Sleep Diseases

35

Liborio Parrino, Andrea Melpignano, and Giulia Milioli

> *The fountains mingle with the river*
> *And the rivers with the Ocean,*
> *The winds of Heaven mix for ever*
> *With a sweet emotion;*
> *Nothing in the world is single;*
> *All things by a law divine*
> *In one spirit meet and mingle.*
> *—Percy Bysshe Shelley*

35.1 Insomnia

Insomnia refers to a set of different clinical pictures in terms of onset, course, etiology, and therapeutic approach. The sleepless individual can complain of having difficulty falling asleep, not being able to maintain a continuous sleep all night, waking up too early in the morning, or simply having a non-restorative sleep. Each of these subjective disorders, also called nocturnal markers of insomnia, has an identifiable neurophysiological correlation within polysomnography, indicating a non-exclusively mental origin of insomnia. Accordingly, the new DSM-5 [1] and the ICDS-3 consider insomnia a disorder and not simply the symptom of an organic or psychiatric disease. However, in clinical practice, the diagnosis of insomnia is almost exclusively anamnestic. According to the European guidelines [2], the diagnostic procedure for insomnia, and its comorbidities, should include a clinical interview consisting of a sleep history (sleep habits, sleep environment, work schedules, circadian factors), the use of sleep questionnaires and sleep diaries, questions about somatic and mental health, a physical examination, and additional measures if indicated (i.e., blood tests, electrocardiogram, electroencephalogram). Wearable actigraph devices record movements that can be used to estimate sleep parameters with specialized algorithms in computer software programs. This technology is being used increasingly in clinical settings as actigraphy has the advantage of providing objective information on sleep habits in the patient's natural sleep environment and/or when extended monitoring is clinically indicated. Although actigraphy has been well validated for the estimation of nighttime sleep parameters across age groups, the accuracy of sleep-onset latency and daytime sleeping is limited [3]. Moreover, when polysomnographic (PSG) recordings are applied, in many cases, conventional sleep patterns of insomniac individuals do not differ significantly from those of good sleepers, and a number of patients with insomnia underestimate the actual objective sleep time. Accordingly, PSG may be useful to rule out other sleep disorders (e.g., sleep-disordered breathing, periodic limb movement disorder) in patients who appear to meet criteria for a chronic insomnia disorder. The discrepancy between subjective and objective data represents a critical issue and raises the question whether alternative metrics of sleep quality (e.g., the analysis of sleep microstructure or related physiological parameters) are more pertinent than the conventional measures of sleep latency, total sleep time, and wake after sleep onset [4].

35.1.1 Insomnia and Instrumental Findings

Although questionnaires and sleep logs may supply relevant information regarding sleep habits, self-reports of sleep latency, number of awakenings, and nocturnal wakefulness are often imprecise due to insomniacs' underestimation of total sleep time. In contrast, PSG can offer objective data on the typical features of insomnia. In particular, sleep macrostructure shows altered metrics with a longer sleep latency, more stage 1 sleep and less SWS sleep [5–7]. In a meta-analysis of PSG studies comparing good sleepers (n. 485) and patients with chronic insomnia disorder (n. 582) [8], Baglioni et al. described consistent differences in sleep latency, total sleep time, sleep efficiency, and wake after sleep onset (with a difference of 12 min in subjective data collected from diaries). A reduction in REM sleep and SWS (slow wave sleep) was also detected. Finally, PSG features may be exploited to evaluate and compare different therapies (CBT or drug) applied in the treatment of insomnia [9, 10].

L. Parrino (✉) · A. Melpignano · G. Milioli
Department of Medicine and Surgery, Sleep Medicine Center, University of Parma, Parma, Italy
e-mail: liborio.parrino@unipr.it

Besides conventional PSG measures, integrative information can be supplied by sleep microstructure. In several studies, EEG spectral analysis in insomniacs revealed an increase of power in beta and sigma band during NREM sleep compared to healthy sleepers [11, 12]. Increased activity in the beta frequency band also during rapid eye movement (REM) sleep has been reported [13–15]. Increased activities in NREM and REM sleep in faster frequency bands suggest an excessive cortical activation and link insomnia to physiological and emotional hyperactivation as predisposing, precipitating, and maintaining factors [16].

Accordingly, insomnia reflects also an altered hormonal and autonomic condition. Compared to good sleepers, insomniacs usually present a higher metabolic rate as well as a faster cardiac rhythm on a 24 h basis [17], and the presence of chronic insomnia (with TST shorter than 5 h) is associated with an increased risk of arterial hypertension and acute cardiovascular diseases [18]. In other words, the impact of insomnia is not simply confined to the sleep metrics (subjective or objective) but reverberates also on the global balance of the living system with a heavy biological burden on wellness and health.

35.1.2 CAP Role in Insomnia

A microstructural component that is always altered in pathologic sleep is the cyclic alternating pattern (CAP).

CAP is a periodic EEG activity occurring under conditions of reduced vigilance (sleep, coma). It is characterized by sequences of CAP cycles defined by an A phase (transient electrocortical events that are distinct from background EEG activity) and by the following B phase (return to background EEG activity).

CAP translates a neurophysiological condition of unstable sleep, and the amount of CAP correlates significantly with the subjective perception of sleep quality [19].

Good sleep quality is associated with low CAP values that undergo age-related differences across the life span.

The enhancement of CAP time and CAP rate is a regular feature in insomniac patients, independent of cultural or genetic factors. A study on a large sample of Caucasian patients with primary insomnia showed that CAP parameters consistently correlate with sleep quality and it can be useful to quantify the effectiveness of hypnotic treatment [20]. Similar findings were described on insomniac Japanese patients in a randomized crossover comparative study with placebo which demonstrated that zolpidem medication consolidates sleep stability with a reduction of CAP rate and improves sleep perception [21].

The subtle information supplied by CAP parameters is clinically useful in insomniac patients who show a mismatch between subjective reports (poor sleep quality, nocturnal awakenings) and conventional PSG parameters. Compared to normal controls, insomniacs with sleep misperception (also defined paradoxical insomnia) show significantly higher amounts of CAP rate in stage 1 and in stage 2, but not in slow-wave sleep. Misperceptors report lower but longer amounts of subjective awakenings (mean: 4) in contrast to objective findings (mean: 11). The mismatch is related to the high amounts of CAP between successive awakenings which are merged together by the patient in a single experience. In other words, if sleep between two successive awakenings is superficial (expressed by sleep stages 1 and 2), unstable (as reflected by increased amounts of CAP), and fragmented (increased arousal index), the time separating the two events is perceived as continuous wake. Misperceptors interpret as wakefulness their difficulty to maintain consolidated sleep [22].

In conclusion, an increased amount of CAP is a typical PSG finding in insomniac patients, even without a clear-cut sleep macrostructure disruption.

Therefore, PSG microstructural measures can feature an important role in the objective identification of a sleep disorder, even when conventional sleep measures appear unaltered.

The additional value of sleep microstructure is also supported by the tight association between CAP and autonomic arousals, which are often neglected in the evaluation of biological price of chronic insomnia.

Finally, microstructural investigation can shed light on the treatment strategies of insomnia as CAP parameters allow us to discriminate hypnotic drugs from placebo, benzodiazepines from Z-drugs, and zopiclone from zolpidem [23].

35.2 Parasomnias

Parasomnias are defined as undesirable motor events or experiences that occur during sleep onset, inside sleep, or during arousal from sleep. Parasomnias may occur during NREM sleep (NREM parasomnias: disorders of arousal, confusional arousals, sleepwalking, sleep terrors) and REM sleep (REM parasomnias: REM behavior disorder, recurrent sleep paralysis, nightmare disorder).

The main pathophysiological mechanism of parasomnias is a boundary failure between wakefulness and sleep [24].

Parasomnias play a relevant role in clinical practice, although they are common and usually benign during childhood when they are considered as an expression of a non-

completed brain maturation. In adulthood they may trigger severe injuries to the patient or to the bed partner and cause social impairment and related medicolegal issues.

35.2.1 NREM Sleep Parasomnias (Disorders of Arousal)

This group includes confusional arousals, sleepwalking, and sleep terrors which are not distinct conditions but rather a continuum of behavioral patterns. They derive from a partial arousal from deep NREM sleep, less frequently from superficial NREM sleep. During the episodes the subject presents a reduced or absent responsiveness and impaired cognition functionality or a dreamlike imagery. Usually patients are amnesiac for the episode. Eating behavior can occur during sleep in a condition of full awareness (nocturnal eating syndrome [25]) or unconsciousness (sleep-related eating syndrome [26]).

Typically the events occur during the first third of sleep, when SWS is predominant. The confusional state can last several minutes or longer [27].

35.2.1.1 Confusional Arousal

The episodes are characterized by mental confusion or confused behavior that occurs while the patient is sleeping. The subjects seem disoriented, nonresponsive to external stimuli, and cognitively impaired but do not show signs of fear. Confusional arousals usually begin with a sitting up in bed and looking around in a dazed deportment without walking outside the bed [28].

During the episodes violent behaviors may appear, especially if the patient is abruptly awakened. Sometimes confusional arousals coexist with sleepwalking. A confusional arousal emerging from REM sleep is rare. Intracerebral recording demonstrated, during an episode of confusional arousal, the occurrence of fast EEG activities in motor, cingulate, insular temporopolar areas and the concomitant presence of slower activity in frontal regions [29].

35.2.1.2 Sleepwalking

With this term we mean a group of behaviors that typically begin from an arousal during deep NREM sleep and proceed to leaving the bed with an impaired state of consciousness [30].

35.2.1.3 Sleep Terror (Pavor Nocturnus)

Episodes of intense fright or terror, usually associated with agitation and screaming, that arise suddenly from NREM sleep. They are common in childhood. The patients during episodes are not completely responsive and are totally

inconsolable [31]. Commonly a strong autonomic activity is present (tachycardia, flushing, mydriasis, sweating).

35.2.2 PSG Features of NREM Parasomnias

EEG can show brief periods of delta activity, a stage 1-like pattern, or repetitive microsleeps or a diffuse, poorly reactive, alpha rhythm.

Especially in sleepwalking, diagnostic PSG may detect high-amplitude hypersynchronous delta waves and, sometimes, frequent arousals from slow-wave sleep. However, these findings do not have a high specificity, since they have been described in the normal population and in subjects with sleep-related breathing disorders [32] (Fig. 35.1).

Video-PSG is mandatory for the diagnosis. A disorder of arousal must be distinguished from sleep apnea-related arousals, paroxysmal arousals in sleep-related hypermotor epilepsy (SHE), or RBD (REM Behavior Disorder). PSG allows us to identify possible triggering factors, such as sleep apnea or periodic limb movements. Sleep deprivation [33], acoustic stimulation during sleep [34], hypnotic agents (e.g., Z-drugs [35]), or antidepressant drugs can evoke parasomnias in predisposed individuals [36].

In NREM parasomnia sleep macrostructure is usually well preserved, but sleepwalkers show numerous awakenings from SWS and decreased delta power [37].

Sleep microstructure can exhibit some alterations. In adult with somnambulism, power spectral analyses of slow-wave activity show high quantity of slow-wave sleep disruption (principally during the first sleep cycle) or a significant increase in delta power just prior to an arousal. An increased slow-wave activity across all NREM sleep cycles has been reported [38, 39].

35.2.3 REM Parasomnias

35.2.3.1 REM Behavior Disorder

REM behavior disorder (RBD) is characterized by abnormal behaviors during REM sleep that may cause injury or sleep disruption. The main finding is an EMG abnormality during REM sleep characterized by an excess of muscle tone (REM without atonia or RWA) and/or an excess of phasic EMG twitch activity during REM sleep [40] (Fig. 35.2).

These abnormal behaviors seem to resemble the dream content (i.e., dream-enacting behavior).

