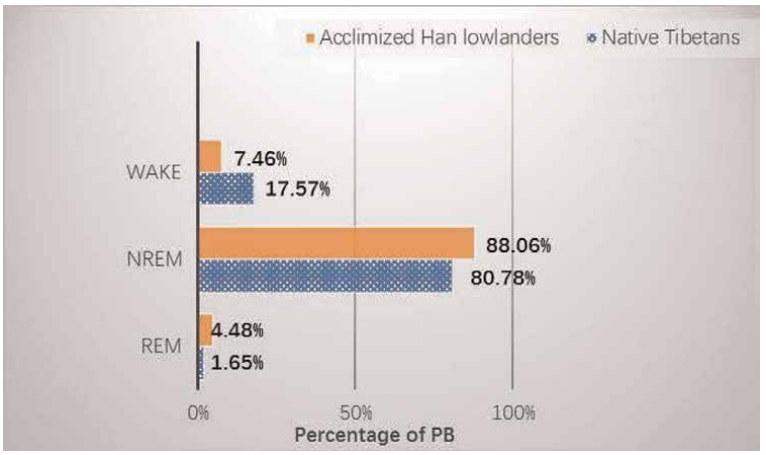

Figure 1.
Periodic breathing during sleep between native Tibetans and acclimatized Han lowlanders at 3800 altitude. Modified from Kong et al. [12].

from ensuing hypocapnia. These changes lead to alterations in chemoreflex control and cerebrovascular responses to changes in arterial O_2 which finally result in hyperventilation. For lowlanders, acclimatization to high altitude magnifies these changes. Briefly, an elevated chemosensitivity causes a more vigorous response to the rise in $PaCO_2$ while the apnea outweighs the improvements in the effectiveness of ventilation in changing the arterial O_2 caused by the chronic hypocapnia leading to the occurrence of PB [14].

The severity of PB is determined to be aggravated by an increasing neural respiratory drive (NRD), which can be measured by the electromyogram of the diaphragm. A sleep study in four healthy mountaineers performed at 3380, 4370, and 5570 m in the Andes, Argentina, confirmed this hypothesis [15]. A high NRD at altitude leads to a higher ventilation to maintain oxygenation, which results in more significant hypocapnia. This triggers apneas and O_2 desaturations, as indicated by the positive correlation between the EMG of the diaphragm and the O_2 desaturation index.

PB is considered to contribute to and/or be a result of sleep fragmentation by frequent arousals which may be responsible for poor sleep quality following altitude ascent. Sleep and arousals lead to greater breathing instability. Apnea is in correspondence to an increase in $PaCO_2$ and decrease in PaO_2 and consequently unstable ventilation. These changes in blood gases also lead to marked alterations in cerebral blood flow (CBF) which, in turn, may result in a sudden elevation (with reduced CBF) or reduction (with increased CBF) in brain stem pH.

Therefore, the uncomfortable sensation of sleep at high altitude is largely due to respiratory disturbance arising from the physiologic ventilatory dilemma of acute ascent, where stimulation by hypoxia alternates with inhibition by hypocapnic alkalosis.

3. Poor subjective sleep quality at high altitude

3.1 Evaluation and prevalence of poor sleep quality at high altitude

Subjective sleep quality at high altitude is usually evaluated by a questionnaire, e.g., sleep log questions, Pittsburgh Sleep Quality Index (PSQI), and Athens Insomnia Score (AIS). The prevalence of sleep disorder may differ considerably at altitude

from observational studies. At a 3500 m hotel, 46% of 100 Iranian ski tourists reported frequent awakenings and other subjective sleep disturbances [16]. At an altitude of 3700 m in Lhasa, Tibet, 36.8% of 180 Chinese stationed soldiers reported poor sleep quality as measured by PSQI [17]. Data analysis from the same sample also indicated that poor sleepers (defined as PSQI > 5) were 1.45 times greater in those with polycythemia than those without polycythemia [95% (confidence interval) CI 1.82–2.56] [4]. Report from early pharmacologic treatment trials in acute mountain sickness (AMS) suggested that 53–71% of participants reported difficulty sleeping [18, 19]. Of note, despite the 3 months of acclimatization, a greater proportion of poor sleepers were still observed in lowlanders stationed at 3800 altitude than the native Tibetans (90.91 vs. 45.45%, P = 0.004) [12].

3.2 Sleep quality and severity of mountain sickness

Poor sleep quality at high altitude was one of the most frequently reported symptoms in mountain sickness as assessed by the Lake Louise Symptom Questionnaire and the Qinghai Chronis Mountain Score [12], which are used to diagnose AMS [20] and evaluate severity of chronic mountain sickness(CMS) [21], respectively. This was confirmed by a study using PSQI and AIS which reports decreased subjective sleep quality at high altitude, especially reduced general sleep quality and prolonged sleep induction [22]. For workers rapidly transported from sea level to high altitude, there are no statistically significant differences in polysomnographic parameters between subjects with AMS and those without AMS [23].

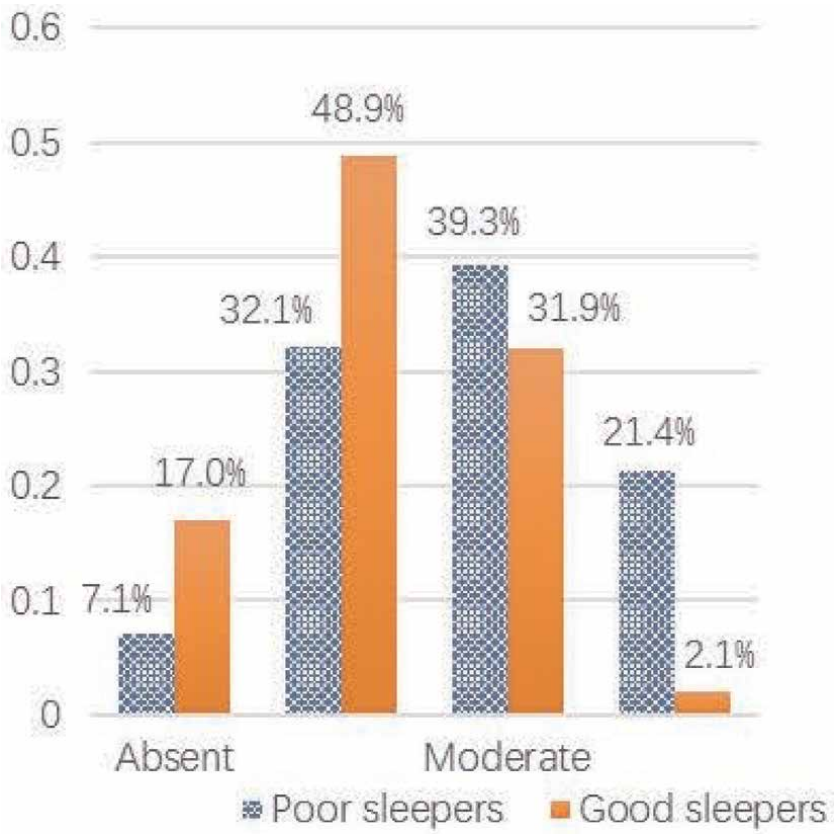

Figure 2.
Sleep quality comparison among different CMS severity at 3996 altitude. Modified from Kong et al. [4].

For people with CMS stationed at Tibet, the proportion of poor sleepers (defined as PSQI > 5) with severe CMS was 12.54-fold higher than that of good sleepers. See **Figure 2**, CMS severity comparison between "good" and "poor" sleepers at 3996 m altitude. Subjects with CMS had higher scores in each sleep component of the PSQI score, except the use of sleep medication. After adjusted for CMS score, age, and education, poor sleep quality was determined to be an independent predictor of impaired intelligence quotient [odds ratio (OR) 1.59, 95% CI 1.30–1.95] and short-term memory (OR 1.18, 95% CI 1.07–1.31). Therefore, for people with CMS, the poorer the sleep quality, the worse was the cognitive function [4].

4. Variation of sleep architecture at high altitude

Polysomnography (PSG) is the gold standard for investigating sleep architecture. However, the technical complexity and logistic demands had brought restriction on its utilization during altitude studies. Although there are several studies that suggest wrist actigraphy-derived data on total sleep time, sleep efficiency and sleep onset latency were similar to those of PSG [24]; actigraphy is insufficient in detecting sleep stage and breathing events.

Objective assessment of sleep architecture at altitude by electroencephalogram was first reported by Joern et al. in 1970 [25]. They found a near absence of stages 3 and 4 and a 50% reduction in rapid eye movement (REM) sleep and reported PB and arousals in one subject. A later study in 1975 confirmed a decrease in deeper sleep and increase in lighter sleep stages and brief arousals after ascending to an altitude of 4300 m at the Pikes Peak when compared to subjects at low altitude [26]. Subsequent studies have generally confirmed the shift at altitude toward lighter sleep stages, with a variable change in duration of REM sleep and increased awakenings associated with PB [27–30].

Alterations in objective sleep parameters have also been observed during acclimatization. A recent literature review on high-altitude sleep concludes that during rapid ascent to high altitude, there is a reduction in total sleep time, sleep efficiency, and deep sleep (stages 3 and 4) (in new nomenclature N3) and a significant increase in arousals and PB [31]. These variations are possibly high altitude dependent, and the effects tend to moderate with acclimatization [6]. Hypnograms of a partially acclimatized lowlander sleeping and a native Tibetan sleeping at high altitude are shown in **Figures 3** and **4**.

Although subjective sleep quality is impaired at high altitude, attempts to find a correlation between objective and subjective measures have failed to find a connection [24]. One study investigated 63 participants who completed a 3-hour flight from sea level to the South Pole (3200 m) and discovered no association between self-reported sleep quality and sleep efficiency, nocturnal oxygen saturation, and apnea/hypopnea index (AHI) obtained from PSG [32]. When assessed by LL score, there was no significant correlation of the subjective sleep measurement compared to sleep efficiency derived from PSG and actigraphy [24]. Another study investigated 165 young male soldiers stationed in Tibet Plateau (3800 m) for at least 3 months. In a multiple regression model adjusted for age, service time, body mass index, Epworth Sleepiness Scale, anxiety, and depression, sleep onset latency (b = 0.08, 95% CI: 0.01–0.15) and NREM latency (b = 0.011, 95% CI: 0.001–0.02) obtained from PSG were slightly positively correlated with global PSQI, while mean nocturnal SpO_2 (b = −0.79, 95% CI: −1.35 to −0.23) and time in stage 3 + 4 sleep (b = −0.014, 95% CI: −0.001 to −0.028) was slightly negatively associated with global PSQI [12].

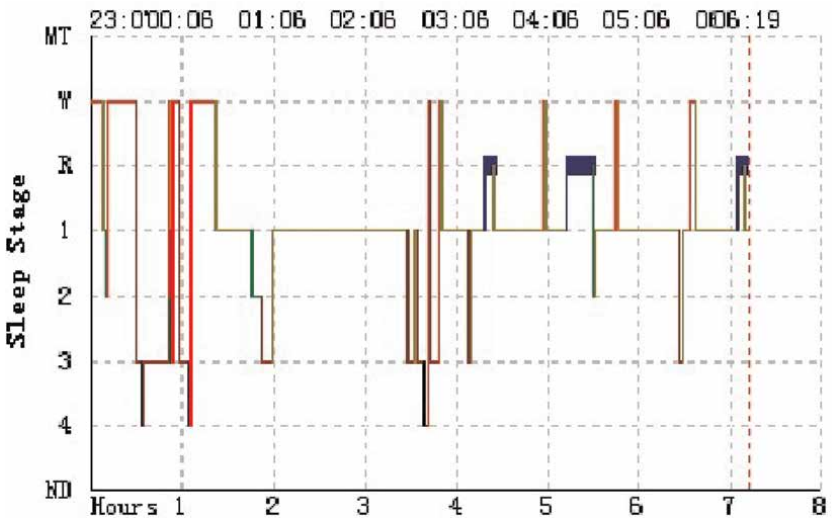

Figure 3.
Hypnogram of a 27-year-old young man sleeping acclimatized for 11 months at altitude of 3800 m. Frequent awake, less proportion of stage 4 and REM sleep might be observed.

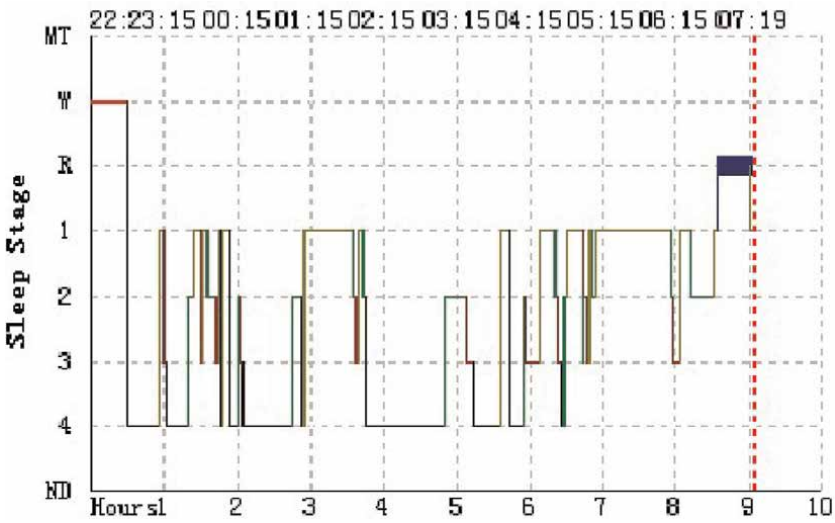

Figure 4.
Hypnogram of a 25-year-old native Tibetan sleeping at altitude of 3800 m. There is sufficient time in stage 4 sleep and scarce REM sleep.

5. Differences in sleep architecture between lowlanders and native highlanders at high altitude

5.1 Sleep patterns of high-altitude natives

Tibetans and Andeans are the native populations to the Tibetan and Andean Plateaus descending from colonizers. Both populations have been exposed to the hypoxic environmental stress of lifelong exposure to high altitude. But native Tibetans and Andean highlanders exhibit different ways of adaptation to chronic hypoxia [33]. Andean highlanders have blunted hypoxia ventilatory response

compared to Tibetans which is thought to be acquired and developed in adolescence [34]. Native Tibetans were reported to have higher maximal oxygen uptake, greater ventilation, and brisker hypoxic ventilatory responses to adapt to the hypoxic environment at high altitude and, therefore, to have a better-quality sleep than Han lowlanders [35] which may largely be attributed to genetic adaptations [36].

Few studies had compared sleep architecture between high-altitude dwellers and non-native highlanders. An elder study investigated the Sherpa highlanders dwelling above 3500 m. The Sherpas exhibited few PB with apnea due to low ventilatory sensitivity to hypoxia at 5300 m altitude [37]. A later study reported the sleep pattern of Peruvian Andeans situated at 4330 m altitude. Sleep architecture is closely resembling to normal of people at sea level with significant amount of NREM sleep and unimpaired REM sleep [38]. Contrary to the previous reports, a recent study surveyed sleep architecture of Peruvian highlanders living in Puno at 3825 m. The highlanders had a longer time in total sleep time and increased wake-after-sleep onset and arousal index but decreased sleep efficiency, which suggest greater disturbances in sleep in highlanders compared with lowlanders [39].