Acting out dreams may consist in many different motor manifestations, such as talking, limb twitching, yelling, punching, kicking, and developing dangerous patterns for the patient or for the bed partner.
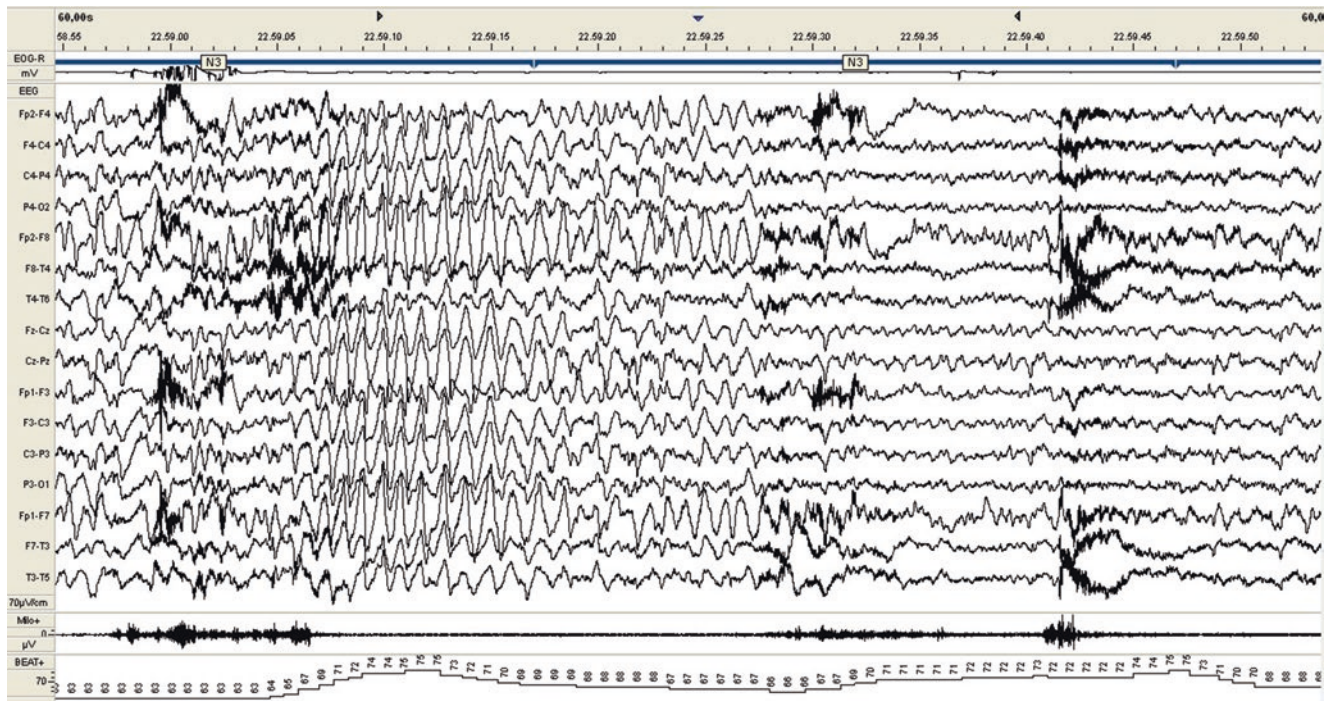
Fig. 35.1 Hypersynchronous delta activity in N3 associated with confusional arousal and sleepwalking in a patient with NREM parasomnia
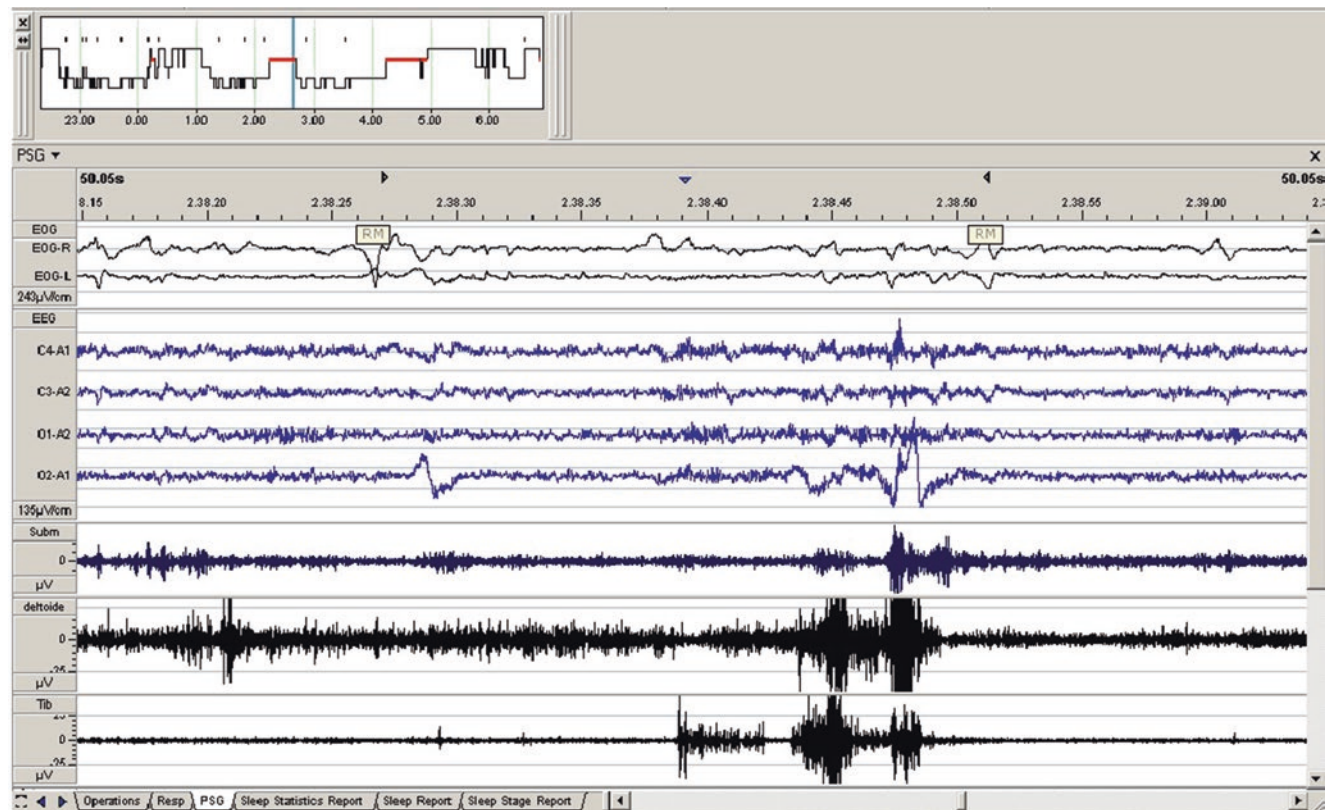

Fig. 35.2 Persistent EMG activity in the chin and phasic EMG activity in tibialis anterior and deltoid muscles in a patient with REM behavior disorder (50 s of recording)

RBD exists both in an acute form and a chronic form. Acute forms are mainly caused by tricyclic antidepressants, serotonin-selective reuptake inhibitors, beta-blockers, or abrupt alcohol withdrawal [41].

The chronic form can be idiopathic (iRBD), when no causes are found, or associated with neurological disorders (secondary form). The main associations are with neurodegenerative disorders, narcolepsy [42], or various kinds of brain stem lesions (ischemic, malignancy, inflammatory, or autoimmune) [43]. The most consistent association of RBD is with Parkinson disease, Lewy body dementia, and multiple system atrophy [44]. Accordingly, RBD can be considered a prodromal stage of synucleinopathies [45].

PSG reveals an excessive amount of continued or intermittent loss of REM atonia and/or excessive phasic muscle twitch activity of the submental and/or limb EMGs during REM sleep.

In the evaluation of RBD, any (tonic/phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in >27% of REM sleep (scored by 30-s epochs) reliably distinguishes RBD patients from controls.

RDB patients may present a decreased autonomic reactivity, for example, a lack in tachycardia during phasic sleep events. In addition, REM sleep also shows a higher prevalence of PLMs (periodic limb movements), which are less connected to EEG arousals or to sleep disruption compared to patients with a PLM disorder or a restless legs syndrome [46].

The architecture of macrostructure is preserved with a maintenance of a NREM-REM cyclicity. However, a larger representation of SWS can be detected with a higher delta power [47].

PSG recording is fundamental also to rule out some mimicking conditions such as arousal disorders, seizures in sleep, although rare in REM sleep, nightmares, post-traumatic stress disorder, or sleep-related respiratory disorders with RBD-like motor events during the breathing recovery [48].

35.3 Sleep-Related Movement Disorders

Some very common disorders are included in this category such as restless legs syndrome (RLS), periodic limb movement disorder (PLMD), bruxism, and propriospinal myoclonus.

Sleep movements can provoke a severe sleep disruption with serious daytime consequences. Recently, they have been associated to increased vascular risk [49]. Usually these movements are simple, stereotyped, and unintentional. Their classification is founded on the body part involved or on the kind of movement. They are also separated in two different groups: primary and associated to other conditions.

35.3.1 Restless Legs Syndrome and Periodic Limb Movements

RLS is a sensorimotor disorder; its main feature is an unpleasant sensation in lower limbs which generates an uncontainable urge to move them. Limb movement induces a transient relief. This sensation appears in rest condition, especially when the patient is waiting to sleep [50]. In this scenario the patient complains of severe secondary insomnia. RLS is usually associated, when eventually the patient falls asleep, to periodic limb movement (PLM). PLM consist in phasic motor events involving usually lower limbs, which arise in sleep, most frequently in light NREM sleep and more commonly in the first sleep cycles of the night. Sometimes they can emerge while the subject is falling asleep (PLM during wake).

PLM jerks appear as toe extension and ankle dorsiflexion with, sometimes, flexion of the knee and hip. Thus, they resemble the Babinski sign and spinal cord flexor reflex, phenomena connected to the spinal disinhibition caused by a lesion of the pyramidal system [51]. The contraction duration is between 0.5 and 10 s, and the episode must be composed of at least four consecutive movements. Between consecutive episodes the time range is 5–90 s. The majority of PLM events are separated by intervals of 20–40 s. Their detection is achieved by means of surface electromyogram of the tibialis anterior muscle. It is possible to record PLM on other muscles or using actigraphy. In the presence of two isolated movements of tibialis anterior muscles, these limb movements are considered as bilateral and thus as a unique phenomenon if they are separated by an interval shorter than 5 s. Otherwise they are considered as monolateral if the interval is longer than 5 s.

The consequences of PLM on sleep are still a matter of debate. They are often associated with EEG arousals or with a heart-breathing rate activation or blood pressure increase [52].

The EEG arousal may precede, be concomitant, or follow the movement. These observations suggest that limb jerks are endowed into a dynamic physiologically oscillating process of sleep, with a 20–40 s periodism which involves different systems, including cortical, vegetative, and behavioral functions. PLM has a close relationship with the oscillations of CAP, which acts as a permissive window (in particular, phase A).

A certain amount of limb movements are physiological during sleep in healthy individuals. In adults, a PLM index (number of limb jerks/hours of sleep) is pathological if higher than 15 [53].

A high PLM index is a common finding in many different sleep disorders such as narcolepsy, RBD, and OSAS. PLM is frequently associated with RLS (80%) [54] and can be considered a PSG marker of this pathology. PLM has been
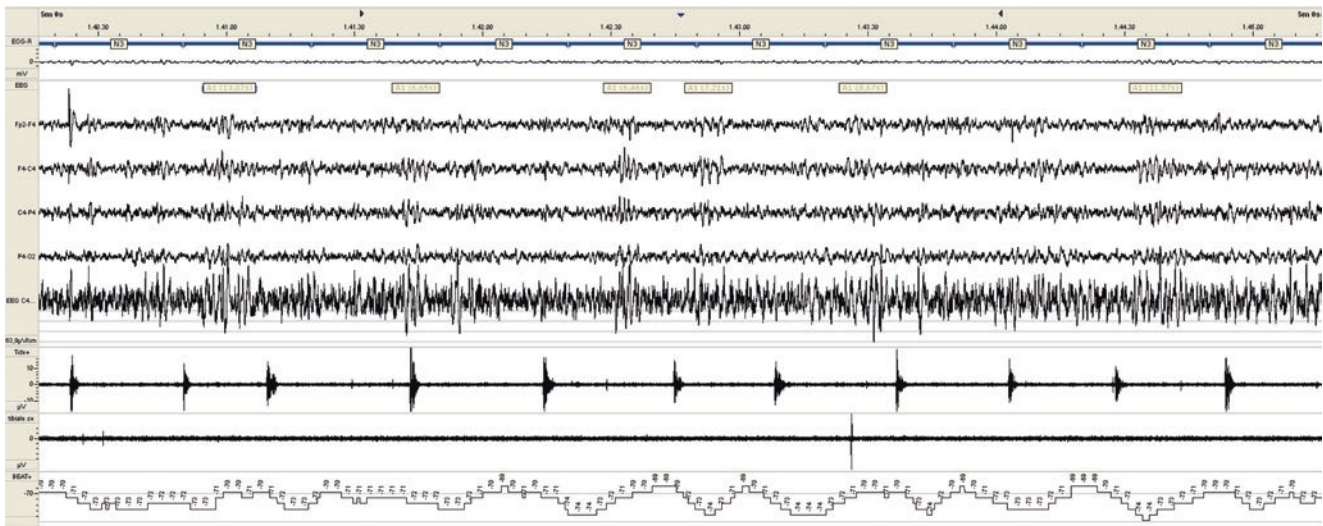
Fig. 35.3 A 5 min sample of PSG of a patient with PLMD. The PSG shows repetitive contractions on the right tibialis muscle associated EEG arousal that may precede, be concomitant, or follow the movement. An increase in the heart rate is synchronous with the movement

reported in other neurological or medical conditions such as heart failure [55] with or without periodic breathing, renal failure, Parkinson disease, Gilles de la Tourette syndrome, spinocerebellar ataxia, iron deficiency and in association with drug administration (SSRI, tricyclic, phenothiazines, lithium). In RBD, PLM events are often present in REM sleep [54].

A PLM > 15 related to poor sleep quality is defined as PLM disorder (PLMD) which is usually described by the patient as difficulty in maintaining sleep, non-restorative sleep, or agitated sleep [53] (Fig. 35.3). Habitually, the patient is not aware about the movements. For this reason it is advisable to perform a PSG with leg EMG or an actigraphic study. It is important to rule out other sleep disorders which can produce sleep movements such as OSAS, insomnia, and epilepsy.

PLM must be distinguished from sleep starts (brief non-periodic motor events lasting 20–100 ms, typical of sleep-wake transitions), REM twitches (phasic muscle tone increases arising in REM sleep), fragmentary myoclonus (incidental EMG findings of small movements of the corners of the mouth, fingers or toes, or by no visible movement at all), and nocturnal leg cramps (prolonged and painful contraction of the gastrocnemius muscle, rarely the tibialis, with a complete arousal of the patient).

35.3.2 Propriospinal Myoclonus at Sleep Onset

Propriospinal myoclonus (PSM) at sleep onset is a disorder of the transition from wakefulness to sleep, rather than a classically defined sleep disorder. This condition is rare and consists of sudden and brief (less than 500 ms) myoclonic jerks which occur during the falling asleep shift (less frequently, during intrasleep wakefulness and upon the final awakening), involving the abdomen, trunk, neck, and sometimes limbs. Patients often report a transient prodrome anticipating motor manifestations [56].

Myoclonic jerks can be isolated or organized in sequences and induce an arousal and secondary insomnia. PSM is usually spontaneous but sometimes can be triggered by external stimuli. PSM is never associated to loss of consciousness.

EMG findings reveal that jerks origin from a single myelomere and diffuse rostrally and caudally at the same time. The propagation velocity is 2–16 ms (less than the physiologic velocity of the voluntary pyramidal system). PSM can be idiopathic or caused by a medullary lesion of various nature.

PSG shows myoclonic nonperiodic EMG bursts and EEG reveals an alpha activity. In particular, myoclonic jerks are associated to an EEG alpha activity spreading from the posterior to the anterior regions. Epileptiform discharges are totally absent. EEG desynchronization, mental activity, or the onset of sleep spindles and K-complexes interrupts jerk occurrence. EEG back-averaging techniques show absence of a premotor cortical potential. PSG is mandatory to rule out other conditions such as epileptic myoclonus, sleep starts, phasic REM twitches, fragmentary myoclonus, or psychogenic myoclonus.

35.3.3 Sleep-Related Bruxism

Bruxism consists of an excess of repetitive and rhythmic masticatory activity occurring during sleep (or wakefulness),

which induce a detrimental effect on sleep structure and/or mandibular pain and/or temporal cephalalgia or tooth injury [53]. These movements are connected to the typical noise caused by tooth scraping. In physiological sleep, non-volitional movements of masticatory muscles are common. These movements can be phasic or tonic. A normal frequency is defined as 1–2 episodes per hour.

Bruxism prevalence is high in children and tends to decrease over age. Primary forms are more frequent but secondary forms are also reported. They can be related to different conditions such as Parkinson disease, drug administration, Down syndrome, cerebral palsy, OSAS, or parasomnia such as RBD.

Etiology is still unknown. Psychosocial components and a genetic predisposition may play a role in the pathogenesis [57]. The role of dental imperfection or of occlusal defects is uncertain. High level of catecholamine in urine has been reported, and this could mean a relationship with stressing situations [58].

Performing a complete video-PSG is not mandatory for the diagnosis. Nevertheless, PSG may be useful to prove the disorder and rule out possible associations with sleep-related respiratory disorders, gastroesophageal reflux, RBD, night terrors, facio-mandibular myoclonus, or epilepsy.

In mild cases, PSG sensitivity is not high due to the night-to-night variability in RMMA (rhythmic masticatory movement activity) and tooth grinding.

PSG must include EMG on masseter muscles (at least one) and video-audio recording to detect the typical noise of grinding. Phasic and tonic muscular activity are scored as movement or artifacts on the EEG channels and as EMG contractions on masseter muscles (Fig. 35.4). Phasic RMMA last from 0.25

to 2 s, with a 1.2 Hz frequency. Tonic activity is more prolonged. It is possible to observe mixed patterns. A single episode of bruxism must be separated from another by an absence of muscle activity of at least 3 s. It is possible to evaluate muscle activity with EMG and observe RMMA with video.

Bruxism can arise in all sleep stages, but it is more frequent in light sleep. Rarely, RMMA can be present in REM sleep. In some patients RMMA occur exclusively in REM sleep.

Bruxism episodes are often associated to EEG arousals and microarousals (up to 80%) and autonomic activation, starting with a raise in sympathetic cardiac activity and with a faster EEG activity in the seconds/minutes preceding a RMMA [59].

Though a clear sleep disruption is rare in bruxism, RMMA induce always microstructure perturbation with an increase of CAP phase A3 subtypes which act as "permissive windows" for the occurrence of RMMA during sleep [60].

35.4 Epilepsy

35.4.1 Impact of NREM and REM Sleep

During NREM sleep, virtually every cell in the brain discharges synchronously [61]. Synchronous synaptic effects, whether excitatory or inhibitory, could augment the magnitude and propagation of postsynaptic responses, including epileptic discharges. Background EEG effects seem to be exacerbated by sudden surges of afferent stimulation associated with transient, synchronous phasic arousal events. Generalized seizures, particularly generalized tonic-clonic or myoclonic convulsions, tend to occur during NREM sleep
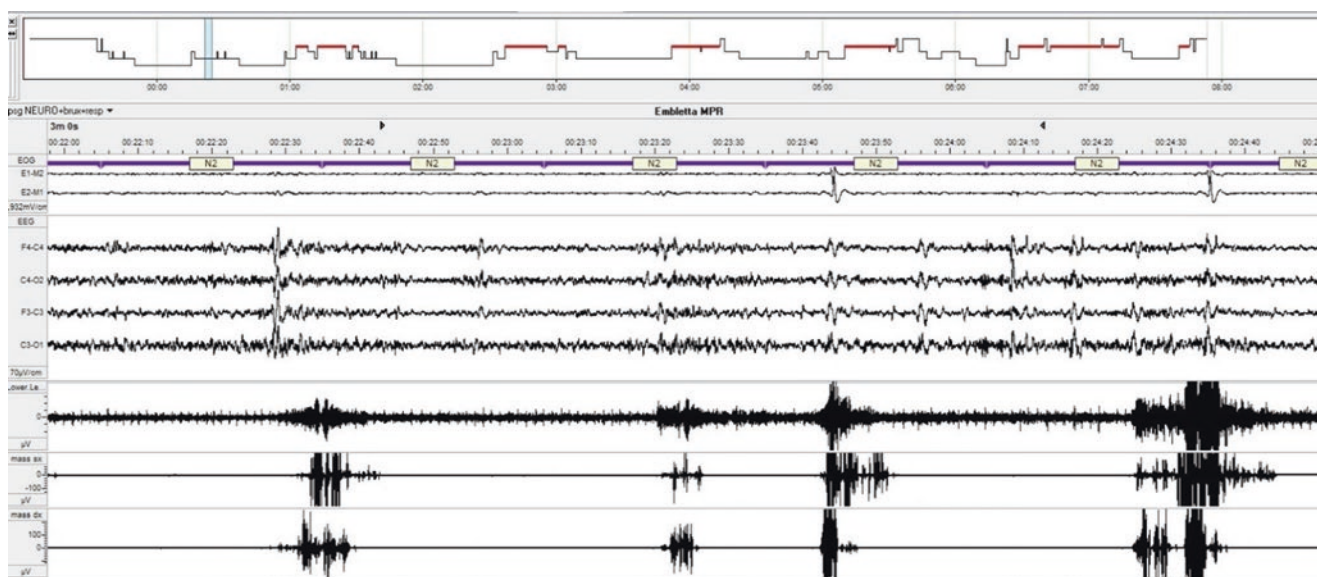

Fig. 35.4 Regular bilater contractions of masseter muscles during N2 in patient with bruxism

or transitional arousal periods characterized by background EEG synchronization, often with phasic events that include sleep EEG transients such as sleep spindles, K-complexes, and ponto-geniculo-occipital waves. In the majority of patients with primary generalized epilepsy, frequent brief bursts of spikes, polyspikes, and spike-wave-like discharges are associated with K-complexes or spindles, which are specific phasic EEG patterns of NREM sleep [62].

Most epileptic syndromes show non-persistence of ictal and interictal discharges during REM sleep. Characterized by asynchronous cellular discharge patterns [63] and skeletal motor paralysis, REM sleep is resistant to propagation of epileptic EEG potentials and to clinical motor accompaniment [64], even though spontaneous phasic activity and focal EEG discharges persist at this time and may be evoked by photic stimulation. Although antigravity muscle tone is preserved in NREM sleep and waking, thus, permitting seizure-associated movement, profound lower motor neuron inhibition occurs in REM, creating virtual paralysis and preventing seizure-related movement.

These findings indicate that substrates of state-specific components rather than integrity of the state per se can be salient determinants of seizure propagation, regardless of the epileptic syndrome.

35.4.2 CAP and Epilepsy

Pioneering contributions in the early 1990s [65–67] focused attention on the dynamic relationship between epileptic paroxysms and EEG phasic events during sleep. These studies highlighted the relevance of arousal instability as an important triggering factor of epileptic paroxysms. In primary generalized epilepsy, in temporal lobe epilepsy, and in patients with focal lesional frontotemporal epilepsy, interictal discharges are commonly activated during unstable sleep, with a number of EEG paroxysms per minute of sleep significantly higher during CAP compared to non-CAP. Phase A has a significant activation influence, whereas phase B exerts a powerful and prolonged inhibitory action. On the contrary, despite the high burst frequency during NREM sleep, interictal epileptiform discharges in benign epilepsy with Rolandic spikes are not modulated by the arousal-related mechanisms of CAP. A sleep condition of highly fluctuating vigilance constitutes a favorable substrate also for the occurrence of focal epileptic seizures. In patients affected by focal epilepsy, the great majority of nocturnal partial motor seizures occur during NREM sleep, more frequently in CAP than in non-CAP sleep and in phase A than in phase B.