5.2 Sleep architecture in partially acclimatized lowlanders

As we mentioned above, acclimatization would help lowlanders to relieve sleep disturbance after ascending to high altitude. This could be supported by an earlier study which claimed over 3 days of acclimatization over 4559 m resulted in a partial recovery of sleep structure with increases in slow wave sleep and REM sleep and a reduction in the arousal index [40].

But little is known whether prolonged hypoxia may help to improve sleep architecture at high altitude. Animal studies showed that there was a 50% reduction in the proportion of slow wave sleep and loss of REM sleep when rats were chronically exposed to hypoxia environment simulating an altitude of 5000 m [41, 42]. A clinical study conducted in Shangri-La, which has an altitude of 3800 m, surveyed the differences in sleep architecture between native Tibetans' and Han lowlanders' stations for at least 3 months. After adjusted for the length of stay at altitude, significant differences in lower mean nocturnal SpO_2 and shorter time in NREM sleep were determined in acclimatized lowlanders than the native Tibetans [12]. **Figure 5** indicates a decreased nocturnal artery oxygen of a 3-month acclimatized lowlander. So, it is reasonable to conclude that the effect of prolonged acclimatization to hypoxia is limited in relieving hypoxemia and improving deep sleep which might be an explanation for the impaired cognition brought about by poor sleep.

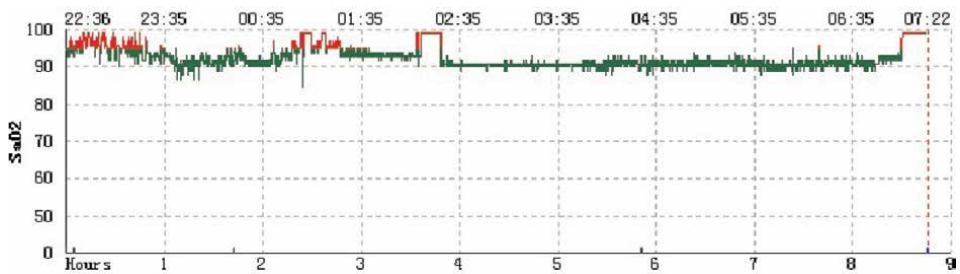

Figure 5.
Decreasing in artery oxygen during sleep of a 24-year lowlander acclimatized for 3 months at 3800 altitude. The lowest SaO_2 is 83% and the mean SaO_2 is 92%.

6. Is sleep disorder an altitude-related illness?

Studies on sleep disorder at high altitude from the above reviewed scientific literature confirm the assumption that altitude-related illness including AMS and HAPE may deteriorate sleep quality either directly or indirectly through complaints of headache, hard breathing, cough, etc. It is widely accepted that HAPE usually develops within 2–4 days after quickly ascending to high altitude, but sleep in the first night at altitude may have been affected. Both susceptible HAPE subjects and healthy mountaineers without HAPE revealed a major reduction in sleep efficiency and in NREM stage 3 and 4 sleep (in new nomenclature N3) in the first night after the ascent to 4559 m within 1 day [43]. The deteriorated ventilation and intermittent hypoxia associated with PB in the first 1–2 nights at high altitude with the associated elevation of pulmonary artery pressure may promote the subsequent development of HAPE in susceptible subjects. Thus, the occurrence of sleep disorder is prior to and/or independent of HAPE but may worsen due to HAPE.

Literature reports also provide empirical evidence that sleep disturbance was discordant from other AMS symptoms and absent in 40% of cases with severe headache, long considered a symptom of AMS. Since sleep disorder correlated poorly with other symptoms of AMS, the sleep component had been removed from the 2018 Lake Louise Acute Mountain Sickness Score [44].

Therefore, it is conceivable that sleep disorder should be viewed as an independent altitude-related illness rather than a symptom of AMS despite the fact that it may overlap other mountain sicknesses. In accordance with the nomenclature of other high-altitude diseases [e.g., high altitude cerebral edema (HACE), high altitude pulmonary edema (HAPE), etc.], high-altitude sleep disorder (HASD) might be an appropriate name.

7. Treatment of HASD

Hypoxemia is the main reason and one of the primary independent contributors to poor sleep quality at high altitudes [12]. In theory, correction of hypoxemia by supplemental oxygen or pharmacological suppression of ventilation may have the potential in treating sleep disorder at high altitude.

7.1 Supplemental oxygen

A case report tested the treatment effect of a nasal demand oxygen delivery device on hypoxemia during sleep at high altitude in a 46-year-old male healthy participant at an altitude of 4600 and 5700 m [45]. The participant received a volume of oxygen delivery dose for 0, 16.7, 33.3, and 50 ml/s at random per pulse for every 2 h during sleep period. Results of the study indicated an increase in arterial blood oxygen saturation and decreases in tidal volume and AHI.

Another controlled trial employed a noninvasive ventilation mode named adaptive servo ventilation (ASV) to stabilize periodic breathing due to hypobaric hypoxemia at an altitude of 3800 m, but it failed to affirm its efficacy in controlling central sleep apnea during sleep. However, in their controlled group, supplemental oxygen improved oxygen desaturation index and oxygen saturation, whereas it reduced the arousal index and NREM stage 1 sleep. But neither ASV nor supplemental oxygen could improve subjective quality as measured by the Stanford Sleep Questionnaire and LL score [46].

In summary, based on current limited studies, supplemental oxygen does improve arterial blood oxygen saturation but could not result to a better sleep quality.

7.2 Diet therapy

Dietary nitrate (NO^{3-}), which is found in beetroot and other vegetables, and inorganic NO^{3-} salts have been shown to have vasodilatory properties [47] and also to reduce oxygen uptake during exercise [48], suggesting NO^{3-} supplementation might play a physiological role during sleep at high altitude. A single-blind placebo-controlled trial examined the effects of dietary NO^{3-} supplementation on the degree of sleep-related hypoxemia in healthy subjects at an altitude from 3700 to 4900 m. Each subject received two 70 ml shots of either beetroot juice (~5.0 mmol NO^{3-} per shot) or placebo (~0.003 mmol NO^{3-} per shot) over two consecutive nights at altitude. Results of the study favored dietary nitrate in increasing fluctuations in arterial O_2 saturation during sleep at altitude in native lowlanders, but it does not improve AHI or oxygenation [49].

7.3 Pharmacological agents

Previous reports suggested that only a few medications may be helpful at high altitudes [50, 51], including theophylline, acetazolamide, zolpidem, zaleplon, temazepam, and integripetal rhodiola herb, a traditional Chinese herb. However, there are often several limitations on pharmacological selection at high altitudes in clinical practice, as current sleeping medications prescribed for sleep disturbances at sea level are not suggested to be used at altitude. For example, it is widely accepted that benzodiazepines (BZDs) may cause hypoventilation, triggering respiratory abnormalities during sleep [52–54]. Therefore, an ideal choice for medication use at high altitude should neither deteriorate ventilation and oxygen saturation nor affect sleep architecture.

7.3.1 Acetazolamide

Acetazolamide is considered to increase ventilation and oxygenation, effectively reducing PB by approximately 50% [55]. A meta-analysis of randomized controlled trials determined that acetazolamide improves sleep apnea at high altitude by decreasing AHI and percentage of PB time and increasing nocturnal oxygenation. Results from clinic trials also suggested that a 250 mg daily dose may be as effective as higher daily doses for healthy trekkers [56].

7.3.2 Non-benzodiazepines

The efficacy and safety of zolpidem and zaleplon in treating sleep disturbances at high altitude had been confirmed by several well-designed clinic trials [57–60]. A recent meta-analysis of randomized placebo-controlled trials revealed that zaleplon and zolpidem improved the total sleep time, sleep efficiency, and stage 4 sleep duration, whereas they decreased the wake-after-sleep onset without impairing ventilation [61] (data are shown in **Figure 6**).

There was no significant difference in ventilation as measured by SpO_2 and PB between participants administered with zaleplon or zolpidem and placebo [58–60]. Furthermore, participants who were administered with zaleplon or zolpidem expressed a significant improvement in the subjective sleep quality, which was

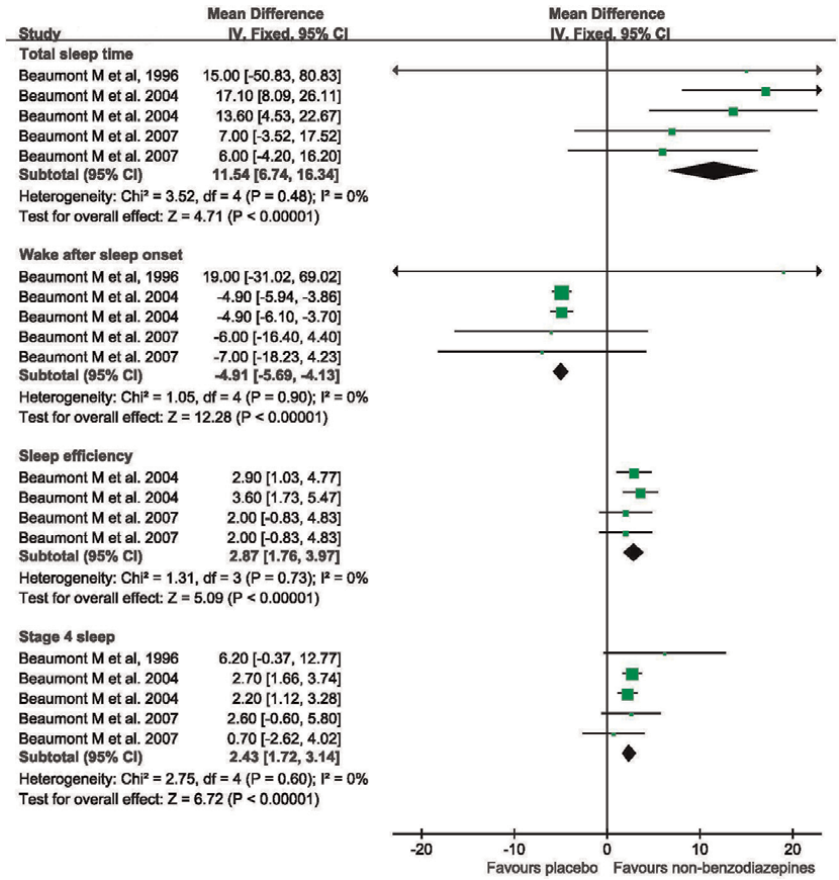

Figure 6.
Summary of non-benzodiazepines in improving sleep architecture at high altitude. Modified from Kong et al. [61].

measured by sleep log question [59, 60] and PSQI (4.15 ± 2.76 in zolpidem group vs. 6.58 ± 3.98 in placebo group, P = 0.047) [60].

7.3.3 Benzodiazepines

Benzodiazepine use in this environment is controversial. Early studies showed that 1 mg of oral loprazolam did not worsen either slow wave sleep depression or apnea and allowed normal sleep reappearance after acclimatization [28, 62]. Later, a randomized, double-blind, placebo-controlled trial conducted at 3000 m altitude validated PaO_2 decreasing and $PaCO_2$ increasing significantly 1 hour after 5 mg of oral diazepam [63], which suggests that it may cause hypoventilation.

On the contrary, temazepam, a short-acting benzodiazepine, was recommended to be safely used by the International Climbing and Mountaineering Federation MedCom Consensus Guide [51]. However, the effect of temazepam on the objective sleep parameters was inconsistent. Nicholson et al. [64] reported that temazepam significantly shortened the mean sleep onset latency and increased the amount of the REM sleep, whereas Nickol et al. [65] reported no differences in the actigraphy-derived sleep parameters. Results on oxygen saturation and PB from the aforementioned studies were also inconsistent. When compared to the placebo, temazepam showed no significant effect on mean oxygen saturation, yet PB significantly decreased [66]. Although Nickol et al. [65] reported that temazepam could decrease

median oxygen saturation, it did not significantly reduce PB during sleep. Because of the inconsistencies in the reported variables, no confirming conclusions can be drawn from available evidence.

To sum up, the use of benzodiazepines should be discouraged at high altitude due to the nocturnal hypoventilation nature of these agents. The efficacy and safety of temazepam need further confirmation by well-designed placebo-controlled trials.

7.3.4 Others

Additional drugs that may be helpful reported by case series include theophylline and the integripetal rhodiola herb, which is a widely used traditional Chinese herb in Tibetan areas. However, strong clinical evidence from randomized controlled trials supporting the effectiveness and safety of these agents has not been demonstrated.

7.4 Recommendations

Evidence from current available studies support the routing use of supplemental oxygen during sleep to increase arterial blood oxygen saturation. Acute dietary NO^{3-} supplementation reduces flow limitation and induces more pronounced SaO_2 desaturations during sleep at high altitude. Acetazolamide at 250 mg daily dose is effective in reducing sleep apnea, decreasing AHI and PB, and increasing nocturnal oxygenation. Both zaleplon and zolpidem improved the objective sleep architecture without impairing ventilation.

8. Conclusions

Our understanding on sleep disorder at high altitude is still limited. Mountain tourists commonly complain about subjective sleep disturbances with difficulty in onset of sleep and frequent awakenings in the first few nights at altitude. But those subjective sensations of poor sleep neither are associated with severity of mountain sickness nor tend to disappear after long exposure to high altitude. And consequently, cognitive function was impaired.

There is no reliable evidence that support the consistency between self-report sleep quality and sleep parameters obtained from PSG. The most frequently reported changes in sleep architecture at high altitude are detected by PSG including a decrease in NREM sleep and occurrence of PB. Different patterns of adoption to hypoxic environment exist among native highlanders. For lowlanders ascending to high altitude, acclimatization would be beneficial in relieving hypoxemia and improving deep sleep; however, PB would not be largely relieved after acclimatization.

The occurrence of HASD is prior to most altitude-related diseases and would last for a longer time. We strongly suggest future study to consider it as an independent high-altitude illness as it had been removed from the diagnosing and managing of AMS by the International Society of Mountain Medicine World Congress Committee.

The treatment principle of HASD should not deteriorate nocturnal ventilation and SaO_2 or affect sleep architecture. The following evidence-based choices are recommended. Effective treatments for altitude-related nocturnal hypoxemia include dietary NO^{3-} supplementation before sleep and supplemental oxygen during sleep. Medication for respiratory disturbance is 250 mg daily dose of oral acetazolamide, which is beneficial in relieving sleep apnea, decreasing AHI and PB, and promoting nocturnal oxygenation. Both zaleplon and zolpidem are optional agents in improving the objective sleep architecture and subjective sleep quality without impairing ventilation.

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Section 2

Obstructive Sleep Apnea

Chapter 8

Diagnosis

Murat Kayabekir

Abstract

Obstructive sleep apnea (OSA) is often confused with the clinical symptoms of other adult/pediatric medical conditions and neurological disorders. Since OSA affects all systems in the body, it is important to establish a correct diagnosis. The first step in the evaluation of a patient with a sleep disorder is to identify the primary symptom. A detailed history of the sleep and wakefulness cycles constitutes the second step. This is followed by the medical history of the patient; a list of previously used medications; family history; detailed information about school, work, family, and social life; and a physical exam of bodily systems. Relevant laboratory tests are performed for differential diagnosis. Polysomnography (PSG) is a golden standard diagnostic method that records electrophysiological signals used for sleep physiology and diseases. PSG is an indispensable method in the diagnosis of OSA.