35.4.3 Sleep-Related Hypermotor Epilepsy

In 2016, the syndrome previously known as nocturnal frontal lobe epilepsy (NFLE) was defined as sleep-related hypermotor epilepsy or SHE [68]. Clinically, SHE is characterized by short-lasting seizures (<2 min) patterned by repetitive and stereotyped motor events in the same subject. Besides complex hypermotor seizures, paroxysmal arousals and minor motor events are the most common clinical manifestations, occurring most commonly during the night. Most seizures occur periodically during non-REM sleep (Fig. 35.5).
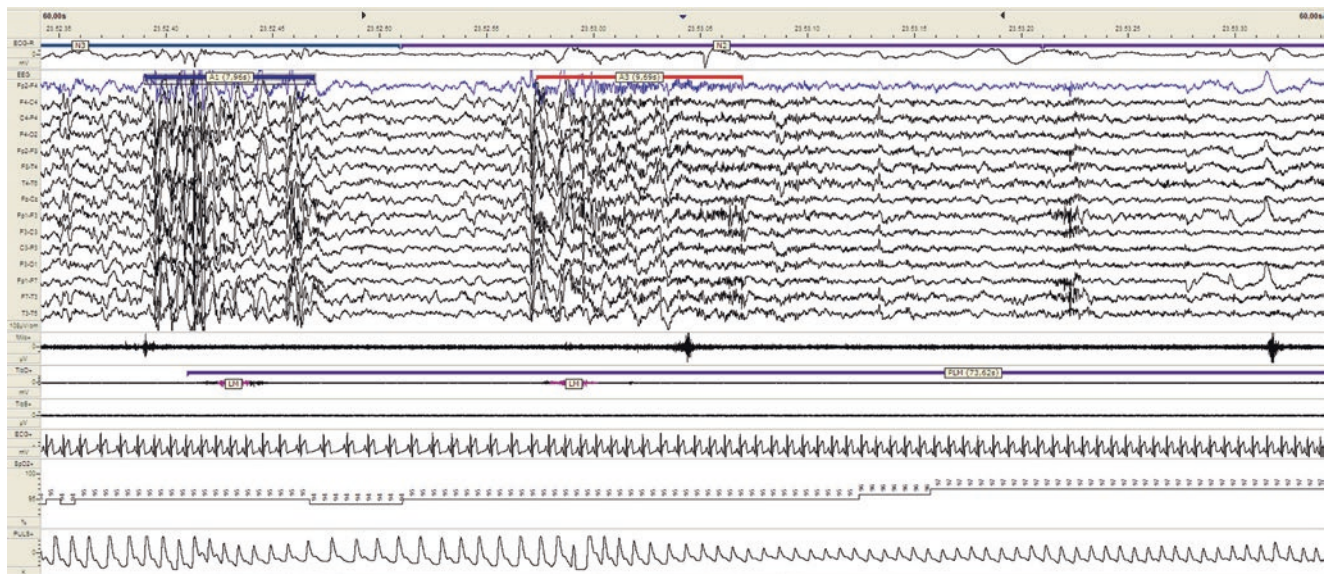

Fig. 35.5 60 s of PSG recording of a patient with a sleep-related hypermotor epilepsy. High-amplitude generalized epileptic discharges, with right frontal prevalence, associated with a minor motor event, trigger the onset of A phases of CAP

Differential diagnosis between SHE and parasomnias can represent a challenging issue. In the large majority of patients, neurologic and neuropsychological assessment is normal [69]. Diagnosis of SHE cannot be excluded even when interictal and ictal features are lacking in the EEG, both during sleep and wakefulness. Clinical history is the starting point for the diagnosis of SHE. According to the new definition, diagnostic criteria of SHE are based on three levels of certainty: witnessed (possible) SHE, video-documented (clinical) SHE, and video-EEG-documented (confirmed) SHE.

New insights into the biology of SHE occurred with the discovery of an autosomal dominant form and identification of the first gene, CHRNA4, encoding a neuronal nicotinic receptor subunit [70].

Further investigation has ascertained that SHE shows similar clinical features both in familial and sporadic cases, although autosomal dominant inheritance is characterized by a marked intrafamilial variation in severity [71, 72]. Three individuals affected by a possible SHE with genetic transmission were described in 1872 by Darwin and Galton [73].

Although SHE may have diverse etiologies, it is defined by clinical manifestations (hypermotor seizures), possibly resulting from shared downstream mechanisms occurring during sleep/wake oscillation changes, suggesting a unique pathogenic network [74, 75].

Because ictal discharges may arise not only from frontal lobe [76, 77] but also from various extrafrontal areas [78], this might suggest the ictal involvement of common cortico-subcortical networks [79] or a release phenomenon of stereotyped inborn fixed motor pattern. Tassinari et al. [80] claim that genetically determined motor behaviors essential for survival (feeding, locomotion, reproduction, etc.) are under the control of central pattern generators (CPGs), neuronal aggregates located in the brain stem and spinal cord. During sleep, transient arousals triggered by epileptic events or brain dysfunction can "activate" or "release" CPGs responsible for involuntary behavioral patterns. In NREM sleep, where muscle tone is still operative, EEG synchrony allows multiple levels of expression (from N1 to N3), and a variety of motor events can take place from seizures to parasomnias. Whether the outcome is a muscle jerk or a major epileptic attack will depend on a number of ongoing factors (sleep stage, delta power, motor chain, body position, etc.), but all events will share the common trait of arousal-activated phenomena. These findings suggest that arousal during sleep is the common condition for the onset of motor patterns which are already written in the brain codes (GPG) but require a certain degree of activation (arousal) to become visibly apparent. In this case, arousal acts as a trigger releasing or facilitating an encoded "kinetic melody" [75, 80, 81]. Stereo-EEG investigation of sleep, nocturnal epilepsy, and parasomnias can shed light upon the specific epileptogenic networks involved during ictal activity and unveil the local electrophysiological dissociated substrate of parasomnias [82, 83].

A common feature is the onset of all episodes during NREM sleep, with different distributions within the sleep stages. Major attacks prevail in N3, leading abruptly to a wake condition. Paroxysmal arousals and minor motor events may recur every night, sometimes several times per night, arising mainly from CAP in stage 2 [84].

Patients affected by SHE frequently report a poor sleep quality, fatigue, and excessive daytime sleepiness ascribed to the presence of recurrent seizures and motor episodes during sleep. In these patients, enhanced sleep fragmentation and higher percentages of wakefulness are common polysomnography findings, as well as increased amounts of CAP rate [85]. The presence of an epileptic focus in the frontal regions likely represents an internal disturbance that interferes subcontinuously with the stability of NREM sleep. Though extremely short-lived, the interictal epileptiform discharges in SHE is an activating event sharing the same pathways of arousal instability.

PSG recordings show that increased arousal instability is very common in SHE, particularly when multiple events occur during sleep (Fig. 35.6). Some studies suggest that macrostructural sleep disturbances and enhanced arousal instability are part of the syndrome. In SHE, stereotyped manifestation not only involve motor behaviors but also polysomnographic (PSG) patterns [74]. Baseline PSG recordings of 40 patients (20 males and 20 females; mean age, 31 ± 10 years) with a diagnosis of SHE were compared with those of 24 age- and gender-balanced healthy subjects without sleep complaints (controls). SHE patients showed a significant increase in wake after sleep onset, slow-wave sleep duration, and REM latency, whereas REM sleep was significantly lower. SHE patients also showed a significant increase of CAP time, CAP rate (72 vs 32% in the control group), CAP cycles, and mean duration of CAP sequences. These findings were associated with a significant enhancement of all subtypes of the A phases of CAP (mainly subtype A1). A total of 139 epileptic motor events supported by video-PSG evidence were counted. NREM sleep included 98% of all seizures, which were especially abundant in the first sleep cycles, decreasing in frequency together with the progressive decline of deep sleep. Ninety percent of total NREM seizures occurred during a CAP sequence, and CAP-related seizures occurred in association with a phase A.

In SHE patients, the robust enhancement of sleep instability was associated with an increased amount of all phase A subtypes of CAP, especially phase A1, without relevant changes of respective percentages. Studies of scalp mapping obtained with electromagnetic tomography during sleep show that slow-wave activity (0.25–2.5 Hz), a main
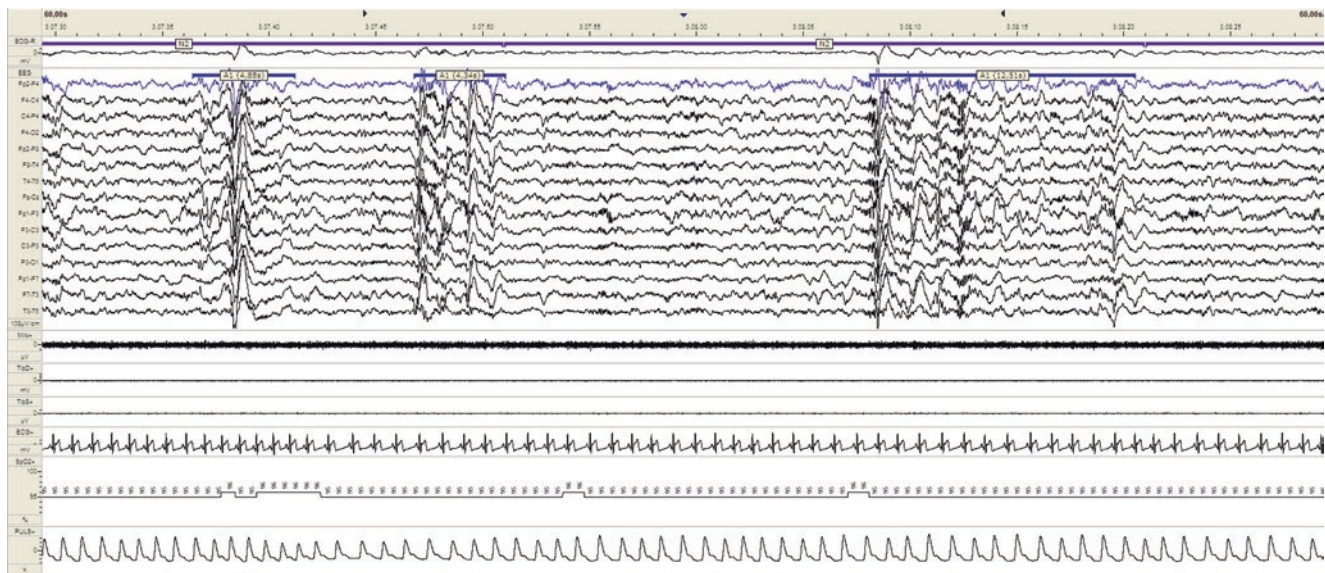
Fig. 35.6 A CAP sequence (unstable sleep) in NREM sleep modulated by epileptic activity in a case of sleep-related hypermotor epilepsy

component of A1 phases of CAP, has a major representation over the frontal and prefrontal regions, whereas fast activities (7–12 Hz), mainly associated with phases A2 and A3, have a parieto-occipital prevalence (Ferri et al. 2005). These findings suggest a primary role of the high-amplitude low-frequency CAP phase A components, that is, EEG delta activity or K-complexes, on the occurrence of ictal episodes [84, 86–90]. In this perspective, subtype A1 of CAP could be considered as frontal lobe arousals, periodically causing an increase of cerebral excitability that triggers the onset of frontal seizures.

According to these premises, diagnosis of SHE based exclusively on video-recorded phenomena, without EEG support, is not satisfactory, especially for paroxysmal arousals and minor motor events [91]. Moreover, a number of sleep parasomnias may occur during NREM sleep, and differentiating these conditions from SHE only through visual patterns can be problematic [79, 92–94]. Therefore, only the integrated evaluation of nocturnal video-EEG features, PSG metrics, and underlying regulatory sleep processes can help to clarify diagnostic uncertainties. These integrative criteria for the diagnosis of SHE can supply precious information on the effects of antiepileptic treatment.

35.5 Hypersomnia of Central Origin

Hypersomnia of central origin is represented by narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, and Kleine-Levin syndrome. Hypersomnia can also be due to medical disorders, medication, and psychiatric diseases or be secondary to insufficient sleep [53].

35.5.1 Narcolepsy Types 1 and 2

Narcolepsy type 1 (NT1) is a chronic, non-degenerative, neurological disorder characterized by excessive daytime sleepiness and cataplexy (a generalized or focal sudden, short-lasting, loss of muscle tone during wake provoked by intense emotion, particularly positive, without loss of consciousness). Cataplexy can be considered a pathognomonic manifestation of narcolepsy type 1 [95].

The cause of NT1 is a massive loss of orexin-producing neurons localized in the lateral hypothalamus [96]. An autoimmune origin for the selective cell loss is suspected: almost 90% of NT1 patients exhibit a specific HLA haplotype positivity (DQB1*0602) [97]. This haplotype is found in 20% of healthy individuals (for this reason it is especially useful if negative in doubtful cases). One of the main diagnostic criteria is the low level of orexin in the CSF (below 110 pg/mL) or < 1/3 of the mean values obtained in normal subjects with the same standardized assay. If low CSF level of orexin is found, a diagnosis of NT1 can be done even if cataplexy is not present [53].