Keywords: anamnesis, symptoms, physical examination, electrophysiology, PSG, sleep breathing disorders, snoring and OSA

1. Introduction

Although OSA is described as an upper airway disorder occurring during sleep; it should be regarded as a clinical syndrome by taking into consideration its adverse effects on bodily systems. In the presence of symptoms like snoring, sleepiness during daytime, not being able to lose weight, weight increase, apnea observed by close family members, arousal with a feeling of suffocation during the night, profuse sweating of the chest and the neck, nocturnal arrhythmias, nocturia, enuresis, sexual impotence, depression, anxiety, forgetfulness, attention deficit, difficulty in concentration, learning problems, personality changes, deterioration of decision-making ability, morning headaches, dry mouth in the morning, bruxism, gastric reflux symptoms, sleeplessness, abnormal motor activity during sleep, and somnambulance, we should keep OSA in mind. However, all these symptoms guide patients to apply to different medical disciplines, causing confusions of diagnosis and eventually leading to delays in correct diagnoses. When patients have OSA, they can go to "neurology, ear nose throat, dentistry, psychiatry, pulmonology, cardiology, pediatric neurology, pediatric cardiology, internal medicine, neurosurgery, and endocrinology" departments. Therefore, we can say that OSA is a multidisciplinary disease. When we consider the increased workload burden in these disciplines, we appreciate that there can be further delays in establishing an OSA diagnosis in the process. So, in hospitals the diagnosis of sleep physiology and diseases should be made by "clinical physiology, electrophysiology, neurophysiology, and sleep laboratories". Through these laboratories, all medical disciplines should be informed with reports for the correct diagnosis and treatment of these patients, and they should be followed up accordingly.

Despite the advances in the field of sleep medicine, neither the societies nor the physicians are sufficiently informed about sleep and sleep disorders. Among sleep disorders, OSA is very frequent in the population, and it leads to significant consequences. It can adversely influence the school and job success of an individual, his/her social life, marriage, and other relationships while resulting in traffic and occupational accidents. OSA can hinder the cognitive functioning of an individual while increasing the risk for psychiatric and other system-related diseases. Sleep apnea syndrome can play a role in the etiology of severe diseases, namely, hypertension, myocardial infarction, heart failure, stroke, and diabetes. Sleep deprivation brought forward by OSA can increase the number of seizure episodes in epilepsy patients.

This insidious disease has been affecting individuals and societies for many years; it can show itself during sleep, and its effects can deteriorate the performance of the individual during daytime. Complaints of snoring and feeling of suffocation that appear during sleep are mainly identified by the spouse and the close family members of the individual. This disease hinders respiration during sleep and influences all bodily systems and mainly the brain during nighttime. Thus, such patients need to be examined at a sleep and electrophysiology lab by obtaining electrophysiological signal recordings (EEG, EMG, ECG, etc.) throughout the night. This method is called PSG; it establishes the definitive diagnosis for OSA and discriminates it from other sleep disorders and general medical conditions.

Currently, PSG and snoring sound analysis are guiding the diagnosis and treatment of OSA while creating an innovative working field for engineering and medicine.

2. Diagnosis

2.1 Approach for an OSA patient and clinical signs

OSA patients generally experience their symptoms during nighttime, and first of all they need to be made aware as they are not aware of them. OSA has many symptoms; the major ones are snoring, apnea as observed by close family members, and excessive sleepiness during daytime. The presence of nocturnal symptoms is more valuable than daytime symptoms when establishing the diagnosis [1]. These patients are generally obese, and they have short and thick necks and narrow upper airways. This type of a body composition is not the rule as the disorder can even be seen in children.

Snoring is the most frequently seen symptom in the presence of sleep breathing disorders. Snoring is a medical and social complaint affecting both sleep and general well-being of children and their parents. When snoring is accompanied by air hunger, feeling of suffocation, or waking up, OSA should be considered. Snoring would not be sufficient by itself for diagnosis as OSA can also happen in the absence of significant snoring. Noisy breathing and increase in the respiratory effort in children during sleep can be the most significant sign. It is typical to have snoring disrupted by frequently repeating apnea in OSA patients. The patients deny snoring. Thus, information needs to be obtained from their partners or close family members. Despite intermissions in snoring and stopping of air exchange in the mouth and nose, abdomen and chest movements continue paradoxically; this results in a panic in people who are witnesses of this situation. Apnea usually ends with a deep breath. At the end of apnea, there can be a loud snoring, a sound of suffocation, coughing, or short arousals [1–6]. Sleep disruption caused by repetitive partial or total airway obstruction in OSA can result in sleepiness during

daytime. This situation is correlated with the severity of the disease; mild cases describe sleepiness only during sedentary circumstances, while in advanced cases, sleepiness can even be observed while eating food, talking, or driving. Patients turn and move in bed, and they describe sweating on the upper part of the chest including the neck [2–5, 7]. OSA patients need to breath from the mouth frequently; they talk about complaints like dryness of the mouth or drooling. Neurophysiological changes are weakening of memory and deteriorations in decision-making ability, attention, and concentration, personality changes include aggressiveness or depression, and decreased libido and impotence can as well be seen [1, 8]. There can be night and morning headaches due to decreases in oxygen concentration; these are blunt and widespread in nature. Increases in weight gain and inability to lose weight can be observed, and negative pressure within the chest and abdominal cavity increases because of obstruction resulting in esophageal reflux; patients usually wake up with a chest pain in the form of burning [1, 9]. These symptoms can make one consider several diseases like depression; hypothyroidism; stress; migraine; febrile diseases; metabolic syndrome; chest pain during nighttime due to coronary spasm; arrhythmias; iron deficiency anemia; Cushing syndrome; endocrine and metabolic diseases; heart, kidney, and liver failures; and enuresis nocturia; therefore, differential diagnosis needs to be made.

2.2 Physical examination findings in OSA

There is not any specific physical examination finding diagnostic for OSA. By approaching from a wider perspective, evaluation should be made for several disciplines (**Figure 1**). OSA is related to multiple anatomic risk factors. The most important one is central-type obesity with increased body mass index and increased neck circumference. On the other hand, many patients with OSA are not obese, yet they can demonstrate decreased oropharyngeal air space, retrognathia or

Figure 1.
The physician speaks with husband and wife. And he learns by the medical history of the patient, a list of previously used medications, family history, and detailed information about school, work, family, and social life. And he makes a physical exam of bodily systems.

micrognathia. Obesity mechanically obstructs pharyngeal soft tissues and results in pharyngeal compression. Also decreased lung volume through CNS-acting signaling proteins (adipokines) may alter airway neuromuscular control [10, 11]. Individuals with OSA have severe obesity due to sleep deprivation, hypersomnia, and altered metabolism. OSA is associated with endocrinopathies like hypothyroidism and acromegaly. Hypothyroidism is a known cause for secondary OSA. Myopathy of oropharyngeal airways, edema, and obesity lead to upper airway obstruction and collapse in these patients. Acromegaly is caused by excessive levels of growth hormones; there is enlargement of craniofacial bones, enlargement of the tongue (macroglossia), and thickening and widening of the laryngeal region. All these factors can contribute to the obstruction of the upper respiratory airways. In addition to acromegaly and hypothyroidism, goiter which is associated with a euthyroid state can as well contribute to OSA. Among factors contributing to the narrowing of upper airways, we can list Down syndrome and storage diseases like mucopolysaccharidosis and amyloidosis (deposition) [12–16].

2.2.1 Craniofacial factors

Cephalometric measurements demonstrate that when compared with controls, individuals with OSA have important changes in the size and position of soft palate and uvula, in the volume and position of the tongue, the position of the hyoid bone, and mandibulomaxillary protrusion. Mandibular retrognathia and micrognathia cause the tongue to stay at a higher position; these can be diagnosed during the examination by observing the patient from the side view. Racial differences in cephalometric features possibly play a role in the development of risks for OSA in the absence of obesity [17, 18].

2.2.2 Nasal factors

Examination of nasal airways should focus on the anatomical abnormalities that might contribute to nasal obstruction. These can be of congenital, traumatic, infectious, or neoplastic in nature [19].

2.2.3 Neck circumference

Increased neck circumference is an important risk factor for OSA. Patients with a neck circumference of more than 48 cm (19.2 inches) have a 20 fold increased risk for OSA [18].

2.2.4 Pharynx examination

There are two well-defined classifications to identify the relationship of the tongue with the pharynx. The Mallampati classification is a method first used by anesthesiology specialists to foresee difficult tracheal intubations. Friedman classification describes prognostic indicators for a successful surgery for sleep disorders by combining the position of the palate with the size of the tonsils [20, 21]. The Mallampati classification is as follows:

Class 1: Soft palate, fauces, uvula, and posterior and anterior pillars are visible.
Class 2: Soft palate, fauces, and uvula are visible.
Class 3: Soft palate, fauces, and only the base of uvula are visible.
Class 4: Soft palate is not visible.

2.2.5 Examination of the tonsils

Enlarged tonsils and adenoids are the primary causes of upper airway obstruction and sleep apnea in children, only a small portion of the adults can have an enlargement of these structures leading to obstruction of the airways. Adenoids cannot be visualized during a routine physical examination or the examination of tonsils, and a tongue depressor might be necessary. The size of the tonsils can be measured on a scale of 1–4 [22].

2.2.6 Neurological examination

During physical examination, the characteristics of the apparent neuromuscular disease can indicate OSA and hypoventilation. For example, progressive muscular atrophy and hand or tongue fasciculations can indicate amyotrophic lateral sclerosis. In amyotrophic lateral sclerosis, phrenic nerve dysfunction is common; during rapid eye movement sleep (REM) it leads to diaphragmatic paralysis due to significant hypoventilation. Furthermore, coexisting OSA can reveal itself during amyotrophic lateral sclerosis with bulbar involvement. In poliomyelitis, there is weakness of thoracoabdominal muscles and accessory muscles of respiration; this can frequently be accompanied with kyphoscoliosis. Postpolio syndrome demonstrated itself with muscular dystrophies; myasthenia gravis and metabolic myopathies exhibit themselves with weaknesses of chest wall muscles and the diaphragm. Myasthenia gravis can as well involve facial structures resulting in OSA. In myotonic dystrophy or muscular dystrophy, there can be craniofacial abnormalities; macroglossia can also be seen (e.g., in Duchenne muscular dystrophy). Lastly, obesity (e.g., steroid use or inactivity) and being overweight can contribute to sleep apnea during the course of a neuromuscular disease [23, 24].

2.2.7 Cardiopulmonary examination

Peripheral edema is a frequent finding in patients with obesity hypoventilation syndrome (as a manifestation of cor pulmonale) as well as in certain patients with obstructive apnea that have left ventricular heart failure. OSA can coexist with chronic obstructive pulmonary disease and asthma. Hypertension is associated with OSA. If a patient with OSA has chronic pulmonary disease, pulmonary hypertension can also be seen. Findings of polycythemia, arrhythmia, cyanosis, right heart failure, and chronic cor pulmonale can be identified [19, 25].

2.3 OSA diagnostic methods

2.3.1 Radiological diagnosis

Cephalometry: It is the standardized lateral radiographic imaging of the head and neck with which bone and soft tissue boundaries are evaluated in individuals with OSA. It is useful in diagnosing frequently encountered craniofacial and upper airway soft tissue anatomy-related anomalies like the hyoid, mandibular, tongue, soft palate, and facial anomalies. Maxillo-mandibular retrognathism has in patients with OSA and it has been accepted as an indicator of maxillary prognathism. Horizontal and vertical length of the mandibula affects the oral floor and the position of the tongue. The length of the horizontal ramus of the mandibula shortens in individuals with snoring and apnea, whereas vertical ramus only shortens in people who snore. Total facial height is found to have increased in OSA patients compared

to the normal population. Hyoid bone is the point where the dilator muscles of the upper airways attach; it is shown to have a lower location in OSA patients [26–28]. The distance between the root of the tongue and posterior pharyngeal wall (posterior airway space, PAS) is shortened in OSA patients. When PAS is measured by cephalometry in OSA patients, it is shown to have significantly narrowed in nasopharyngeal and oropharyngeal regions, gets larger towards the hypopharyngeal region, and gets within normal limits at the level of epiglottis. Computerized tomography (CT) is an imaging technique that provides detailed information about the size, cross-sectional area, and neighboring tissues of the upper respiratory system thanks to its superior bone and soft tissue resolution. It is not routinely used. Magnetic resonance (MR) is a noninvasive technique providing excellent views of all soft tissues of the upper respiratory system including the adipose tissues, and the images are obtained in the supine position by covering axial, sagittal, and coronal planes. It is superior to CT when evaluating PAS which is important for surgical treatment. Its biggest advantage is not having radiological exposure. MRI examinations of upper respiratory systems of individuals with OSA have been compared and significant increased have been shown in the adipose tissues of the supportive wall structures of soft palate, tongue and the pharynx. In another study, the narrowing of the upper airways was not due to adipose pads; it was reported to take place due to significant thickening of the lateral pharyngeal wall. Fluoroscopy is an imaging technique allowing for a dynamic evaluation of the upper airways when the patient is awake of sleeping. Tongue and pharyngeal regions are covered with barium, and for better visualization of the hypopharynx, the head is kept at an angle of 30 degrees. Its disadvantages are radiation exposure, not being able to obtain cross-sectional images, and not being able to perform bone structure measurements [28–30]. Acoustic reflection relies on the reflection of sound waves sent onto the upper respiratory tract, it does not utilize radiation, and it is a noninvasive imaging technique. In a study employing this technique, cross-sectional areas of the pharynx and glottis were found to have significantly reduced demonstrating a correlation between the degree of OSA and the horizontal cross-sectional area of the pharynx.

2.3.2 Endoscopic diagnosis

Nasopharyngolaryngoscopy is a diagnostic technique spanning the upper airways from the nose to the glottis to analyze the dynamic changes of the airways and to identify the level at which airways collapse. Fiberoptic nasopharyngoscopy only shows the open-closed status of the airways; it cannot measure and interpret the surrounding soft tissue areas. By having the patient perform Müller maneuver, the degree and the level of the collapse is diagnosed [29, 30].

2.3.3 Polysomnography (PSG)

The process of recording sleep with electrophysiological signals is called "polysomnography," ("PSG"). Sleep recordings that appear on computer screen or paper are called "polysomnogram." Electrophysiological signals recorded throughout one night during sleep and wakefulness are as follows: "Electroencephalogram (EEG), electromyogram (EMG; chin, arms and legs), electrooculogram (EOG), electrocardiogram (ECG), snoring, and oronasal air flow (L/s), chest and abdomen movements (respiratory effort recordings), oxygen saturation, and body position and real time-video-image recordings" [31].

PSG is a gold standard technique for OSA diagnosis. For this test, patients are prepared by sleep technicians (**Figure 2**).

Figure 2.
Patient is prepared for PSG by the sleep technician. She is wearing an airflow cannula which is very important for the diagnosis of OSA.

When defining respiratory events in PSG, we need to perform "scoring of sleep and scoring of respiratory events."