Other manifestations consist of phenomena of REM sleep dissociation such as sleep paralysis, hallucination during sleep onset or during awakenings, intense and even lucid dreaming, and sometimes REM without atonia.

Daytime sleepiness is characteristically incoercible and sudden (sleep attacks) and can appear in situations of passive activity but sometimes may occur in more active circumstances. Usually the daytime sleep lasts less than 20 min and it is deeply restoring. One of the hallmarks of narcolepsy is an early appearance, within 15 min after the sleep onset, of REM sleep (sleep-onset REM periods—SOREMPs). In

addition to these features, a difficulty in maintenance of nocturnal sleep is often reported.

Narcolepsy type 2 is not a well-defined pathologic entity, and it is also called "narcolepsy without cataplexy." Orexin level is normal (in the 8% of cases, an intermediate level was found) or not measured. Other features of NT1 can be part of the clinical picture. About 45% of narcolepsy type 2 cases have been reported to be HLA DQB1*0602 positive, so HLA haplotype alone cannot determine the narcolepsy type [98].

Both types of narcolepsy can be caused by a central nervous system disorder such as autoimmune or paraneoplastic syndrome, neoplasia, or other hypothalamic lesions.

35.5.2 Objective Findings

If a clear history of cataplexy is present, a nocturnal PSG is not mandatory, but it is useful to rule out other conditions that can worsen sleepiness such as sleep apneas and PLM. During nocturnal PSG, SOREMPs are often detected (Fig. 35.7). For diagnostic purposes, SOREMPs are explored during the multiple sleep latency test which consists of five nap opportunities. This test is performed the day after the video-PSG and allows to measure sleep latency (i.e., the propensity to fall asleep/an objective measurement of sleepiness). Narcoleptic subjects show a mean sleep latency below 8 min (characteristically <3 min) and the presence of at least two SOREMPs (for the diagnosis a single SOREMP is sufficient if one SOREMP occurs during the PSG). The minimal duration of nocturnal PSG is 7 h.

An actigraphic study with a sleep log lasting at least 7 days is endorsed to rule out insufficient sleep syndrome, shift work, or other circadian sleep disorders which can mimic a narcolepsy [53].

Sleep macrostructure in narcolepsy is not dramatically altered (with a possible presence of a SOREMP), but an increase in stage N1 is reported [99]. Shorter REM latency, sleep fragmentation with repetitive awakening, middle-of-the-night insomnia, or a REM without atonia with RDB can

be found. As a translation of impaired arousal regulation, a significant decrease in CAP rate is reported [100, 101].

35.6 Sleep-Related Breathing Disorders

Sleep-related breathing disorders are divided into obstructive sleep apnea (OSA) disorders, central sleep apnea (CSA) disorders, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder, depending upon the pathophysiologic mechanism of respiration abnormalities during sleep.

35.6.1 Obstructive Sleep Apnea

OSA is the most frequent sleep-related breathing disorder characterized by repetitive collapse of the upper airways during sleep, leading to episodes of complete (apnea) or partial (hypopnea) upper airway obstruction. These events, lasting a minimum of 10 s, often result in reduction of blood oxygen saturation and brief arousals from sleep (Figs. 35.8 and 35.9).

The prevalence of OSA (3–7% in men and 2–5% in women) enhances with age, weight increase, and presence of certain medical conditions [102]. The gold standard for the diagnosis of OSA is the overnight PSG involving simultaneous recordings of multiple physiological signals, including the electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), oronasal airflow, thoracic and abdominal effort, and oxyhemoglobin saturation (Fig. 35.8).

PSG allows identification and classification of all types of respiratory events, i.e., apnea, hypopnea, and respiratory effort-related arousal (RERA). An apnea is defined as the complete cessation of airflow for at least 10 s and is further classified as obstructive, central, or mixed, based on whether effort to breathe is present during the event. The obstructive apnea is characterized by continuous or increased inspiratory effort throughout the entire period of absent airflow
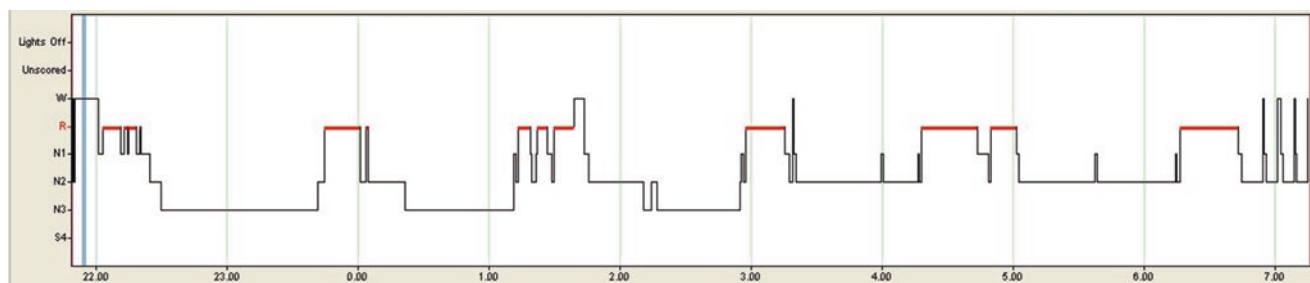

Fig. 35.7 A hypnogram of a 19-year-old patient with narcolepsy type 1. In this case we can observe a sleep-onset REM period (SOREMP) episode
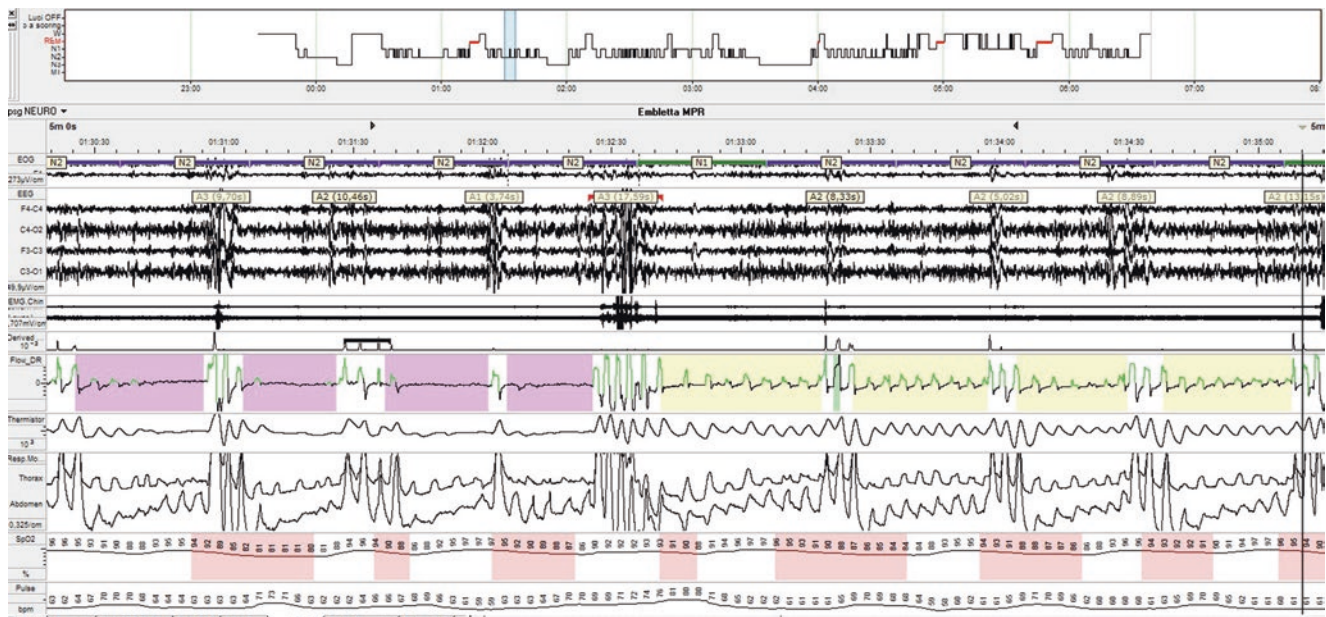
Fig. 35.8 Obstructive apneas and hypopneas in PSG. In the pink purple boxes, the obstructive sleep apnea events; in the yellow boxes, the hypopneas events; in the pink boxes, the desaturation events (5 min window)
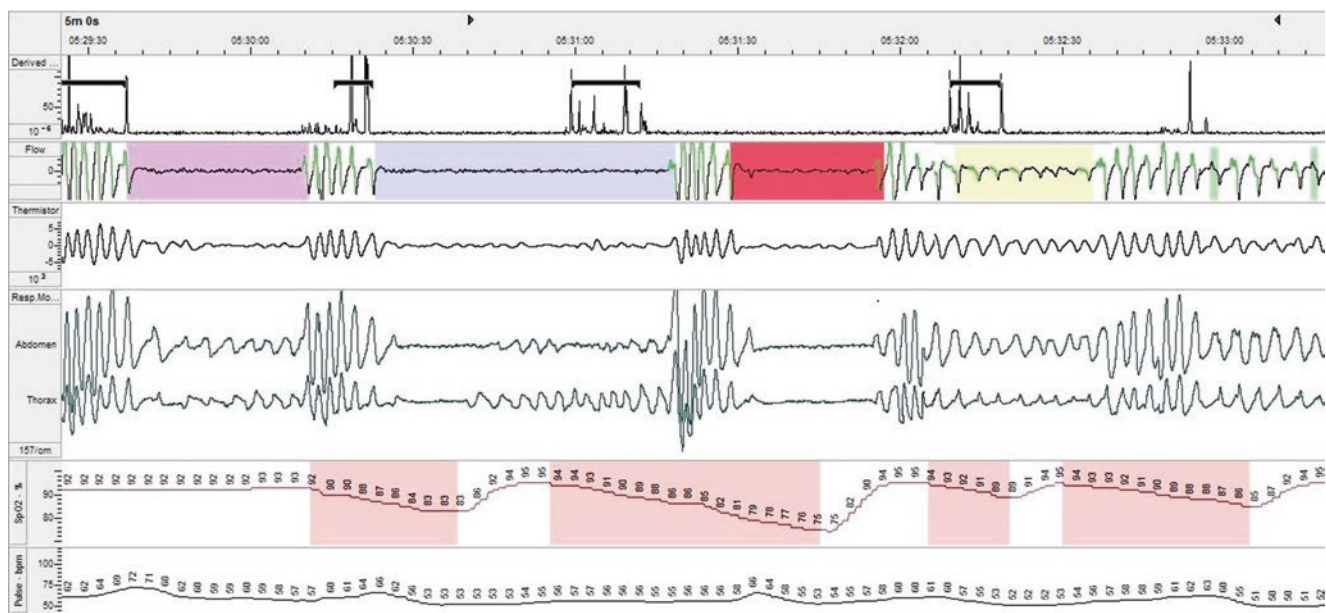

Fig. 35.9 Obstructive, mixed, and central apneas and hypopnea in PM. In the purple box, obstructive sleep apnea event; in the blue box, mixed apnea event; in the red box, the central apnea; in the yellow box, the hypopneas; in the pink boxes, the desaturation events (5 min window)

(Figs. 35.8 and 35.9), whereas central apnea is associated with absent inspiratory effort (Fig. 35.9). An initial period of central apnea followed by a period of obstructive sleep apnea constitutes a mixed apnea (Fig. 35.9) [103].

A hypopnea is defined as a reduction in airflow (30% in nasal airflow) that is followed by an arousal from sleep or a decrease in oxyhemoglobin saturation [103] (Figs. 35.8 and 35.9).

The more subtle respiratory events are RERA defined by obstructive upper airway airflow reductions (which do not meet the criteria of apnea or hypopnea) associated with progressive negative esophageal pressure lasting at least 10 s and culminating in an arousal (Fig. 35.10) [103].