Scoring of sleep is done through staging of sleep. For staging sleep, polysomnography recordings are separated into 30 s intervals (epoch); each epoch is scored with a sleep stage. Sleep stages are as follows: "Stage N1, Stage N2, Stage N3, Stage R, and Stage W (wakefulness)." Every 30 s interval needs to be staged with one of these stages. Three main physiological signals are used when staging sleep: "EEG, EMG, and EOG." For each epoch, these three parameters are assessed, and a sleep stage name is assigned to each 30 s interval. Sleep staging is based on certain principles [31].

Electrophysiological signal recordings that are required for the interpretation of respiratory events in PSG are as follows: "oxygen saturation, nasal/oronasal air flow (nasal cannula, thermistor), thoracic respiratory effort, abdominal respiratory effort, EEG recordings (absolutely needed to identify arousal), body position, tracheal microphone, ECG, and leg EMG recordings." Measurement of thoracic and abdominal movements is the most frequently used technique in sleep laboratories in the identification of respiratory effort [31].

The American Academy of Sleep Medicine (AASM) has published the rules to be used when reporting sleep and sleep-associated events as well as respiratory event scoring based on [31, 32].

Apnea is the cessation of air flow in the mouth and nose for l0 seconds of longer. There are three types of apnea. (i) Obstructive apnea consists of the absence of air flow despite respiratory effort (**Figure 3**). (ii) Central apnea consists of the absence of airflow in the absence of respiratory effort (**Figure 4**). (iii) Mixed apnea consists of the absence of airflow in the absence of respiratory effort, followed by increase in respiratory effort despite the absence of airflow (**Figure 5**). Nowadays, mixed apneas are scored as obstructive apnea.

Hypopnea is a 50% reduction in air flow (currently this value is reduced down to 30%) for 10 s or longer together with a 3% decrease in oxygen saturation and arousal (**Figure 6**).

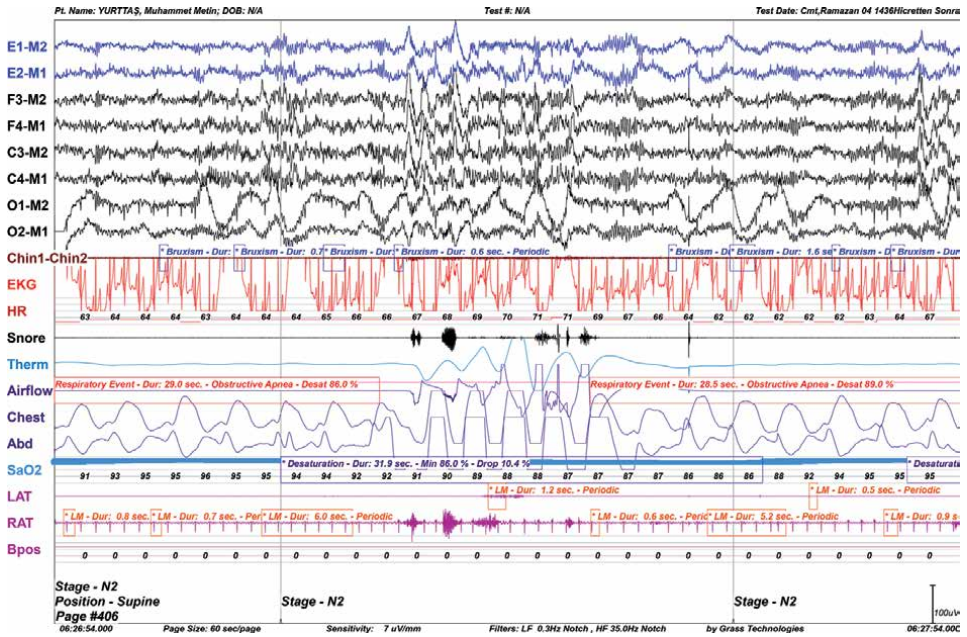

Figure 3.
Polysomnographic record image of obstructive apnea.

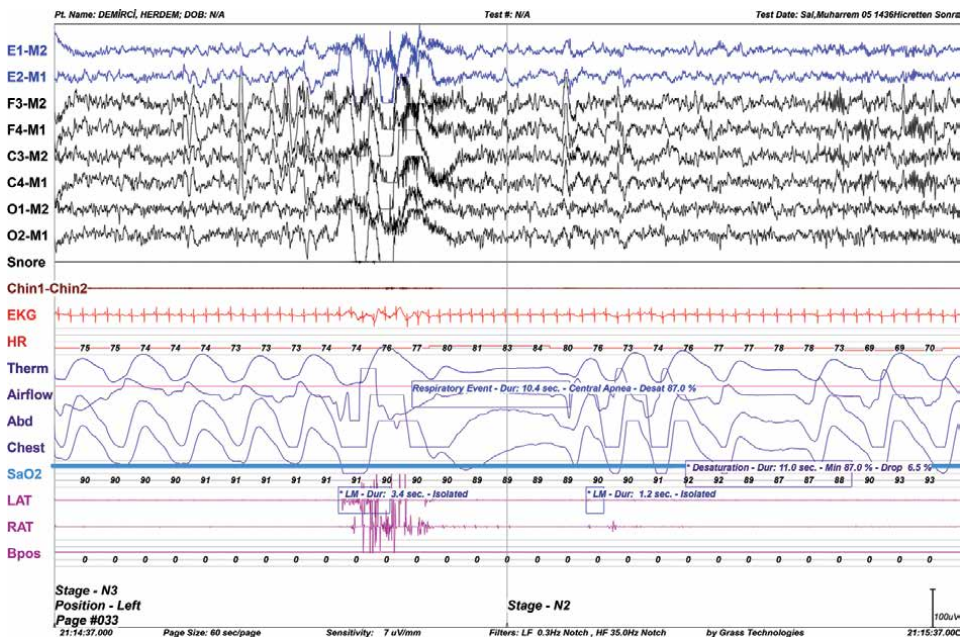

Figure 4.
Polysomnographic record image of central apnea.

Arousal is shifting to a more superficial level of sleep and wakefulness for short periods of time.

Respiratory effort-related arousals (RERA) are seen in the absence of cessation or reduction of air flow during the respiratory effort.

Apnea index (AI) defines the number of apneas that are seen during 1 h when sleeping.

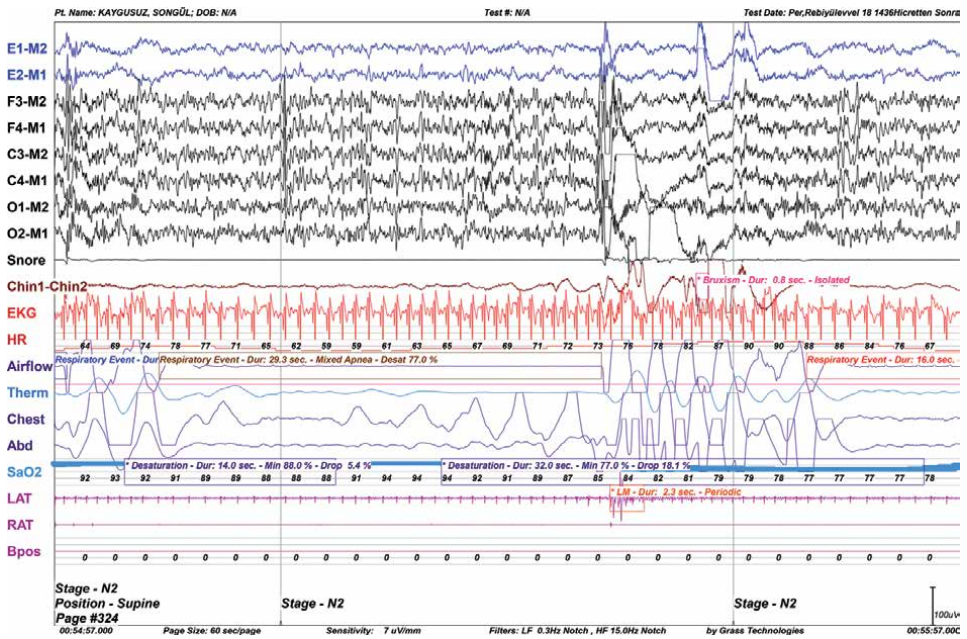

Figure 5.
Polysomnographic record image of mixed apnea.

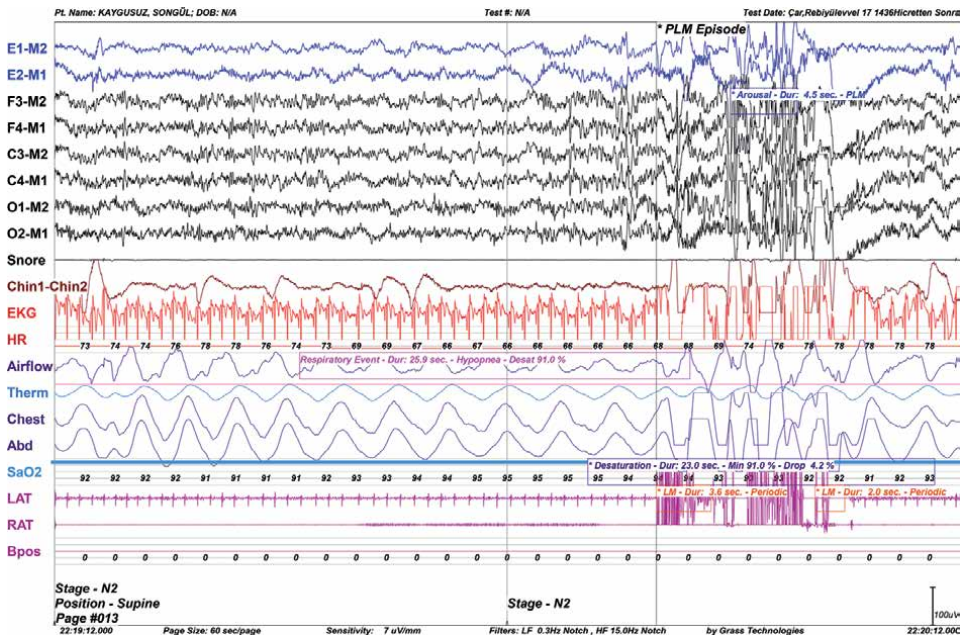

Figure 6.
Polysomnographic record image of hypopnea.

Apnea-hypopnea index (AHI) is calculated by the total number of apnea and hypopneas divided by the time spent while sleeping. When RERA is added to this number, the name of the index is respiratory disturbance index (RDI).

Characteristic PSG findings for OSA are as follows: (i) Increases in the duration of superficial sleep and decreases in the duration of deep sleep and REM. (ii) Apneas and hypopneas repeat frequently. (iii) Oxygen desaturation repeats frequently. (iv)

REM sleep can increase the frequency and duration of apneas and the degree and the duration of oxygen desaturation. Sleeping in supine position contributes to this increase. (v) It is typical to see paradoxical thoracic and abdominal movements during apnea. (vi) During apnea, the heart rate possibly slows down, and it increases in the period following the apnea; arrhythmias can be observed. (vii) In respiratory sound recordings, an irregular loud snoring that is interrupted by apneas is heard.

The degree of the disease is identified by AHI value calculated on the basis of PSG assessment: "AHI < 5, normal; AHI = 5–15, mild OSA; AHI = 16–30, moderate OSA; AHI > 30, severe OSA" [33].

2.3.4 Auxiliary diagnostic techniques

Several auxiliary tests are required to support the diagnosis, to identify the complications, and to aid in the differential diagnosis in OSA patients. Blood tests are helpful in identifying the diseases that might lead to OSA and their complications. Hemograms can play a role in idiopathic polycythemia when establishing a preliminary diagnosis of OSA. Thyroid hormone profile (T3, T4, TSH) is a routine test to discriminate between OSA and hypothyroidism [34, 35]. Lung X-rays can help identify certain lung diseases and their complications that accompany OSAS. OSA-related respiratory function tests have a ratio of greater than 1 for "forced expiratory flow 50% /forced inspiratory flow 50%" and saw tooth pattern in flow-volume curve. Individuals with OSA have normal arterial blood gas levels during daytime; in cases having chronic hypercapnia during daytime while they are awake, coexistence of chronic obstructive pulmonary diseases or diseases leading to alveolar hypoventilation like neuromuscular insufficiency should be considered [36]. In an obese patient who is hyper-somnolent and who snores, a diagnosis of OSA should be eliminated. In an individual having findings of right heart failure and pulmonary hypertension on echocardiogram, if these findings cannot be explained, possible coexistence of OSA should be considered [37, 38]. In OSA, sleep is interrupted due to apnea episodes frequently recurring during the night, and the patients are excessively sleepy the next day. In the identification of sleepiness, the most commonly used method is "Epworth Sleepiness Scale" [39]. A diagnostic method for objective demonstration of excessive sleepiness during daytime is "Multiple Sleep Latency Test (MSLT)". Despite the fact that it does not have a direct role in the diagnosis of OSA, it helps to differentiate diseases like central hypersomnia and narcolepsy that cause similar symptoms. Having short sleep latency is a non-specific sign for sleep pressure during daytime and is often seen for OSA patients [40].

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Chapter 9

Cognitive Impairment and Obstructive Sleep Apnea

Liliana Otero, María del Carmen Figueredo, Alain Riveros-Rivera and Patricia Hidalgo

Abstract

Obstructive sleep apnea (OSA) is a frequent sleep disorder characterized by repetitive interruption of ventilation caused by partial or complete collapse of the upper airway during sleep. OSA is highly prevalent in the world and it has been associated with cardiovascular disease and cognitive impairment in children and adults. The cognitive impairment in individuals with OSA includes deficiencies in attention and constructional abilities, delayed long-term visual and verbal memory, and executive functions. Although, the pathogenesis of cognitive impairment in patients with OSA is complex and remains incompletely understood, several mechanisms, such as hypoxia, inflammation and sleep fragmentation have been proposed. The aim of this chapter is to describe some findings reported in the literature to explain the association between OSA and cognitive impairment.

Keywords: obstructive sleep apnea, cognitive impairment, hypoxia, sleep fragmentation

1. Introduction

Obstructive sleep apnea (OSA) is a breathing disorder of sleep produced by partial or complete obstruction of the upper airways. This sleep disorder is characterized by breathing cessation and reduction of airflow resulting in temporary decrease, in cerebral oxygenation and sleep disruption [1]. The prevalence of OSA is approximately 10% in men and 3% in women between the ages of 30–49%, but rising to 17% in men older than 50 years and 9% in women post-menopause. It has been reported that prevalence of OSA has increased since 1990 in the United States and other countries. However, 80% of individuals with OSA remain undiagnosed and untreated [2].

The pathophysiology of OSA includes oxygen desaturation, alteration in sleep architecture and abnormal ventilation [3]. Hypoxemia and sleep fragmentation (arousals) cause excessive daytime sleepiness increasing the risk of road and work accidents [4] and reduced quality of life [5]. Additionally, OSA increase the risk of cardiovascular, cerebrovascular and metabolic diseases [6], neurocognitive impairment [7] and death [8]. One at time, cardiovascular diseases and metabolic consequences of OSA increase the risk of cognitive impairment. Cognitive deficits in individuals with OSA include attention and vigilance, episodic memory, delayed long-term visual and verbal memory, visuospatial/constructional abilities and executive functions [9–11]. Some studies reported that psychomotor function and

language do not seem compromised, [12] whereas others demonstrated to psychomotor function is affected by OSA and this domain does not improve with CPAP therapy [13]. Although the cognitive impairment in individuals with OSA is largely recognized as mild cognitive impairment, [14] OSA has also recognized as modifiable risk for dementia, neuropsychiatric disorders and stroke [15, 16]. However, the pathophysiology of cognitive impairment in adults with OSA is complex and the whole mechanisms involved in cognitive deficit have not been clarified yet.

2. Sleep's role in memory

Since, Hervey de Saint Denys published *Les Rêves et les Moyens de les Diriger* in 1867, was established that sleep benefits the retention of memory [17]. Rosa Heine was the first person, in 1914, who demonstrated that learning before a period of sleep results in a lower rate of forgetfulness in the following 24 hours than learning before a period of wakefulness. These results demonstrated the importance of sleep for memory. Likewise, Ellenbogen et al. showed that sleep after learning benefits the consolidation of memories and strengthens the traces of memory against future interference. Current research findings show an active sleep role in the consolidation of memory, learning and brain plasticity [18].

Sleep is defined as "a natural and reversible state of reduced response to external stimuli and relative inactivity, accompanied by decreased consciousness" [19]. Sleep has four basic states, rapid eye movement (REM), no REM sleep 1 (N1), NREM sleep 2 (N2) and NREM sleep 3 (N3). Slow wave sleep (SWS) is observed in N3. In humans, SWS predominates in the early stages of the sleep and REM in the final period, alternating in a cyclic manner. In terms of memory, forming and recovering memories is a fundamental ability to achieve adaptation. Memory functions involved different process such as encoding, consolidation and retrieval. During encoding, the stimulus results in the formation of a new memory fragment that is stabilized in consolidation process avoiding forgetting and incorporating the memory into preexisting knowledge complexes. Consolidation occurs during SWS and REM sleep stabilizes transformed memories [20, 21]. Also, it has been suggested the possibility that cholinergic tone during delayed REM sleep is necessary for the successful consolidation of memory [22, 23].

Theories that propose a differential role of the sleep stages in memory are based on the "dual process hypothesis." In this dual hypothesis, SWS has a benefit in the declarative memories of events, such as learning word lists, word pairs or spatial locations, and processing dependent on the hippocampus [24], while REM sleep, benefits the consolidation of non-declarative memories (related to procedural memory, including mirror tracing, priming, implicit memory, and the emotional modulation of memories). A complex learning task can often involve both procedural and declarative learning components (complex motor movements, language learning). Emotive and sensitive events are better evoked than neutral ones, due to stimuli of the amygdala in the process of coding in the hippocampus. Changes registered in REM sleep for patients with mood disorders and lived dreams, clarify the link between REM sleep and the increase in amygdala activity. This activity has been related with the emotive and sensitive recycling during this stage of sleep. REM sleep seems also to be related with strength and weakened of emotional memory [25]. Findings from electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) show activity in brain regions (hippocampal) correlated with REM and SWS sleep, following both declarative and procedural learning. Although other theories hypothesized that memory consolidation occurs during different sleep states [26], neural processes of memory consolidation have been

observed during sleep and wakefulness [27]. Additional findings show that sleep enhances memory performance in brain-damaged individuals, except in patients with Parkinson [23].

The effect of sleep on memory is lasting and adaptive. Coding and initial recovery depends on the integrity of the hippocampus. The beneficial effect of sleep is linked to the interaction between slow oscillatory activity during SWS, thalamocortical sleep spindles and spontaneous reactivations of hippocampal memory [28]. In humans, slow wave sleep is correlated with hippocampus-dependent memory and REM sleep is associated with emotional memory. Currently, it is considered that an active consolidation of memory is established specifically during sleep and originates from the reactivation of newly coded memory representations that are integrated into the long-term knowledge networks. Findings from fMRI suggest that the process of consolidation in declarative memory is gradual. Then, the early activity after learning is observed in hippocampal locations, and after reinforced during sleep, long-lasting changes of memories are observed in medial prefrontal cortical activity. REM and NREM sleep are important for preservation, integration, and recollection of episodic memory [29]. In summary, sleep enhances learning of skills, semantic, episodic and emotional memories and stimulates creativity.

Some factors such as age, psychiatric and neurodegenerative conditions, sleep disruption and sleep apnea impair episodic memory [30, 31]. In patients with OSA cognitive processing, memory, vigilance, divided attention and executive functioning are affected. These deficits are observed identifying decreased ability to digest information, decreased ability to register, store, retain, and retrieve information, inability to maintain attention over the time, inability to respond to more than one task or stimuli, disorganization, emotional liability, impulsivity and difficulty maintaining motivation [32]. Beyond physiologic functions, the role of sleep in brain plasticity and memory consolidation processes is relevant, but the mechanisms involved in these processes remain to be fully understood. Therefore, it is necessary to perform future investigations to elucidate the pathophysiology of sleep disorders in neurocognitive impairment.

3. Physiopathology of cognitive impairment in obstructive sleep apnea

Neurocognitive impairment has over the years been associated with OSA but the prevalence of neurocognitive impairment in patients with OSA is not known [12]. One in four patients with OSA has neurophysiological impairment [33]. OSA patients are 7.5 to 20 times more likely to have difficulties with concentration, learning new tasks and execution monotonous tasks [34]. While current test for cognition not specifically assess impairments in OSA [35], some studies suggest that in the association between OSA and cognitive dysfunction, multitude of susceptibility and protective factors have been including, but others important factors should be considered. Susceptibility factors associated with neurocognitive impairment include: increased nocturnal awakenings, latency to REM sleep, [36, 37] changes in cerebral blood flow, neurovascular and neurotransmitter changes, intermittent hypoxemia, neuroinflammation, oxidative stress, ischemic precondition, hypercapnia [38, 39] and neural regulation in OSA [40]. Nevertheless, it is necessary to investigate the role of other factors such as genetic susceptibility, duration of OSA, hypertension, metabolic dysfunction, systemic inflammation, cerebral blood flow and blood-brain barrier [41].

Excessive daytime somnolence exhibit in patients with OSA increase the risk of cognitive decline and dementia. Sleep deprivation impair neuronal excitability, decrease myelination, produce cellular oxidative stress, misfolding of cellular

proteins, and alter molecular signaling pathways that regulate synaptic strength, plasticity-related gene expression and protein translation. These alterations create microinfarcts and brain atrophy that are associated with lower nocturnal oxygenation and reduction in NREM SWS sleep [42–44]. In OSA the proportion of stage N2 NREM sleep is increased and proportions of stages N1, N3 and REM sleep are decreased. During the NREM SWS abstraction of rules and integration of knowledge take place while in REM sleep creativity is beneficiated. In patients with OSA both sleep stages are reduced and fragmented, suggesting that some of the cognitive impairment is due to this dysregulation [45–47]. Frequently, obstructive events during NREM sleep have been associated with cognitive deficits and REM sleep events have been associated with greater sympathetic activity, hypertension and cardiovascular instability in patients with OSA. However, some studies reported that OSA reduction of REM sleep produce dissociation of REM traits to other sleep stages, affecting memory formation and consolidation [48, 49]. Gray matter atrophy in the prefrontal cortex observed in OSA and aging can mediate the degree of SWS disruption and consequent impaired overnight episodic hippocampal memory. Although several models have been proposed to explain the pathophysiology of cognitive impairment in OSA patients, the exact mechanisms of this association remain elusive [40, 50].

It has been suggested in meta-analysis and systematic review that cognitive deficit in patients with OSA is the result of poor night-time sleep and changes in the brain. Hypoxemia produces alteration of the prefrontal cortex and other CNS regions [51]. Then, global cognitive function is associated with hypoxemia and attention and vigilance dysfunction with sleep fragmentation. Sleep fragmentation is produced by the frequent sleep arousals that associated with apneic episodes contribute to abnormal sleep architecture, less restorative sleep and increased daytime sleepiness [14]. Therefore, treatment with continuous positive airway pressure (CPAP), should improve cognition and sleepiness. Evidence from clinical trials demonstrate that CPAP improves attention, vigilance memory executive functions and sleepiness, but deficits in learning memory and psychomotor function persist [52]. These findings suggest that improvements in sleepiness is not always associated with improvements in cognition, and it has been suggested that the improvement of cognition could be related with duration and severity of OSA [53].

Large-scale, multicenter, randomized, double-blind cohort study, the Apnea Positive Pressure Long-term Efficacy Study (APPLES), investigated the effects of CPAP on cognitive function in patients with OSA [53]. In this study, patients with severe OSA improved more than those with mild OSA. Although attention/psychomotor and learning/memory functions did not improve at either the 2-month or 6-month follow-up, improvement in the verbal delayed recall test was observed in patients on CPAP for 6 hours a day. Therefore, it was suggested that long-term memory deficits might be reversible with optimized CPAP treatment. Other studies following 3 and 12 months of treatment with CPAP show changes in gray frontal and hippocampal regions) and white matter correlated with improvements in memory, attention and executive functions [54, 55].

While several studies show that CPAP improves some cognitive domains, other studies reported less responsive for psychomotor activities. Additionally, the relationship between cognitive impairment and OSA severity is complex and the findings are inconsistent [9]. This complexity is represented by individual differences, genetic profiles and difficulties to measure OSA severity and cognitive impairment. Sleepiness questionnaire scores are not objectives and AHI (apnea/hypopnea index,

number of apnea and hypopnea events per hour of sleep) cannot measure the individual differences in the length of each event. Furthermore, oxygen desaturation index cannot identify the sleep cycle when hypoxia and arousal occur. Therefore, novel measures that separate sleep fragmentation and oxygen desaturation and measures to identify these events in each sleep cycle because cognitive functions are related with sleep cycles are needed [41].

Several factors contribute to individual differences in the relationship between OSA and cognition. Aging is associated with changes in morphology, size and reflex sensitivity of upper airway, resulting in a reduction in upper airway dilator muscle function at sleep in older people [56, 57]. Also, it has been suggested that co-morbidities such as hypertension, hyperlipidemia, diabetes, metabolic syndrome, and Alzheimer disease are the primary causes of the neurological damage. Other individual differences are related with genetic predisposition, mood, changes in macro and microcirculation in the brain, gender and experience of sleepiness [58].

4. Brain changes associated with OSA

There is evidence of structural and functional brain changes in critical areas for cognition in patients with OSA. Numerous investigations have reported changes in the electroencephalogram of OSA patients compared with healthy individuals. These changes show abnormal cortical excitability associated with neurocognitive deficits [59, 60]. In the prefrontal model sleep disruption, intermittent hypoxemia, and hypercapnia observed in OSA produce cellular and biochemical stresses that alter neuronal and glial viability within prefrontal regions of the brain cortex, affecting the efficacy of restorative process occurring during sleep. This model explains the relationship between sleep fragmentation and nocturnal hypoxemia with predominantly frontal deficits. However, the neuroanatomic regions that have most commonly been reported in OSA are thalamus and frontoparietal cortex [61]. Degenerative areas in brain include: hippocampus (memory and new learning), the thalamus (sensory and motor signaling and in regulating sleep and alertness) and the amygdala (regulation of emotion) [16]. The findings in fMRI suggested a dysfunctional connectivity of the posterior default mode neuronal network and changes in network in the anterior insula, posterior-medial frontal cortex and thalamus (right amygdala-hippocampus complex and the insular cortex) [62, 63].

Several studies reported that OSA is a risk factor for cerebral small vessel disease (C-SVD). C-SVD is a group of pathologic processes that affect small arteries and veins, arterioles, and capillaries. Restricted blood flow in diseased small vessels, produce low perfusion pressure and hypoperfusion of the affected brain areas. Subsequently, chronic hypoperfusion develop ischemic C-SVD [64, 65]. Changes in white matter associated with OSA has also been reported. Degradation of multiple areas of subcortical tracts of the superior and inferior parietal lobe, deep frontal white matter and arcuate fasciculus. The white matter fiber integrity was recuperated after 12 months of CPAP treatment and this recuperation was associated with improvement in memory, attention, and executive functions [55]. The gray matter is also affected in patients with OSA. Some studies report that extent of gray matter volume loss increases correlated positively with OSA severity. Decreased gray matter has been observed in the frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum [66, 67] (**Figure 1**).

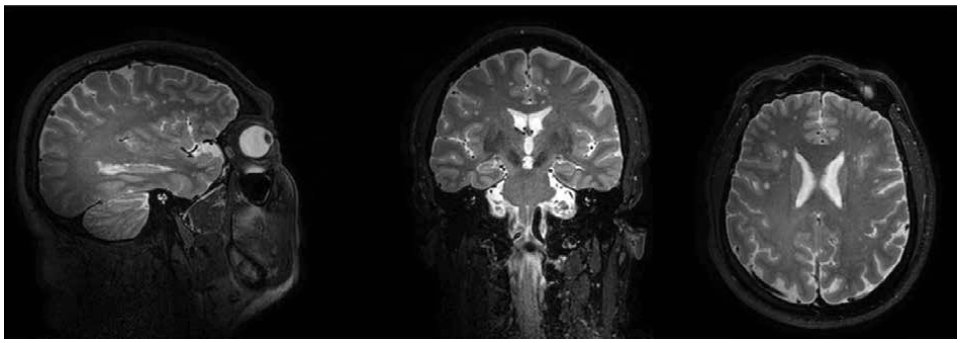

Figure 1.
Magnetic resonance imaging in patient with cognitive impairment and OSA and in healthy individual.

5. Mechanisms associated to cognitive impairment in OSA

OSA causes oxygen desaturation producing arousals and nocturnal intermittent hypoxemia. The intermittent hypoxia is linked to cerebral microvascular and neurovascular changes. Several models have been proposed to explain the pathophysiology of neurocognitive impairment in patients with OSA. Some of these models include: prefrontal model sleep disruption, neuroinflammatory process, hypoperfusion and endothelial dysfunction. Neuroinflammatory process is one of the mechanisms proposed to explain the association between OSA and cognitive impairment. Healthy microglia of central nervous system (CNS) show a surveillance phenotype that synthesizes neuroprotective growth factors. In OSA ischemic condition actives several genes including vascular endothelial growth factor (VEGF), erythropoietin, atrial natriuretic peptide (ANP), hypoxia inducible factor-1 (HIF-1), and brain-derived neurotrophic factor (BDNF) [68]. Altered resting cerebral blood flow pattern and hypoperfusion in several CNS regions have been demonstrated in patients with OSA during sleep and awake states [69]. Repetitive hypoxia and reoxygenation promote oxidative stress producing blood-brain barrier hyperpermeability and neuroinflammation. These alterations result in plasma proteins leaking into the arteriolar walls and perivascular spaces (Virchow-Robin spaces) and subsequent accumulation of macrophages and fibrosis in the arteriolar walls leading to the development or progression of C-SVD. Severe and prolonged hypoxia can activate microglia toward a toxic, pro-inflammatory phenotype causing white matter damage and lacunar infarction and accumulation of plasma proteins in the small arterial walls. Additionally, inflammation at the blood-brain barrier alters the transport of molecules across the barrier, resulting in progressive synaptic plasticity and neuronal dysfunction. This maladaptive neuroinflammatory process, observed in patients with OSA, increases hippocampal apoptosis, impaired synaptic plasticity, and cognitive impairment [70–74].