Sleep apnea severity is assessed by the respiratory disturbance index (RDI), which is the number of apneas, hypopneas, and RERA occurring per hour of sleep.
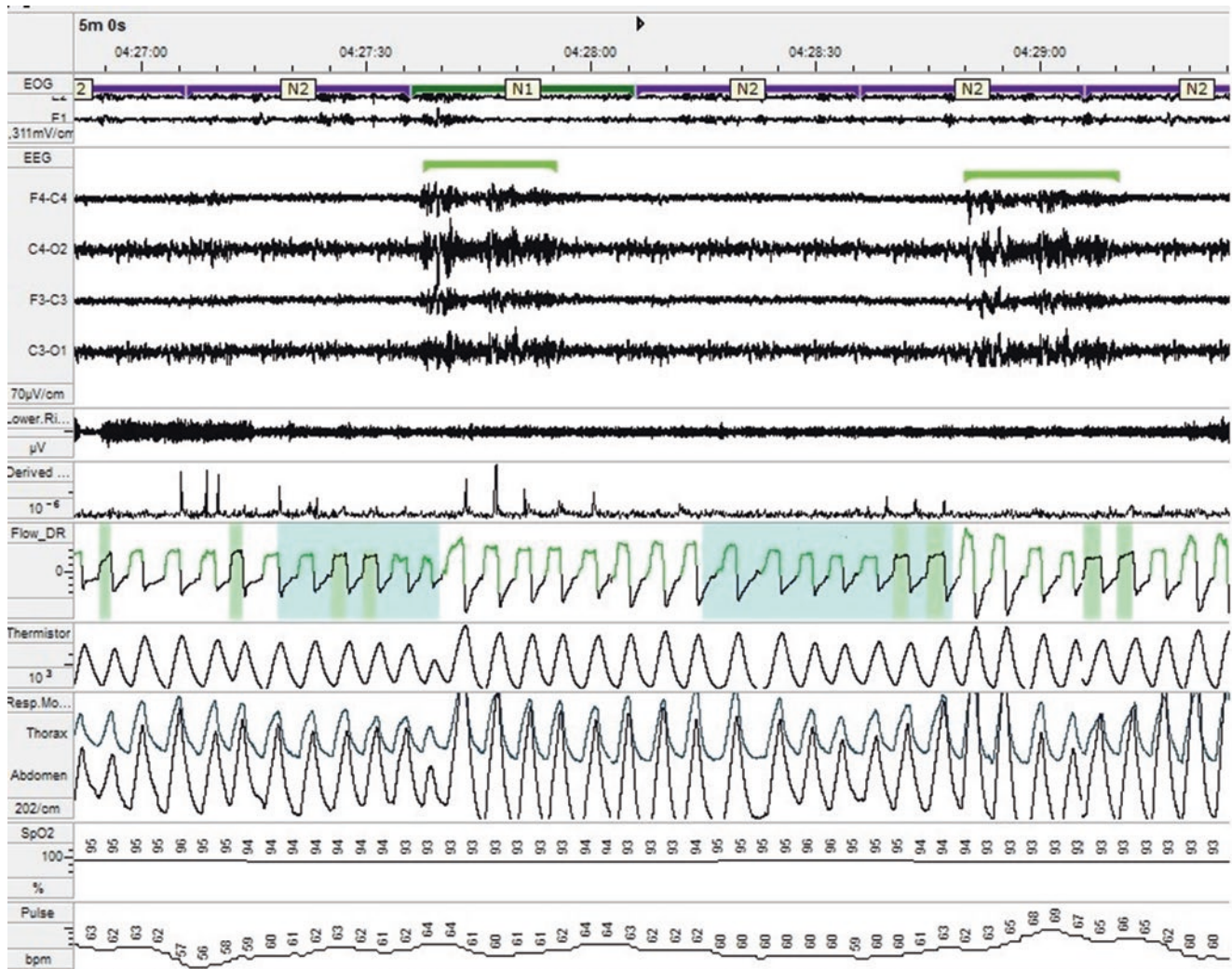
Fig. 35.10 Respiratory effort-related arousals (RERA) in PSG: in the light blue box, the RERA. The EEG arousals are highlighted with the green lines (5 min window)

Although considered as a "gold standard," the PSG is an expensive and technically intense procedure. For these reasons portable monitoring (PM) is becoming an increasingly accepted cost-effective alternative approach [104]. Although PM is less time-consuming, it lacks neurological signals (EEG, EOG, EMG) and therefore precludes the identification of arousals and the use of this criterion in the definition of respiratory events.

The apnea-hypopnea index (AHI), the number of apneas and hypopneas for hours of sleep, is the parameter used for OSA severity classification in PM. Although the AHI is the most commonly used parameter to evaluate OSA, a number of studies show that arousal scoring in OSA patients is important to clarify the impact of this disease on sleep [105, 106].

In terms of sleep architecture, patients with OSA often show reduction of slow-wave sleep and REM sleep with increase in NREM stage 2. Increased time spent awake after sleep onset and shortened sleep latency are other findings.

Immediately preceding the recovery of normal breathing, the EEG may provide evidence of a brief cortical arousal from sleep, the submental electromyogram may demonstrate a burst of activity indicating activation of upper airway dilating muscle, and microphones may record a sudden resumption of loud snoring. At the time of cortical arousals, there is often a surge in both sympathetic nervous system activity and systemic blood pressure. The respiratory events may be also accompanied by bradyarrhythmias, tachyarrhythmias, or both. Some studies have shown that the sleeping brain can even solve respiratory events with involvement of slow EEG activity (subcortical arousal) without involving a cortical arousal. The latter is triggered only when thalamocortical structures fail to modulate breathing or when ascending reticular volleys are required to restore respiration [107].

Compared to healthy subjects, OSA patients show abnormal sleep microstructure characterized by increased cortical arousals index and enhanced amounts of CAP, with longer and more desynchronized EEG patterns. The increase of A3 subtypes permits scoring of CAP also in REM sleep. All CAP-related respiratory events originate in close temporal connection with a phase B, while effective breathing is always recovered during a phase A (especially A2 and A3). These data suggest that phase B of CAP offers a vulnerable background for upper airway collapse and for attenuation of biochemical and neural mechanisms in the control of the ventilatory drive [108].

The best treatment for moderate-to-severe OSAS is the application of continuous positive airway pressure (CPAP) devices. In OSAS patients effectively treated with nasal CPAP, therapy induces an immediate enhancement of sleep N3, a more consolidated REM sleep, a reduction of stages N1 and N2, number of arousals, and CAP rate. However, a normal sleep architecture is established only after sustained CPAP treatment. The improvement is associated with a robust reduction of A3 subtypes and an expansion of A1 percentages [109].

35.6.2 Central Sleep Apnea Syndromes

Central sleep apnea (CSA) is characterized by an unstable ventilatory drive during sleep, resulting in repetitive central sleep apnea or hypopnea events (Fig. 35.11). CSA syndromes include CSA with Cheyne-Stokes breathing (CSB), CSA due to high-altitude periodic breathing, primary CSA, central apnea induced by drugs and medical conditions, and treatment-emergent central sleep apnea.
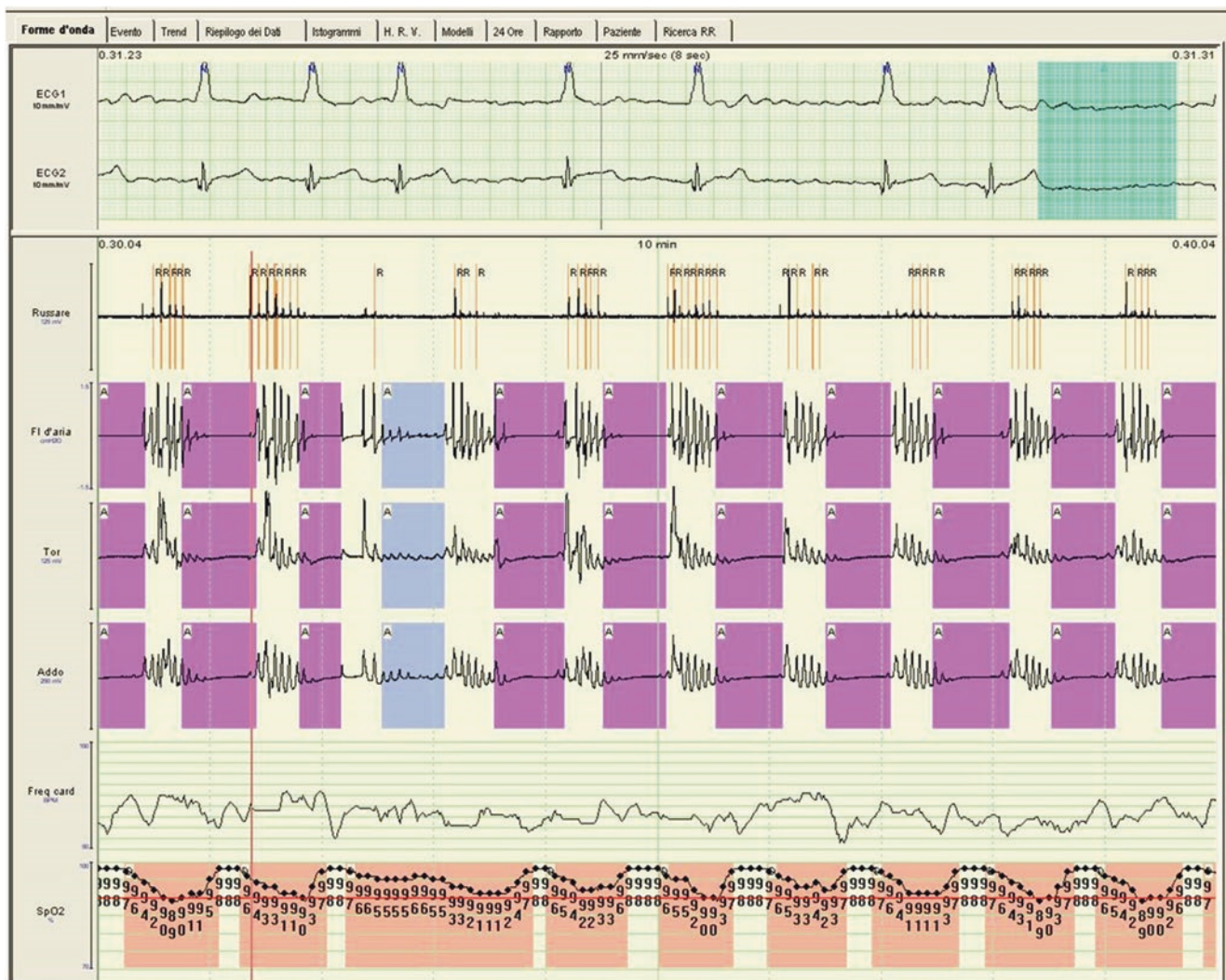

Fig. 35.11 Recurrent central apnea events in patients with atrial fibrillation (10 min window)
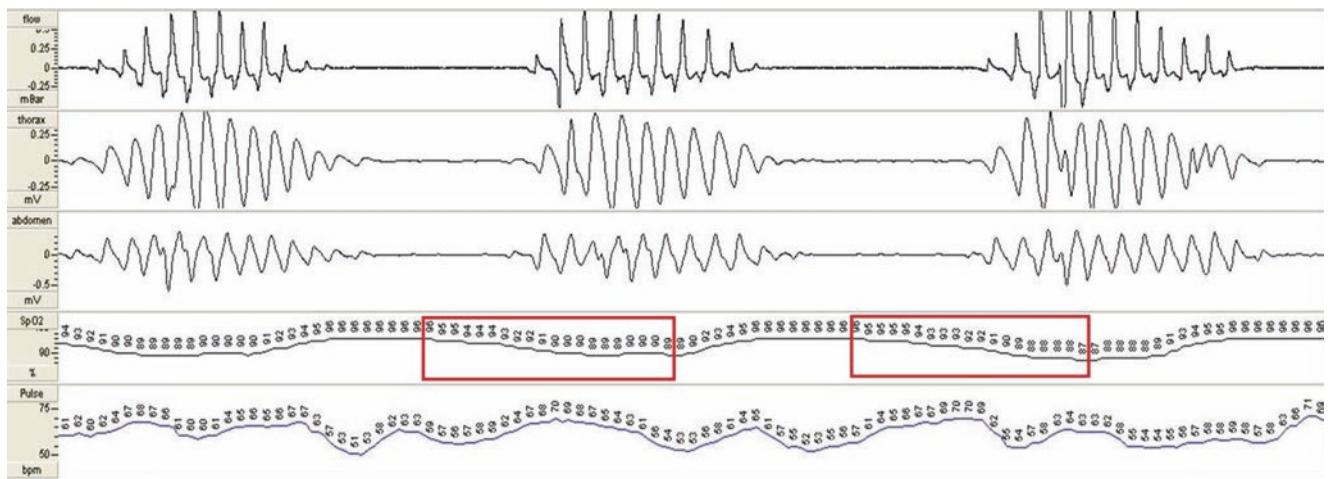
Fig. 35.12 PM in a patient with Cheyne-Stokes breathing (3 min window)

Primary CSA is uncommon and may constitute <5% of patients referred to a sleep lab [110]. Conversely, within certain clinical populations, the presence of CSA may be extremely high (congestive heart failure, neurological disorders, and sometimes renal failure) [111].