In hypoperfusion model, the cognitive impairment is explained in this way: in normal conditions the cerebral autoregulation mechanism protects the brain through maintaining cerebral perfusion during blood pressure changes. In OSA this system is impaired because of changes in nocturnal intracranial hemodynamics and oxygen saturation, resulting in cerebral hypoperfusion in the regions with poor collateral circulation. Chronic hypoperfusion in small arteries and arterioles leads to ischemic changes in white and gray matter. Although cerebral blood flow is increased to compensate for oxygen desaturation in patients with OSA, this mechanism is not enough and the chronic hypoxemia promotes the progression of C-SVD resulting in lacunar infarcts, white matter abnormalities and gray matter

loss. Damage to prefrontal and frontal lobes, basal ganglia and hippocampus are associated with abnormal myelin and axonal integrity. Prolonged hypoxic–ischemic damage to the frontal and prefrontal cortex is associated with executive dysfunction in patients with moderate to severe OSA, but this damage could improve with CPAP treatment [75–79].

In endothelial dysfunction model, neurocognitive impairment is produced for several mechanisms. The apneic episodes cause repetitive intracranial blood flow impairing the endothelial cells of small arteries and arterioles and decreasing endothelial vasodilator production. Nitric oxide regulates cerebral blood flow in response to hypercapnia, but in OSA nitric oxide is decreased, and the vasodilatory capacity of cerebral vasomotor reactivity in response to hypercapnia is compromised. Altered cerebral vasomotor reactivity associated with poor microvascular blood flow produce white matter lesions. Additionally, disruption of nitric oxide pathways causes a cascade of neuronal metabolic deficiencies, resulting in destabilizing neurons, synapses, and neurotransmission, and generating synaptic loss and neuronal damage [80–83].

Investigations about the impact of patients with OSA treated with CPAP in the cognitive function have showed that daytime sleepiness decrease and cognitive function improves. The amount of improvement depends of biologic variability present in each patient [55, 84, 85]. Previous studies had been demonstrated that sleep disruption impaired cognitive function and the mechanisms of cognitive harm in OSA and chronic obstructive pulmonary disease (COPD) are similar. However, the pathophysiology of neurocognitive impairment in OSA and insomnia seems to be different, and the cognitive deficit in individuals with OSA is greater [46, 85, 86]. Therefore, other mechanisms such as changes in the brain could explain the cognitive impairment associated with OSA. Additionally, in some patients with OSA cognitive deficit persist, even after prolonged treatment with CPAP. For this reason, it is necessary to design future studies to identify appropriate treatment that can be administered before irreversible atrophic and metabolic changes occur [41, 87, 88]. Further studies should be performed to elucidate mechanisms of neurocognitive impairment and to identify genetics profiles for prediction of neurocognitive effects of CPAP in patients with OSA and other comorbidities.

6. Conclusions

- Obstructive sleep apnea is associated with cognitive impairment and is a modifiable risk factor for dementia.
- Sleep fragmentation, hypoxia, maladaptive pathways, neuroinflammation, hypoperfusion and endothelial dysfunction contribute with neurocognitive impairment in patients with OSA.
- Future studies should be conducted to identify novel diagnosis and therapeutic tools for OSA and cognitive impairment.
- The exact pathophysiology of cognitive impairment in OSA patients remain elusive as the role of therapy for OSA on cognitive impairment.

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Chapter 10

Neuropsychological Alterations in Children Affected by Obstructive Sleep Apnea Syndrome

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Abstract

Sleep-related breathing disorders are a group of clinical conditions ranging from habitual snoring to obstructive sleep apnea syndrome (OSAS) during the lifespan. In children, other risk factors are represented by adenotonsillar hypertrophy, rhinitis, nasal structure alteration, cleft palate, velopharyngeal flap surgery, pharyngeal masses, craniofacial malformations, genetic syndrome (i.e. Down syndrome, Crouzon syndrome, and Apert syndrome), genetic hypoplasia mandibular (i.e. Pierre Robin syndrome, Treacher Collins syndrome, Shy-Drager syndrome, and Cornelia De Lange syndrome), craniofacial traumas, chronic or seasonal rhinitis, asthma, neuromuscular syndromes, brainstem pathologies (i.e. Arnold-Chiari malformation and Joubert syndrome), achondroplasia, and mucopolysaccharidosis. OSAS may affect the executive functioning such as motivational ability, planning, behavior modulation, ability to complete an action program, identification of functional strategies to achieve the goal, problem solving, flexibility, monitoring and self-assessment of behavior in relation to results, change of task, or behavior in the light of emerging information, which may be all impaired by nocturnal intermittent hypoxia also during the developmental age. The clinical presentation of OSAS can mimic other neurobehavioral symptoms, such as ADHD syndrome, learning problems, or can exacerbate the Fragile X syndrome, and generalized non-convulsive epilepsy symptoms.

Keywords: sleep-related breathing disorders, pediatric OSAS, executive dysfunction

1. Introduction

Sleep-related breathing disorders are a group of clinical conditions ranging from habitual snoring to obstructive sleep apnea syndrome (OSAS), frequent in all ages of life. OSAS is a clinical condition still underdiagnosed both in adults and particularly in children, with high cost of care for general population [1, 2]. OSAS can be considered the most severe nocturnal respiratory disorder characterized by repeated episodes of obstructive and/or hypopnea during sleep caused by complete or partial

obstruction of the upper airways. The nocturnal episodes of total or incomplete breathing interruption are identified and recorded in the apnea/hypopnea index per hour (AHI), and the nocturnal oxygen desaturation is expressed as oxygen desaturation index per hour (ODI). In children, in contrast to the adult, definition of OSAS, which requires an AHI ≥ 5 episodes per hour of sleep lasting more than 10 seconds, with persistent thoracoabdominal movements [1], does not require so.

In 1976, OSAS syndrome was identified and described in pediatric age by Guilleminault et al. [3], and from that time on, studies on this pediatric pathology have multiplied, considering its important impact on all aspects of life often linked to the intermittent nocturnal hypoxia not ever associated with the nocturnal respiratory events (hypopneas and apneas).

2. Epidemiology

In the developmental age, prevalence in preschool and school age for primary snoring ranges from 3.2 to 12.1%, while for OSAS, it varies from 1.1 to 2.9%. The peak incidence is observed between 3 and 6 years and coincides with the age of maximum development of lymphatic tissue. In all the studies found in the literature, it can in fact be noted that the incidence of OSAS is greater in children with adenotonsillar hypertrophy [4].

The prevalence of OSAS in Italy shows a prevalence in children of 4.9% for primary snoring and of 1.8% for OSAS [5].

On the other hand, African American children were reported four to six times more likely to have OSAS than children of Caucasian origin [6], while the predisposition to OSAS in African Americans has been attributed to different upper airway anatomy and pharyngeal neuromotor control in addition to other genetic and environmental factors [6].

In clinical practice, there are many screening tests for the identification of sleep-related breathing disorders in pediatric age.

Furthermore, in children, sleep is less fragmented than adults because the behavioral awakenings seem to be less frequent in children than in adults with a lower incidence of daytime excessive somnolence.

3. Risk factors

OSAS is a complex and multifactorial syndrome, and it is believed that some specific genes may play a crucial role in its pathogenesis, particularly involved in the expression of the CLOCK gene [7], IL-10 polymorphisms [8], and insulin variable number of tandem repeat (INS VNTR) sequence regulation [9].

In general, there are some conditions that may predispose to OSAS, such as alterations of craniofacial structures, obesity with fat deposition on side walls of the pharynx, endocrine changes, alcohol intake, and cigarette smoking [10] both in adults and in children.

In pediatric population, the main risk factor is adenotonsillar hypertrophy [11, 12], but others are rhinitis [13], nasal structure alteration [14, 15], cleft palate, velopharyngeal flap surgery, pharyngeal masses, craniofacial malformations [16], genetic syndrome (i.e. Down syndrome, Crouzon syndrome, and Apert syndrome), genetic hypoplasia mandibular (Pierre Robin syndrome, Treacher Collins syndrome, Shy-Drager syndrome, and Cornelia De Lange syndrome) [17, 18], craniofacial traumas [19, 20], chronic or seasonal rhinitis [13],

asthma [21, 22], neuromuscular syndromes [23], brainstem pathologies (Arnold-Chiari malformation and Joubert syndrome) [24], achondroplasia [25], and mucopolysaccharidosis [26].

On the other hand, worldwide pediatric obesity tends to be prevalent in children with respiratory disorders during sleep; however, it does not represent the main risk factor unlike the adult and is even a complication of OSAS especially after the adenotonsillectomy [27, 28].

4. Pathophysiology

In OSAS, due to a reduction in the size of the upper airways and a reduction in the activity of the pharynx dilator muscles, there are an increase in critical pressure (transmural pressure value at which the area of the pharyngeal section is equal to zero) and an enormous reduction in the pharyngeal lumen [29].

The obstructive events will therefore lead to the appearance of hypoxemia and hypercapnia, which will first cause an increase in respiratory effort, and then a wake-up, of a few seconds, which will serve to restore the patency of the upper airways; all these will repeat cyclically during sleep, causing an alteration of the structure.

In the adult, there is a reduction in nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, and consequently, the major symptom is daytime sleepiness; in children, on the other hand, intermittent hypoxia has a role in the appearance of neocognitive deficits, which are the most common signs and symptoms in the case of OSAS in the developmental age [29].

Behavioral awakenings in the child with OSAS are less frequent than in adults, and this on the one hand allows the child to retain the benefits of sleep, and on the other hand, it can cause long periods of hypoventilation. Moreover, in children, the desaturation of O_2 can also be achieved during short apnea due to the reduced functional lung capacity and the most frequent respiratory rate in pediatric age [29].

In OSAS, there is also a state of chronic systemic inflammation, mainly linked to intermittent hypoxia, which promotes the activation of some factors responsible for inflammation such as C-reactive protein (PCR) and IL-6 and is therefore responsible for a state of oxidative stress [30].

Oxidative stress and increased production of oxygen-free radicals represent the pathophysiological substrate of the onset of cardiovascular, cerebrovascular, and metabolic complications [31, 32].

5. Clinical signs

Clinical signs of OSAS appear to be different in pediatric age with respect to adulthood, and therefore, the diagnostic and therapeutic management overlapping may be considered a severe clinical mistake.

In adults with OSAS, the most common presentation is excessive daytime sleepiness (EDS) that results from sleep fragmentation and from the frequent nocturnal intermittent hypoxic episodes [33], while in nonobese children, EDS is a rare complain. Conversely, children with OSAS tend to be not drowsy but rather hyperkinetic during the day, and often, these children are misdiagnosed with attention-deficit/hyperactivity disorder (ADHD) and treated with methylphenidate.

This common diagnostic mistake is derived from the lack of evaluation of sleep habits in children presenting with suspected hyperactivity behavior

that may highlight the presence of ADHD-like symptoms and not of ADHD syndrome [34, 35].

In pediatric age, the symptoms and major signs of suspected nocturnal respiratory problems are mainly oral breathing [36], nocturnal hyperkinesia, snoring or breathing pauses [37], nocturnal positional abnormalities [38], behavioral problems [39, 40], poor academic performance [41], failure to thrive and growth delay, recurrent airway infections [37], recent enuresis onset [42, 43], and night sweating and drooling [44].

6. Polysomnography (PSG)

Pediatric respiratory disorders during sleep find their diagnostic gold standard in the overnight polysomnography. This term commonly means the simultaneous and continuous recording during the night of functional parameters suitable for defining the cardiorespiratory events in relation to the various phases of sleep. Normally, during the test, two or more electroencephalogram (EEG) channels, two or more electromyographic channels, chest and abdomen movements, oronasal flow, oxygen saturation in the blood, and CO_2 measurement are recorded. The polysomnographic result must always be contextualized with the symptoms and signs and referred to the general clinical picture since there is not always a correspondence between the severity of the polysomnographic instrumental data (in terms of number of events and levels of O_2 desaturation) and the gravity of symptoms [45].

The severity identification of SRBD is identified by apnea/hypopnea index (AHI) and oxygen desaturation index (ODI). In pediatric age, AHI cut-off has been established between 1.2 and 1.3 nocturnal events per hour, while for ODI are conflicting and nonconclusive results.

7. Diagnosis and classification

For the diagnosis of OSAS, the anamnesis, the physical examination, and the polysomnographic examination that allows an early diagnosis and therefore an early therapy to prevent the development of complications are fundamental.

During the visit, a careful history assessment must be made, considering if there is the presence of familiarity for OSAS and if there are symptoms such as snoring, attention deficit, predominantly oral breathing, nocturnal hyperkinesia, behavioral problems and academic performance, recurrent airway infections, recently onset enuresis, night sweats, and nocturnal sialorrhea [43].

On physical examination, the signs and findings most closely linked to a high risk of respiratory disorders in sleep are adenotonsillar hypertrophy, rhinitis, macroglossia, and obesity [43].

Analyzing the oronasal flow is used to assess ventilation and to identify and differentiate central apnea from obstructive apnea, whereas hypopneas are more difficult to identify as they are not greater than 50% of respiratory flow. Analyzing thoracoabdominal movements and respiratory effort, on one hand, and quantitative and qualitative information on breathing, on the other hand, can be obtained.

The respiratory parameters are useful for the diagnosis of OSAS, and the American Academy of Sleep Medicine distinguishes respiratory events in central, obstructive, and hypopneic episodes [46].

Central apnea is caused by the damage to the nerve centers that regulate ventilation and is characterized by a complete cessation of ventilation with no thoracoabdominal movements. In the child, it can be an occasional event that becomes

pathological if there are more than three episodes per hour of sleep with a desaturation of >3% [46].

The obstructive apnea is instead caused by a complete or partial obstruction of the upper airways associated with inspiratory effort evidenced by the variation of thoracoabdominal movements in an attempt to overcome the obstruction. In children, even only one obstructive event per hour of sleep has a pathological character (AHI ≥ 1/h) [46].

Obstructive hypopnea consists of a reduction in oronasal flow >50%, with a desaturation of >3% for at least two respiratory cycles, and accompanied by thoracoabdominal movements [46].

Children may present four grades of OSAS severity classified by the Italian Society of Sleep Medicine [46] as follows:

minimum OSAS: AHI between one and three episodes per hour and/or the presence of continuous snoring for at least 50% of sleep associated with O_2 desaturations above 4% and average SaO_2 > 97%;
mild OSAS: 3 < AHI < 5 and average SaO_2 > 97%;
moderate OSAS: 5 < AHI < 10 and average SaO_2 > 95%; and
severe OSAS: AHI > 10 or with average SaO_2 < 95%.

Adenotonsillectomy is the main treatment in children, but if this failed or in the case of obese patients, continuous positive airway pressure (CPAP) or other positive pressure devices need to be considered [43].

8. The link between the severity of respiratory disturbance in sleep and neurocognitive disorders

According to many reports [47–49], neurocognitive alterations seem to be the direct effect of nocturnal intermittent hypoxia, sleep fragmentation, hormonal imbalance, systemic subclinical inflammation [50, 51], and endothelial dysfunction [52].

Nocturnal intermittent hypoxia causes a chronic state of neuroinflammation due to the production of proinflammatory cytokines such as interleukin (IL)-10, IL-6, IL-1, and TNF-α [53], although also serum C-reactive protein (CRP), pentraxin-3 (PTX-3), procalcitonin (ProCT), IL-33, and its soluble receptor ST2 (sST2) may be identified as putative biomarkers for OSAS severity almost in adults [54]. Interestingly, in children affected by OSAS and cognitive alteration, there is an increase in PCR and proinflammatory cytokines that are reduced following the adenotonsillectomy [51, 52].

Oxidative stress also directly and indirectly causes endothelial and vascular alterations that provoke an alteration in cerebral perfusion and play an important role in the onset of neurocognitive alteration in OSAS children [53].

Although IGF1, the insulin-like growth factor, is mainly produced by the liver under the stimulation of growth hormone (GH), its mechanism of action is mediated by its specific receptor, IGF1R, which is present on many cell types in many tissues, where it promotes cell proliferation and differentiation, especially at cartilage and muscle levels, so it is essential for growth processes in children. IGF1 can also be produced from other tissues as well as from the liver, including the brain, where it is synthesized without control by circulating GH. IGF1 promotes neuron survival and differentiation. It is involved in brain plasticity processes and regulates synapse formation, neurotransmitter release, and neuronal excitability. In children with OSAS, it was seen that high systemic levels of IGF1 appear to have a neuroprotective role because they reduce the risk of cognitive impairment [55, 56].

In children, sleep is essential for the processes of learning and memorization, and therefore, any alteration, such as its fragmentation, can cause impairment in the executive and behavioral functioning and in the emotional recovery [57].

Furthermore, in many children with OSAS and neurocognitive deficits, there was a high presence of ε4APOE allele, known to be present above all in people suffering from Alzheimer's disease [58]. Through magnetic resonance spectroscopy studies, it has been shown that in children with OSAS, there is a decreased hippocampal volume and focal reductions of gray matter in the frontal and parietal lobes [59, 60].

Moreover, in children with OSAS, in addition to the presence of neurocognitive disorders, a growth retardation is frequently found, in which at least three causes contribute to provoke it, namely, a feeding difficulty secondary to adenotonsillar hypertrophy, an increase in metabolic activity for respiratory effort during sleep, and an alteration of hormonal regulation with reduction of the nocturnal secretion of growth hormone and insulin-like growth factor [48].

Frequently endocrine alterations are associated with OSAS, as sleep fragmentation can have an impact on hormones that regulate glucose tolerance. In fact, diabetic children suffer more frequent and longer-lasting episodes of sleep apnea than healthy controls [61, 62].

However, in the developmental age, neurocognitive impairment due to OSAS seems to be more relevant than endocrinological and cardiovascular effects since it might not be reversible.

9. Executive functions: a complex construct

The executive functions (EFs) are defined as those cognitive skills necessary to plan, implement, and successfully complete a behavior aimed at a purpose. They do not represent a single entity but a complex of distinct, independent, and "subtly" interacting "subprocesses" necessary to perform a task and to achieve an end in an articulated and flexible way. Lezak et al. [63] attribute to them the concept of "umbrella term," as the umbrella is a compound of distinct elements that together support a "structure," in the same way that the executive functions constitute a unique and "meta-construct" all-inclusive to think, intuit, concentrate, adapt in order to achieve goals, and develop problem-solving strategies. EFs may be identified as a "module" of the mind that regulates the processes of planning, control, and coordination of the cognitive system, which, in turn, governs the activation and modulation of cognitive processes and schemes. EFs are transversal functions, differently from the so-called vertical functions (i.e. motor skills, language, reading, writing, calculation), and therefore, they can only be partially isolated and studied in their singularity. In this perspective, EFs are invisible as they are inextricably linked to the task and domain in which the activity is carried out and, therefore, cannot be analyzed independently of the performance. "They are higher-level, non-domain-specific cognitive functions, which enable us to formulate objectives/plans and to remember them over time; to choose and initiate actions that allow to achieve the objectives, to monitor the behavior and adjust it in order to reach those objectives" [64, 65].

On the other hand, the "label" of "skills that come into play in situations and tasks in which the use of routine behaviors and skills is no longer sufficient for their success" by addressing the set of mental processes aimed at development of adaptive cognitive-behavioral patterns in response to new and demanding environmental conditions [63].

EFs are essential and basic for the following:

- learning new actions;
- making the action plan and decision-making processes;
- selecting the correct answer and inhibiting the wrong one;
- correcting the errors;
- requiring the variable combinations of actions for new behaviors;
- conducting the complex activities;
- constant monitoring of behavior and evaluating the result; and
- having the ability to regulate and overcome the strong habitual responses.

Over the past 40 years, cognitive psychology and neuropsychology have paid particular attention to these skills, and despite the progress made in their study and description in the event of injury or developmental deficit, their multicomponent nature continues to make them difficult to analyze as well as a fully shared definition. The literature has provided different definitions and interpretations, and to date, there is still no unanimous agreement on the construct; different subdomains of executive functions are identified, which are the basis of other higher-order functions such as reasoning, problem solving, planning, understanding the behavior, and thinking of others.

Specifically, the main EFs are as follows:

- working memory: it is the ability to keep the plan and the work area mentally active and to have a mental set of reference on which to operate even in the presence of distracting tasks or situations;
- inhibition: it is the ability to self-control, to resist temptations, and to act impulsively; the ability to focus attention on relevant data by ignoring distractors and inhibiting inadequate motor and emotional responses;
- selective and sustained attention;
- flexibility: understood both in cognitive terms (shifting from one set to another based on information from the context) and in terms of creativity and sudden adaptation; and
- fluency: thinking ability capable of generating new and different solutions to a problem.

Their use is indispensable in all types of problem solving, not only the most complex and abstract ones such as solving mathematical problems, but also those related to the acquisition of social skills and the understanding of others' thoughts (metacognition) since the sensitivity to other people's goals, emotions, or desires requires an uncoupling from one's internal mental states. We turn to multiple domains that extend from the simple to the most complex and are in any case

interrelated. It is precisely the transversal nature and the structural complexity that characterizes them, associated with their slow development process, to explain why multiple neuropsychiatric disorders of the developmental age (pervasive developmental disorders, behavioral disorders, speech disorders, learning disorders, and disorders of the nonverbal area) present, with varying degrees of symptomatic severity, a common deficit for executive functioning. There are also motivated situations in which a deficiency of theirs manifests itself with clinical signs and symptoms that are often nuanced, nonspecific, and not immediately diagnostic (instability of behavior and emotionality, distractibility, difficulty in moving from one activity to another, and atypia communication). To this lively theoretical debate on what and what the EFs are, a new theoretical contribution has recently been added linked to the different types of cognitive and behavioral deficits that have emerged from injuries to the different areas of the prefrontal cortex, which has allowed a further classification in hot and cold executive functions [63].

The "hot" executive processes involve the emotional-emotional sphere and are associated with the activity of the ventromedial prefrontal cortex (VMPFC); the "cold" executive ones concern cognitive and nonemotional processing and are associated with the activity of the dorsolateral prefrontal cortex and can be measured by neuropsychological tests used in clinical practice (DLPFC) [66].

The "hot" executive functions recall phenomena such as empathy, the theory of the mind, emotional, and affective regulation, which coordinate the cognitive with the emotional sphere in order to adequately address the primary impulses with socially acceptable strategies. The "cold" executive functions intervene in cognitive, abstract, and decontextualized tasks (problem solving, abstraction, planning, working memory, and elaboration of strategies). Despite this distinction, they are closely related and combined in different situations of daily life.

In summary, the EFs are a particular set of cognitive operations activated in pursuit of objectives, responsible for planning, the ability to set goals, to classify, to know how to execute an order, to control and monitor one's behavior, to know how to order a series of activities in order to achieve a goal, and to manage, more generally, all mental activities [63].

These functions are modified in some pathological conditions such as posterior cranial fossa neoplasms [67], localized posttraumatic lesions to the frontal lobe [68], neurodegenerative syndromes (i.e. Parkinson's disease and Alzheimer's disease) [69, 70], cerebrovascular malformations (i.e. Moya-Moya syndrome) [71], ADHD [72], and OSAS [73].

The close relationship between cognitive functions has long been known and sleep, with particular reference to disorders respirators for which it has been widely demonstrated in the developmental age the association with learning disorders and more generally with alterations of the cognitive performance [74] that appears in such subjects dominated by slowness in concept development [75, 76] which however do not seem to be related to degree of severity of the respiratory disorder [77].

Several studies have focused on the role of the frontal lobes as possible relay zones between the OSAS and the cognitive alterations [78, 79]; however, studies conducted on executive functions of subjects with OSAS have pay attention exclusively to adulthood [79], leaving aside the impact of this disease in the developmental age.

In this context, the close interconnection between OSAS and alteration specifications charged to executive functions. Furthermore, as reported in other studies, the modified card sorting test (MCST) is related especially to changes in blood flow for the frontal and hippocampal regions [80]. These data reflect the conclusions of recent neuroimaging studies on subjects suffering from OSAS, which would present a level reduction of the gray substance of the fronto parietal regions and

hippocampus [81, 82], confirming the presence of an interconnection between sleep mode and performance also in subjects of the developmental age.

The neurocognitive OSAS effects have been known for over a century. In 1892, Sir William Osler described, in the child, an association between night snoring, upper respiratory tract obstruction, and intellectual retardation [83].

In 1889, William Hill confirmed what Osler had previously described and showed that the removal of adenoids and tonsils caused not only the disappearance of nighttime respiratory symptoms but also the recovery of intellectual function [84].

In general, children affected by OSAS may present many specific problems in different day-life functioning areas including reductions in working memory, speed movement, cognitive flexibility, and planning. As main effect of this alteration, learning ability and scholastic efficiency may be altered precociously [85].

The exact etiopathogenetic link between nocturnal respiratory disorders and daytime behavioral symptoms is not still known. Certainly, the fragmentation of sleep due to frequent microarousal, hypoventilation, and the imbalances in blood gases that these children experience during sleep plays an important role in the genesis of these disorders.

Brain studies in rodent models have shown that hypoxia and anoxia produce cellular damage [86] within the CA1 region of the hippocampus and adjacent cortex.

This laid the groundwork for further studies, which confirmed the reduction of gray matter in subjects with OSAS in the right upper temporal sulcus and in the left cerebellum area, areas dedicated to attention processes, working memory, and motor coordination. In fact, many studies [87, 88] have revealed reductions in gray matter in the inferior temporal gyrus, including the parahippocampal gyrus, extended toward the anterior temporal pole. The precise function of the average time frame is unclear. Recent attempts to link structural deficits resulting from OSAS with functional consequences have concluded that structural deficits are associated with memory impairment and difficulty in motor coordination, although these data are not conclusive [89].

On the other hand, the complete brain magnetic resonance imaging (MRI) scanning in OSAS subjects showed loss of gray matter in a single large region of the cerebellum, more dominant on the left. Patients with right focal lesions often show verbal deficits, while those with lesions on the left seem to suffer more from spatial deficits. The left region, in fact, is the one most involved in the development of the movement. Moreover, Yaouhi et al. [90] reported significant loss of gray matter in bilateral inferior parietal gyrus, right temporal cortex, occipital cortex, right thalamus, left putamen, left caudate nucleus and left pallidum, right hippocampal gyrus, right cerebellar hemisphere, and cerebellar vermis in OSAS subjects.

10. Conclusions

Motivational ability, planning, behavior modulation, ability to complete an action program, identification of functional strategies to achieve the goal, problem solving, flexibility, monitoring and self-assessment of behavior in relation to results, change of task, or behavior in the light of emerging information may be all impaired by nocturnal intermittent hypoxia also during the developmental age. The final effects of this impairment may be identified in such clinical condition mimicking other neurobehavioral symptoms, such as ADHD [34], while learning problems may be sustained by OSAS [91, 92], or in Fragile X syndrome [93], in epilepsy [94], and in EEG abnormalities [95], suggesting that the sleep screening may be considered as mandatory in neurodevelopmental disorders.

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Chapter 11

Surgical Treatment Options for Obstructive Sleep Apnea

Jimmy Hanna and Anthony Izzo

Abstract

Given the increased prevalence of obstructive sleep apnea (OSA) multiple treatment modalities including medical and surgical have been developed. First-line therapy for most of the people with obstructive sleep apnea (OSA) consists of behavioral modification, including weight loss if appropriate, and positive airway pressure (PAP) therapy. Patients who fail or do not tolerate PAP therapy, treatment options include oral appliances and surgical therapy. Surgical therapies have variable efficacy and are very important tool on OSA management in selected patients. This chapter will review the current surgical approaches sleep specialists use when other treatment options fail to accomplish the valuable outcome.

Keywords: obstructive sleep apnea (OSA), continuous positive airway pressure (CPAP), role of surgery, surgical treatment, follow up and monitoring

1. Introduction

Positive airway pressure (PAP) is considered the gold standard treatment for patient with OSA [1]. Multiple studies showed the effectiveness of the CPAP therapy with reducing subjective symptoms of OSA, and cardiovascular and neurocognitive risks [2, 3].

The efficacy of CPAP treatment is limited due to patient's compliance to therapy. Patient will achieve normal functioning with greater nightly CPAP durations [4]. Patient who fail or intolerant to CPAP therapy should consider alternative treatment options which surgery one of them.

Surgical procedures aim to improve airway patency by recognizing the location(s) of obstruction. Patients need to be selected in awareness of the individual underlying pathology, pathophysiology and anatomy, and severity of the disease and comorbidities.

The anatomical cause of OSA is generally heterogeneous, with multiple potential levels of airway obstruction; therefore, many different surgical procedures have been developed for the treatment of OSA [5].

2. Presurgical evaluation

Polysomnogram (PSG) and home sleep testing do not provide information about the location of the obstruction. Therefore, a complete history that include the chief complaint, other significant symptoms, past medical history and surgical history are helpful. Some symptoms can help identify potential surgical approaches.

Components	Classification
Structures	V–velum, including soft palate, uvula or lateral pharyngeal wall
	O–oropharyngeal walls (including palatine tonsils and lateral wall tissue)
	T–tongue base
	E–epiglottis
Degree of obstruction	0–No obstruction
	1–Partial obstruction
	2–Complete obstruction
	X–Not visualized
Configuration of collapse	Anteroposterior
	Lateral
	Concentric

Adapted from Ref. [9].

Table 1.
VOTE classification system [9].

The history should also include the patient past experience with continuous positive airway pressure (CPAP), an oral appliance, and/or weight loss.

Thorough physical exam to evaluate the structures that impact the upper airway. The nasal airway is evaluated in detail, checking for external deformity, nasal valve collapse, septal position, turbinate size, and nasal polyps.

Oral cavity and oropharynx examination provide information into the protentional upper airway surgery. It provides insight of the tongue size and position, dental health, and palate position.

Trans-nasal flexible laryngoscopy provides adequate evaluation of the lower pharyngeal and laryngeal airway. It gives great view of the entire upper airway while the tongue in native position.