Typically, CSA is considered to be the primary diagnosis when ≥50% of apneas and hypopneas are scored as central in PSG or PM. CSA is usually characterized by normal or reduced $PaCO_2$ levels (normocapnic or hypocapnic) and a respiratory cycle length (apnea or hypopnea plus hyperpnea duration) shorter than 45 s.

CSB is a type of periodic breathing with a crescendo-decrescendo cyclic pattern separated by central apneic or hypopneic events. In CSB, the respiratory cycle length is longer than 45 s (Fig. 35.12).

Treatment-emergent CSA is a type of CSA syndrome characterized by the development or persistence of central apneas or hypopneas during application of CPAP (central apnea index ≥5 events) in patients with predominant obstructive events (obstructive or mixed apneas or hypopneas) during the diagnostic sleep study. The percentage of treatment-emergent CSA patients varies from 2 to 20%, depending on the characteristics of the investigated population [112].

During PSG with CPAP, the treatment-emergent CSA patients show adequate treatment during REM sleep and stage N3 sleep but persistent sleep fragmentation and repetitive episodes of central events during stages N1 and N2 [53].

35.7 Conclusions

Sleep or sleeplike states occur throughout the animal kingdom and appear encoded in our genes. Sleep is also essential for survival. The ultimate outcome of prolonged sleep deprivation in animals is death. The amount of recommended sleep is age-dependent, ranging between 7 and 9 h in adults and between 7 and 8 h in elderly [113]. Mortality hazard increases significantly in individuals reporting sleep durations ≤6 and ≥8 h.

Sleep is also a health imperative. The risk of arterial hypertension rises significantly in subjects that chronically sleep <5 h [114] with 7 to <8 h sleep per night as the referent category [115]. After adjustment for age and sex, sleeping length shorter or longer than 7.7 h/night is associated with an increased BMI. Type 2 diabetes and impaired glucose tolerance are more commonly found when usual sleep times last ≤6 or ≥9 h/night [116]. The risk of chronic diseases becomes even greater when health is jeopardized by sleep disorders, in particular OSAS and persistent insomnia [117]. These considerations strongly indicate that sleep is a mandatory and nonnegotiable daily experience and that any factor disrupting or impairing sleep duration and quality represents a severe menace of disability and death.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017;26:675–700.
3. Martin JL, Hakim AD. Wrist actigraphy. Chest. 2011;139:1514–27.
4. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of sleep medicine clinical practice guideline. J Clin Sleep Med JCSM. 2017;13:307–49.
5. Merica H, Blois R, Gaillard JM. Spectral characteristics of sleep EEG in chronic insomnia. Eur J Neurosci. 1998;10:1826–34.

6. Gaillard JM. Is insomnia a disease of slow-wave sleep? Eur Neurol. 1976;14:473–84.

7. Frankel BL, Coursey RD, Buchbinder R, Snyder F. Recorded and reported sleep in chronic primary insomnia. Arch Gen Psychiatry. 1976;33:615–23.

8. Baglioni C, Regen W, Teghen A, Spiegelhalder K, Feige B, Nissen C, et al. Sleep changes in the disorder of insomnia: a meta-analysis of polysomnographic studies. Sleep Med Rev. 2014;18:195–213.

9. Miller CB, Espie CA, Bartlett DJ, Marshall NS, Gordon CJ, Grunstein RR. Acceptability, tolerability, and potential efficacy of cognitive behavioural therapy for insomnia disorder subtypes defined by polysomnography: a retrospective cohort study. Sci Rep. 2018;8:6664.

10. Winkler A, Auer C, Doering BK, Rief W. Drug treatment of primary insomnia: a meta-analysis of polysomnographic randomized controlled trials. CNS Drugs. 2014;28:799–816.

11. Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE. Beta/gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. Sleep. 2001;24:110–7.

12. Spiegelhalder K, Regen W, Feige B, Holz J, Piosczyk H, Baglioni C, et al. Increased EEG sigma and beta power during NREM sleep in primary insomnia. Biol Psychol. 2012;91:329–33.

13. Freedman RR. EEG power spectra in sleep-onset insomnia. Electroencephalogr Clin Neurophysiol. 1986;63:408–13.

14. Perlis ML, Merica H, Smith MT, Giles DE. Beta EEG activity and insomnia. Sleep Med Rev. 2001;5:363–74.

15. Marzano C, Ferrara M, Sforza E, De Gennaro L. Quantitative electroencephalogram (EEG) in insomnia: a new window on pathophysiological mechanisms. Curr Pharm Des. 2008;14:3446–55.

16. Bonnet MH, Arand DL. Hyperarousal and insomnia: state of the science. Sleep Med Rev. 2010;14:9–15.

17. Bonnet MH, Arand DL. 24-hour metabolic rate in insomniacs and matched normal sleepers. Sleep. 1995;18:581–8.

18. Li Y, Vgontzas AN, Fernandez-Mendoza J, Bixler EO, Sun Y, Zhou J, et al. Insomnia with physiological hyperarousal is associated with hypertension. Hypertension. 2015;65:644–50.

19. Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev. 2012;16:27–45.

20. Terzano MG, Parrino L, Spaggiari MC, Palomba V, Rossi M, Smerieri A. CAP variables and arousals as sleep electroencephalogram markers for primary insomnia. Clin Neurophysiol. 2003;114:1715–23.

21. Ozone M, Yagi T, Itoh H, Tamura Y, Inoue Y, Uchimura N, et al. Effects of zolpidem on cyclic alternating pattern, an objective marker of sleep instability, in Japanese patients with psychophysiological insomnia: a randomized crossover comparative study with placebo. Pharmacopsychiatry. 2008;41:106–14.

22. Parrino L, Milioli G, De Paolis F, Grassi A, Terzano MG. Paradoxical insomnia: the role of CAP and arousals in sleep misperception. Sleep Med. 2009;10:1139–45.

23. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Multidrug comparison (lorazepam, triazolam, zolpidem, and zopiclone) in situational insomnia: polysomnographic analysis by means of the cyclic alternating pattern. Clin Neuropharmacol. 1997;20:253–63.

24. Terzaghi M, Sartori I, Tassi L, Didato G, Rustioni V, LoRusso G, et al. Evidence of dissociated arousal states during NREM parasomnia from an intracerebral neurophysiological study. Sleep. 2009;32:409–12.

25. Milano W, De Rosa M, Milano L, Capasso A. Night eating syndrome: an overview. J Pharm Pharmacol. 2012;64:2–10.

26. Inoue Y. Sleep-related eating disorder and its associated conditions. Psychiatry Clin Neurosci. 2015;69:309–20.

27. Nobili L, Arnulf I. Parasomnias: pathophysiology and psychopathology. In: Bassetti CL, Dogas Z, Peigneux P, editors. European

sleep medicine textbook. Regensburg: European Sleep Research Society; 2014. p. 377–88.

28. Ohayon MM, Priest RG, Zulley J, Smirne S. The place of confusional arousals in sleep and mental disorders: findings in a general population sample of 13,057 subjects. J Nerv Ment Dis. 2000;188:340–8.

29. Terzaghi M, Sartori I, Tassi L, Rustioni V, Proserpio P, Lorusso G, et al. Dissociated local arousal states underlying essential clinical features of non-rapid eye movement arousal parasomnia: an intracerebral stereo-electroencephalographic study. J Sleep Res. 2012;21:502–6.

30. Sleep-related movement disorders and disorders of motor control. In: Walters E, Baumann C, editors. Parkinson Disease and other movement disorders: motor behavioural disorders and behavioural motor disorder. 2014.

31. Ohayon MM, Guilleminault C, Priest RG. Night terrors, sleepwalking, and confusional arousals in the general population: their frequency and relationship to other sleep and mental disorders. J Clin Psychiatry. 1999;60:268–76.. quiz 277

32. Bargiotas P, Arnet I, Frei M, Baumann CR, Schindler K, Bassetti CL. Demographic, clinical and polysomnographic characteristics of childhood- and adult-onset sleepwalking in adults. Eur Neurol. 2017;78:307–11.

33. Pilon M, Zadra A, Joncas S, Montplaisir J. Hypersynchronous delta waves and somnambulism: brain topography and effect of sleep deprivation. Sleep. 2006;29:77–84.

34. Pilon M, Desautels A, Montplaisir J, Zadra A. Auditory arousal responses and thresholds during REM and NREM sleep of sleepwalkers and controls. Sleep Med. 2012;13:490–5.

35. Hwang T-J, Ni H-C, Chen H-C, Lin Y-T, Liao S-C. Risk predictors for hypnosedative-related complex sleep behaviors: a retrospective, cross-sectional pilot study. J Clin Psychiatry. 2010;71:1331–5.

36. Yeh Y-W, Chen C-H, Feng H-M, Wang S-C, Kuo S-C, Chen C-K. New onset somnambulism associated with different dosage of mirtazapine: a case report. Clin Neuropharmacol. 2009;32:232–3.

37. Montplaisir J, Petit D, Pilon M, Mongrain V, Zadra A. Does sleepwalking impair daytime vigilance? J Clin Sleep Med JCSM. 2011;7:219.

38. Guilleminault C, Poyares D, Aftab FA, Palombini L, Abat F. Sleep and wakefulness in somnambulism: a spectral analysis study. J Psychosom Res. 2001;51:411–6.

39. Guilleminault C, Kirisoglu C, da Rosa AC, Lopes C, Chan A. Sleepwalking, a disorder of NREM sleep instability. Sleep Med. 2006;7:163–70.

40. Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep. 2002;25:120–38.

41. Parish JM. Violent dreaming and antidepressant drugs: or how paroxetine made me dream that I was fighting Saddam Hussein. J Clin Sleep Med JCSM. 2007;3:529–31.

42. Bonakis A, Howard RS, Williams A. Narcolepsy presenting as REM sleep behaviour disorder. Clin Neurol Neurosurg. 2008;110:518–20.

43. Iranzo A, Graus F, Clover L, Morera J, Bruna J, Vilar C, et al. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. Ann Neurol. 2006;59:178–81.

44. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain J Neurol. 2007;130:2770–88.

45. Iranzo A, Fernández-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One. 2014;9:e89741.

46. Fantini ML, Michaud M, Gosselin N, Lavigne G, Montplaisir J. Periodic leg movements in REM sleep behavior disor-

der and related autonomic and EEG activation. Neurology. 2002;59:1889–94.

47. Ferini-Strambi L, Zucconi M. REM sleep behavior disorder. Clin Neurophysiol. 2000;111(Suppl 2):S136–40.

48. Iranzo A, Santamaría J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. Sleep. 2005;28:203–6.

49. Alessandria M, Provini F. Periodic limb movements during sleep: a new sleep-related cardiovascular risk factor? Front Neurol. 2013;4:116.

50. Ekbom KA. Restless legs syndrome. Neurology. 1960;10:868–73.

51. Bara-Jimenez W, Aksu M, Graham B, Sato S, Hallett M. Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. Neurology. 2000;54:1609–16.

52. Pennestri M-H, Montplaisir J, Fradette L, Lavigne G, Colombo R, Lanfranchi PA. Blood pressure changes associated with periodic leg movements during sleep in healthy subjects. Sleep Med. 2013;14:555–61.

53. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

54. Manconi M, Ferri R, Zucconi M, Fantini ML, Plazzi G, Ferini-Strambi L. Time structure analysis of leg movements during sleep in REM sleep behavior disorder. Sleep. 2007;30:1779–85.

55. Hanly PJ, Zuberi-Khokhar N. Periodic limb movements during sleep in patients with congestive heart failure. Chest. 1996;109:1497–502.

56. Vetrugno R, Provini F, Meletti S, Plazzi G, Liguori R, Cortelli P, et al. Propriospinal myoclonus at the sleep-wake transition: a new type of parasomnia. Sleep. 2001;24:835–43.