Drug induce sleep endoscopy (DISE) using mild sedation (midazolam or propofol) required in some upper airway procedures like upper airway stimulation therapy [6]. It has been shown to be a valid assessment of the upper airway, with moderate-to-substantial test-retest reliability and moderate-to-substantial inter-rater reliability. It allows the evaluation of the airway in a situation as close to sleep as possible [7, 8].

VOTE (Velum, Oropharynx, Tongue base, and Epiglottis) system specifies grades for the degree of obstruction at the velum, oropharynx, tongue base, and epiglottis, as well as the type of collapse (**Table 1**).

Several other diagnostic modalities have showed some value to supplement a physical examination, including lateral cephalogram, 3-dimensional cone beam computed tomographic scan, sleep endoscopy, or cine-magnetic resonance imaging (MRI) [10, 11].

A comprehensive counseling should be undertaken prior to the surgery, discussing potential site of the obstruction and non-surgical treatments options.

3. Surgery selection

There are different surgical procedures used to treat OSA. American Academy of Sleep Medicine recommends that patient should be advised about potential surgical success rates and complications, the availability of alternative treatment options. The desired outcomes of treatment include resolution of the clinical signs and symptoms of obstructive sleep apnea and the normalization of sleep quality, the apnea-hypopnea index, and oxyhemoglobin saturation levels [12, 13].

3.1 Nasal procedures

Nasal obstruction has identified as an important target in the treatment of OSA. The main goal is to relive the obstruction as an adjunctive measure to improve the outcomes of continuous positive airway pressure (CPAP) by reducing CPAP pressure requirements, an oral appliance, or other surgery. Although nasal surgery in isolation does not have a consistent effect on the apnea-hypopnea index in OSA patients, it does have strong evidence on improving snoring, subjective sleep quality, daytime sleepiness, sleep-related quality of life measures, and other important OSA outcome measures [14, 15].

- Turbinate reductions reduce the obstruction caused by inferior turbinate.
- Septoplasty straightening a deformity of the nasal septum.
- Nasal valve surgery improves the airflow in patient with nasal valve obstruction.
- Rhinoplasty corrects any anatomical deformities that compromise the nasal airway.

The most common adverse outcomes for most of the intranasal procedures are postoperative temporary bleeding and temporary nasal congestions. More serious adverse effects could also occur but rare like cerebrospinal fluid leak.

3.2 Upper pharyngeal procedures

3.2.1 Tonsillectomy

The extent to which tonsillar hypertrophy contributes to OSA in adults remains unclear. Tonsillectomy with adenectomy is the first line treatment in pediatric patients with severe OSA and adenotonsillar hypertrophy. It also showed substantial improvement in AHI severity, oxyhemoglobin saturation and sleep quality in obese patient with OSA [16]. Patients who undergo tonsillectomy often experience significant reduction in the CPAP pressure required [17]. The most common postoperative complains include postoperative hemorrhage. Other risks such as pain, fever, and infection could also occur.

3.2.2 Uvulopalatopharyngoplasty (UPPP)

It represented as the first surgical procedure specifically designed to treat obstructive sleep apnea (OSA) and remains the most commonly performed surgical procedure to treat OSA.

There are multiple approaches have been introducing to address the narrowing or collapse of the retropalatal region (**Table 2**). It traditionally involved removal of the uvula, a portion of the soft palate, tonsils and closure of the tonsillar pillars. All the new techniques involve resection or repositioning of the palatal tissues and pharyngeal walls to increase the dimension of the pharyngeal airway to reduce obstruction.

To determine the likelihood for successful resolution of OSA after UPPP, a staging system was developed based on tonsil size, tongue-palate position, and BMI (**Table 3**) [18].

Relocation pharyngoplasty	**Advancing the soft palate and splinting the lateral pharyngeal wall**
Lateral pharyngoplasty	Microdissection of the superior pharyngeal constrictor muscle within the tonsillar fossa, sectioning of this muscle, and suturing of the created laterally based flap of that muscle to the same side palatoglossus muscle
Zetapalatopharyngoplasty (Z-palatoplasty)	Widen the space between the palate and posterior pharyngeal wall, between the palate and tongue base, and either to maintain or even widen the lateral dimensions of the pharynx
Expansion sphincter pharyngoplasty	Consist of tonsillectomy, expansion pharyngoplasty, rotation of the palatopharyngeal muscle, a partial uvulectomy, and closure of the anterior and posterior tonsillar pillars
Palatal advancement	Soft palate is elevated by advancing it towards the hard palate.

Table 2.
UPPP different procedure approaches.

Stage	**Friedman palate position (Figure 1)**	**Tonsil size (Figure 2)**	**BMI**
I	1–2	3–4	<40
II	1–2	0–1-2	<40
	3–4	3–4	<40
III	3–4	3–4	<40
IV	Any	any	>40

Adapted from Ref. [18] and Figures are adapted from Ref. [18].

Table 3.
Friedman clinical staging system for sleep-discorded breathing.

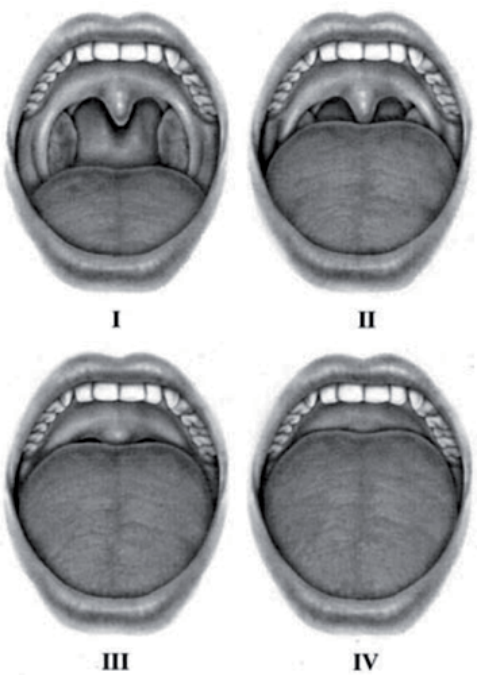

Figure 1.
The Friedman Palate Position is based on visualization of structures in the mouth with the mouth open widely without protrusion of the tongue. Palate grade I allows the observer to visualize the entire uvula and tonsils. Grade II allows visualization of the uvula but not the tonsils. Grade III allows visualization of the soft palate but not the uvula. Grade IV allows visualization of the hard palate only. Adapted from Ref. [18].

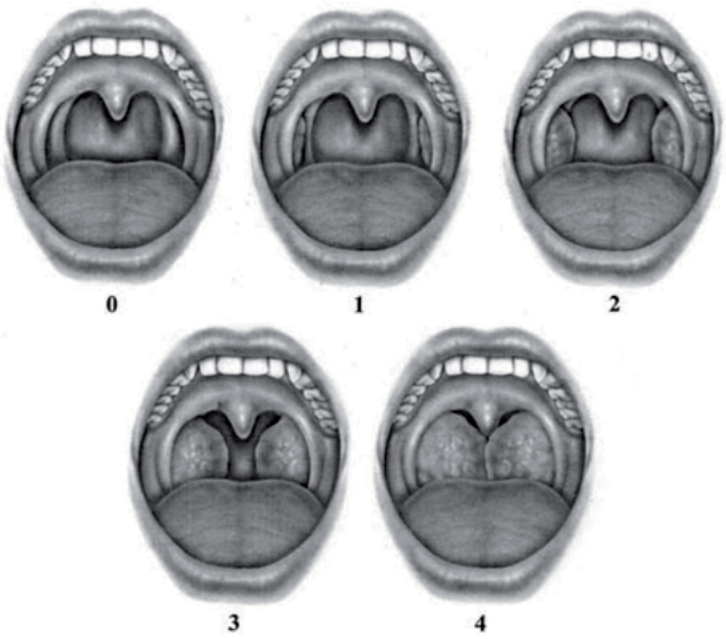

Figure 2.
Tonsil size is graded from 0 to 4. Tonsil size 0 denotes surgically removed tonsils. Size 1 implies tonsils hidden within the pillars. Tonsil size 2 implies the tonsils extending to the pillars. Size 3 tonsils are beyond the pillars but not to the midline. Tonsil size 4 implies tonsils extend to the midline. Adapted from Ref. [18].

Patients with stage I found to have successful outcome of 80% when treated with UPPP. Stage II patients has success rate of 37.9% and only 8.1% for patients with stage III [18].

In a study where they used DISE to evaluate the site of the obstruction with the Friedman clinical staging system for patients selected for UPPP. There was a significant success rate. The result of the surgery as defined by 50% reduction in preoperative AHI with postoperative AHI < 20/h was seen to be 95.2%. There were significant changes in major presenting symptoms (e.g., snoring, excessive daytime sleepiness, disturbed sleep, morning headaches, dry mouth, and forgetfulness) documented 6 months after surgery. Postoperative change in AHI done after 6-month interval was seen to be statistically significant with P value <0.00 [19].

Most common adverse effects of UPPP are severe transient throat pain and chronic subjective dysphagia [20, 21]. Trouble with smell and taste, pharyngeal dryness, globus sensation, voice change, and pharyngonasal reflux were presented after UPPP [20]. The new technique used in UPPP like radiofrequency tissue volume reduction (RFTVR) is safer and less painful than resection technique [20].

For patients, who may still need a CPAP therapy after UPPP surgery, important considerations may include compromise CPAP therapy by increasing mouth air leak and reducing the maximal level of pressure that can be tolerated, especially in procedures with greater resection of soft palate [22, 23].

4. Lower pharyngeal and laryngeal procedures

Multiple procedures were designed to improve the obstruction in the lower pharyngeal airway.

4.1 Tongue reduction procedures

Multiple techniques to improve lower pharyngeal airway by decreasing the volume of the tongue tissues:

1. Radiofrequency tissue ablation: It is a minimal invasive procedure. Application of a temperature-controlled radiofrequency probe to multiple locations in the base of the tongue. It generates submucosal scar tissues that anticipated to reduce the tongue volume.

2. Lingual tonsillectomy: Improves airway by removing obstructing lingual tonsil tissue.

3. Partial midline glossectomy: Resection of the midline tongue base tissue.

4. Submucosal lingualplasty: Resection of submucosal lingual tissue of the tongue base.

4.2 Tongue advancement

Multiple procedures tend to improve lower pharyngeal airway by advance or stabilize the tongue base and pharyngeal muscular:

1. Tongue-base suspension: stabilize the tongue and prevent retrolingual collapse by placing a suture to the anterior mandible to create a tongue base sling.

2. Genioglossus advancement: Advancing the genial tubercle of the anterior mandible forward and create an osteotomy around it.

3. Hyoid suspension: Suspend the hyoid bone to the thyroid cartilage or mandible by using permanent suture. It helps stabilize the base of the tongue and lower pharynx.

Multiple studies showed the effectiveness of lower pharyngeal and laryngeal procedures. It demonstrates improvements in respiratory physiology during sleep, daytime somnolence and quality of life. Successful sleep study outcomes defined as a reduction in AHI of 50% or more and an AHI of less than 20, was achieved in 35–62% of patients [24].

Adverse effects reported were based on the surgical techniques that been used. Pain, hemorrhage, tongue infection airway complications, taste change and dysphagia seen in partial glossectomy, lingualplasty and lingual tonsillectomy [25].

Postoperative pain and submandibular edema were the two most common complications followed radiofrequency tissue ablation [26].

4.3 Maxillomandibular advancement

The maxilla and the mandible are advanced together with both upper and lower teeth to widen the retrolingual and the retropalatal segments of the upper airway. It is beneficial mainly for patients with craniofacial issues, but it is not limited for patients with this problem. The maxilla is moved by a Le fort I osteotomy and the mandible by a sagittal split osteotomy. It is a major operation but showed a significant increase in the pharyngeal airway dimensions and decrease AHI score below the threshold of 20.

4.4 Hypoglossal nerve stimulation

New treatment for OSA by Implantable neurostimulator device was approved by US Food and Drug Administration in 2014. It keeps the lower pharyngeal airway open during sleep by activates the protrusion muscles of the tongue via the hypoglossal nerve.

Eligibility criteria include:

- Age > = 21 years old
- Moderate or severe OSA (AHI > 20 but less than 65 events per hour)
- Predominantly obstructive events (central and mixed apneas <= 25 percent of AHI).
- Unable to tolerate CPAP
- DISE shows no concentric velopharyngeal collapse or any other anatomical findings.
- BMI < 32 kg/m^2

Hypoglossal Nerve Stimulation showed 68% decrease in AHI score, oxygen desaturation index score decreased by 70%, and improved quality of life [27].

Most common reported adverse outcomes are infection, hemorrhage, and tongue weakness. It is still unknown whether there are long term risks.

4.5 Tracheostomy

The most immediate, effective and definitive treatment for OSA is placing a permanent cannula in the neck to bypassing the upper pharyngeal airway. Patient will be able to breath, speak and eat by capping the tube during waking time and open the cannula during sleep. Tracheostomy significantly decreases apnea index, oxygen desaturation index, sleepiness, and mortality in OSA patients [28].

It requires a long-term care to reduce complications (e.g., pneumonia, mucus plugging, peristomal infections). Therefore, it is recommended primarily for patient with sever and life threating OSA who failed all the other treatment options and in morbid obese patients.

5. Weight loss by bariatric surgery

OSA is seen in about 45% of bariatric patients [28]. Surgically induced weight loss showed significantly improves obesity-related sleep apnea. It decreased the mean RDI to 15 ± 2 from 51 ± 4 (preoperatively). In addition, oxygen saturation, sleep efficiency, repaid eye movement latency and the requirement for continuous positive airway pressure [29].

6. Multilevel surgery

Patient with OSA could have multiple locations of collapse in upper and lower pharyngeal tracts. Those patients would benefit from multilevel surgery. DISE is

now a standard procedure during the presurgical evaluation which gives the surgeon personalized anatomical information. A combination of multilevel procedures improved the outcome compare to single-site procedure.

In a meta-analysis that used 49 multilevel surgery articles showed success rate of 66.4% for mixed multilevel surgeries (reduction in the AHI of 50% or more and an AHI of less than 20) [30].

7. Follow up and monitoring

Surgical follow up is based on the type of the surgery. It should include wound management and complications. Patient also needs a long-term follow up by a sleep specialist to evaluate the need for adjunctive use of positive airway pressure or other therapies.

8. Conclusion

There has been a significant improvement in the current surgical techniques for the treatment of the OSA. Surgical management is usually warranted in appropriately selected patients who could not or failed CPAP or other alternative therapies. Also, for patient with anatomical abnormalities that can be corrected. Currently DISE is very useful method and widely used to determine the levels of collapse.

A comprehensive discussion between surgeon and patient prior to the surgery is warranted, discussing realistic expectations of the treatment benefits and complications. Surgical treatments showed long-term benefits in appropriately selected patients but no complete elimination of OSA.

Patient who undergo any surgical procedure will require long term monitoring for recurrence or worsening of OSA.

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The field of sleep medicine has grown and expanded over the last few decades, becoming more complex as technology and knowledge have proliferated enabling more precise diagnoses and treatments. With an improved understanding of sleep medicine and its inextricable interrelationship with neurology, it has assumed a leading role within the general neurological practice. This book provides important insights into the most common sleep and neurological disorders, discussing their interdependence, diagnoses, and treatments.

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