57. Hermesh H, Schapir L, Marom S, Skopski R, Barnea E, Weizman A, et al. Bruxism and oral parafunctional hyperactivity in social phobia outpatients. J Oral Rehabil. 2015;42:90–7.

58. Lobbezoo F, Lavigne GJ, Tanguay R, Montplaisir JY. The effect of catecholamine precursor L-dopa on sleep bruxism: a controlled clinical trial. Mov Disord. 1997;12:73–8.

59. Carra MC, Huynh N, Lavigne G. Sleep bruxism: a comprehensive overview for the dental clinician interested in sleep medicine. Dent Clin N Am. 2012;56:387–413.

60. Macaluso GM, Guerra P, Di Giovanni G, Boselli M, Parrino L, Terzano MG. Sleep bruxism is a disorder related to periodic arousals during sleep. J Dent Res. 1998;77:565–73.

61. Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. Science. 1993;262:679–85.

62. Shouse MN, Scordato JC, Farber PR. Sleep and arousal mechanisms in experimental epilepsy: epileptic components of NREM and antiepileptic components of REM sleep. Ment Retard Dev Disabil Res Rev. 2004;10:117–21.

63. Jones BE. Paradoxical REM sleep promoting and permitting neuronal networks. Arch Ital Biol. 2004;142:379–96.

64. Shouse MN, Siegel JM, Wu MF, Szymusiak R, Morrison AR. Mechanisms of seizure suppression during rapid-eye-movement (REM) sleep in cats. Brain Res. 1989;505:271–82.

65. Terzano MG, Parrino L, Garofalo PG, Durisotti C, Filati-Roso C. Activation of partial seizures with motor signs during cyclic alternating pattern in human sleep. Epilepsy Res. 1991;10:166–73.

66. Terzano MG, Parrino L, Anelli S, Boselli M, Clemens B. Effects of generalized interictal EEG discharges on sleep stability: assessment by means of cyclic alternating pattern. Epilepsia. 1992;33:317–26.

67. Terzano MG, Parrino L, Spaggiari MC, Barusi R, Simeoni S. Discriminatory effect of cyclic alternating pattern in focal lesional and benign rolandic interictal spikes during sleep. Epilepsia. 1991;32:616–28.

68. Tinuper P, Bisulli F, Cross JH, Hesdorffer D, Kahane P, Nobili L, et al. Definition and diagnostic criteria of sleep-related hypermotor epilepsy. Neurology. 2016;86:1834–42.

69. Provini F, Plazzi G, Tinuper P, Vandi S, Lugaresi E, Montagna P. Nocturnal frontal lobe epilepsy. A clinical and polygraphic overview of 100 consecutive cases. Brain J Neurol. 1999;122(Pt 6):1017–31.

70. Phillips HA, Scheffer IE, Berkovic SF, Hollway GE, Sutherland GR, Mulley JC. Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q 13.2. Nat Genet. 1995;10:117–8.

71. Ross SA, Wong JY, Clifford JJ, Kinsella A, Massalas JS, Horne MK, et al. Phenotypic characterization of an alpha 4 neuronal nicotinic acetylcholine receptor subunit knock-out mouse. J Neurosci. 2000;20:6431–41.

72. De Fusco M, Becchetti A, Patrignani A, Annesi G, Gambardella A, Quattrone A, et al. The nicotinic receptor beta 2 subunit is mutant in nocturnal frontal lobe epilepsy. Nat Genet. 2000;26:275–6.

73. Parrino L, Pavesi G. When sleep-related hypermotor epilepsy (SHE) met Charles Darwin and Francis Galton. Neurology. 2017;89:502–5.

74. Parrino L, De Paolis F, Milioli G, Gioi G, Grassi A, Riccardi S, et al. Distinctive polysomnographic traits in nocturnal frontal lobe epilepsy. Epilepsia. 2012;53:1178–84.

75. Tassinari CA, Cantalupo G, Högl B, Cortelli P, Tassi L, Francione S, et al. Neuroethological approach to frontolimbic epileptic seizures and parasomnias: the same central pattern generators for the same behaviours. Rev Neurol (Paris). 2009;165:762–8.

76. Nobili L, Francione S, Mai R, Cardinale F, Castana L, Tassi L, et al. Surgical treatment of drug-resistant nocturnal frontal lobe epilepsy. Brain J Neurol. 2007;130:561–73.

77. Ryvlin P, Minotti L, Demarquay G, Hirsch E, Arzimanoglou A, Hoffman D, et al. Nocturnal hypermotor seizures, suggesting frontal lobe epilepsy, can originate in the insula. Epilepsia. 2006;47:755–65.

78. Nobili L, Cossu M, Mai R, Tassi L, Cardinale F, Castana L, et al. Sleep-related hyperkinetic seizures of temporal lobe origin. Neurology. 2004;62:482–5.

79. Bisulli F, Vignatelli L, Provini F, Leta C, Lugaresi E, Tinuper P. Parasomnias and nocturnal frontal lobe epilepsy (NFLE): lights and shadows--controversial points in the differential diagnosis. Sleep Med. 2011;12(Suppl 2):S27–32.

80. Tassinari CA, Rubboli G, Gardella E, Cantalupo G, Calandra-Buonaura G, Vedovello M, et al. Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach. Neurol Sci. 2005;26(Suppl 3):s225–32.

81. Parrino L, Halasz P, Tassinari CA, Terzano MG. CAP, epilepsy and motor events during sleep: the unifying role of arousal. Sleep Med Rev. 2006;10:267–85.

82. Parrino L. Down the rabbit-hole: new perspectives from stereo-EEG in the investigation of sleep, nocturnal epilepsy and parasomnias. Sleep Med Rev. 2016;25:1–3.

83. Gibbs SA, Proserpio P, Terzaghi M, Pigorini A, Sarasso S, Lo Russo G, et al. Sleep-related epileptic behaviors and non-REM-related parasomnias: insights from stereo-EEG. Sleep Med Rev. 2016;25:4–20.

84. Terzaghi M, Sartori I, Mai R, Tassi L, Francione S, Cardinale F, et al. Coupling of minor motor events and epileptiform discharges with arousal fluctuations in NFLE. Epilepsia. 2008;49:670–6.

85. Zucconi M, Oldani A, Smirne S, Ferini-Strambi L. The macro-structure and microstructure of sleep in patients with autosomal dominant nocturnal frontal lobe epilepsy. J Clin Neurophysiol. 2000;17:77–86.

86. Sforza E, Montagna P, Rinaldi R, Tinuper P, Cerullo A, Cirignotta F, et al. Paroxysmal periodic motor attacks during sleep: clinical and polygraphic features. Electroencephalogr Clin Neurophysiol. 1993;86:161–6.

87. Terzano MG, Monge-Strauss MF, Mikol F, Spaggiari MC, Parrino L. Cyclic alternating pattern as a provocative factor in nocturnal paroxysmal dystonia. Epilepsia. 1997;38:1015–25.

88. Provini F, Plazzi G, Montagna P, Lugaresi E. The wide clinical spectrum of nocturnal frontal lobe epilepsy. Sleep Med Rev. 2000;4:375–86.

89. Nobili L, Sartori I, Terzaghi M, Stefano F, Mai R, Tassi L, et al. Relationship of epileptic discharges to arousal instability and periodic leg movements in a case of nocturnal frontal lobe epilepsy: a stereo-EEG study. Sleep. 2006;29:701–4.

90. Terzaghi M, Sartori I, Mai R, Tassi L, Francione S, Cardinale F, et al. Sleep-related minor motor events in nocturnal frontal lobe epilepsy. Epilepsia. 2007;48:335–41.

91. Vignatelli L, Bisulli F, Provini F, Naldi I, Pittau F, Zaniboni A, et al. Interobserver reliability of video recording in the diagnosis of nocturnal frontal lobe seizures. Epilepsia. 2007;48:1506–11.

92. Zucconi M, Ferini-Strambi L. NREM parasomnias: arousal disorders and differentiation from nocturnal frontal lobe epilepsy. Clin Neurophysiol. 2000;111(Suppl 2):S129–35.

93. Derry CP, Davey M, Johns M, Kron K, Glencross D, Marini C, et al. Distinguishing sleep disorders from seizures: diagnosing bumps in the night. Arch Neurol. 2006;63:705–9.

94. Derry CP, Harvey AS, Walker MC, Duncan JS, Berkovic SF. NREM arousal parasomnias and their distinction from nocturnal frontal lobe epilepsy: a video EEG analysis. Sleep. 2009;32:1637–44.

95. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet. 2007;369:499–511.

96. Burgess CR, Scammell TE. Narcolepsy: neural mechanisms of sleepiness and cataplexy. J Neurosci. 2012;32:12305–11.

97. Mignot E, Lin X, Hesla PE, Dement WC, Guilleminault C, Grumet FC. A novel HLA DR17,DQ1 (DQA1–0102/DQB1–0602 positive) haplotype predisposing to narcolepsy in Caucasians. Sleep. 1993;16:764–5.

98. Oka Y, Inoue Y, Kanbayashi T, Kuroda K, Miyamoto M, Miyamoto T, et al. Narcolepsy without cataplexy: 2 subtypes based on CSF hypocretin-1/orexin-a findings. Sleep. 2006;29:1439–43.

99. Pizza F, Vandi S, Iloti M, Franceschini C, Liguori R, Mignot E, et al. Nocturnal sleep dynamics identify narcolepsy type 1. Sleep. 2015;38:1277–84.

100. Ferri R, Miano S, Bruni O, Vankova J, Nevsimalova S, Vandi S, et al. NREM sleep alterations in narcolepsy/cataplexy. Clin Neurophysiol. 2005;116:2675–84.

101. Terzano MG, Smerieri A, Del Felice A, Giglia F, Palomba V, Parrino L. Cyclic alternating pattern (CAP) alterations in narcolepsy. Sleep Med. 2006;7:619–26.

102. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165:1217–39.

103. The AASM Manual for the Scoring of Sleep and Associated Events. Version 2.1. American Academy of Sleep Medicine. 2014.

104. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable monitoring task force of the American Academy of sleep medicine. J Clin Sleep Med JCSM. 2007;3:737–47.

105. Masa JF, Corral J, Gomez de Terreros J, Duran-Cantolla J, Cabello M, Hernández-Blasco L, et al. Significance of including a surrogate arousal for sleep apnea-hypopnea syndrome diagnosis by respiratory polygraphy. Sleep. 2013;36:249–57.

106. Milioli G, Bosi M, Grassi A, Riccardi S, Terzano MG, Cortelli P, et al. Can sleep microstructure improve diagnosis of OSAS? Integrative information from CAP parameters. Arch Ital Biol. 2015;153:194–203.

107. Poyares D, Guilleminault C, Rosa A, Ohayon M, Koester U. Arousal, EEG spectral power and pulse transit time in UARS and mild OSAS subjects. Clin Neurophysiol. 2002;113:1598–606.

108. Terzano MG, Parrino L, Boselli M, Spaggiari MC, Di Giovanni G. Polysomnographic analysis of arousal responses in obstructive sleep apnea syndrome by means of the cyclic alternating pattern. J Clin Neurophysiol. 1996;13:145–55.

109. Parrino L, Smerieri A, Boselli M, Spaggiari MC, Terzano MG. Sleep reactivity during acute nasal CPAP in obstructive sleep apnea syndrome. Neurology. 2000;54:1633–40.

110. Central sleep apnea. In: Carney PR, Berry RB, Geyer JD, editors. Clinical sleep disorders. Philadelphia, PA: Lippincott Williams and Wilkins; 2004. pp. 331–46.

111. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. Int J Cardiol. 2006;106:21–8.

112. Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. J Clin Sleep Med JCSM. 2009;5:205–11.

113. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health. 2015;1:233–43.

114. Vgontzas AN, Liao D, Bixler EO. Insomnia and hypertension. Sleep. 2009;32:1547.

115. Gottlieb DJ, Redline S, Nieto FJ, Baldwin CM, Newman AB, Resnick HE, et al. Association of usual sleep duration with hypertension: the sleep heart health study. Sleep. 2006;29:1009–14.

116. Luyster FS, Strollo PJ, Zee PC, Walsh JK. Boards of directors of the American Academy of sleep medicine and the Sleep Research Society. Sleep: a health imperative. Sleep. 2012;35:727–34.

117. McDermott M, Brown DL, Chervin RD. Sleep disorders and the risk of stroke. Expert Rev Neurother. 2018;18(7):523–31.