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EFNS TASK FORCE/CME ARTICLE

Report of an EFNS task force on management of sleep disorders in neurologic disease (degenerative neurologic disorders and stroke)

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A task force to develop guidelines for diagnostic evaluation and treatment of sleep disorders in degenerative neurologic disorders and stroke was initiated by the European Federation of Neurological Societies (EFNS). The aims were to provide evidence-based recommendations in the management of sleep disorders associated with degenerative neurologic disorders and stroke.Neurological patients often have significant sleep disorders like sleep-related breathing disorders (SBD), insomnia, sleep-related motor and rapid eye movement behavioral disorders affecting nocturnal sleep and daytime function. A polysomnography (PSG) is usually a diagnostic minimum for the diagnoses of the most commonly reported sleep disorders in patients with neurologic diseases. A full video-PSG/video-EEG-PSG should be considered in patients with nocturnal motor and/behavior manifestations.Respiratory polygraphy has a moderate sensitivity and specificity in the diagnosis of SBD without neurologic diseases, but its value in patients with neurologic diseases has not been evaluated. Oximetry has a poor sensitivity-specificity for the identification of SDB. Continuous and bi-level positive airway pressure devices are the most effective treatment of SDB in patients with neurologic diseases. There is a need for further studies focusing on the diagnostic procedures and treatment modalities in patients with sleep disorders and degenerative neurologic diseases and stroke.

Objectives

- To review the different sleep disorders occurring in degenerative neurologic diseases and stroke.
- To review the different methods of sleep evaluation available in these patients.
- To report the evidence supporting that the evaluation and treatment of sleep disorders in patients with degenerative neurologic disorders and stroke improves the management of these diseases.

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This is a Continuing Medical Education article, and can be found with corresponding questions on the Internet at http://www.efns.org/content.php?pid=132. Certificates for correctly answering the questions will be issued by the EFNS.

Background

Sleep is an active process generated and modulated in the nervous system subject to a complex set of neural systems located mainly in the hypothalamus, brainstem and thalamus. Sleep is altered in many neurologic diseases due to several mechanisms: lesions of the areas that control sleep, lesions or diseases that produce pain, paralysis or poor mobility (caused by tremor, rigidity, dystonia or other motor disturbances) or treatments given to control neurologic symptoms. Hypersomnolence, sleep attacks, sleep fragmentation, nocturnal stridor, nocturnal behavioral phenomena like rapid eye movement (REM) sleep behavior disorder (RBD) or nocturnal seizures, restless leg syndrome, periodic leg movements in sleep, etc. are sleep problems that are increasingly recognized as common features of several neurologic disorders. Furthermore, obstructive sleep apnea syndrome (OSAS) is one of the most common sleep problems, with a prevalence of more than 2–4% of the adult population. In patients with neurologic diseases like stroke, dementia, Parkinson's disease (PD) and atypical Parkinsonian syndromes, myelopathies, motor neuron diseases, polyneuropathy, diseases related to the motor end-plate and myopathies, OSAS and other SBD occur even more often with prevalences

exceeding more than one-third of the patients (Table 1). OSAS is strongly associated with increased cardiovascular and cerebrovascular risks and causes significant family, social problems. It is also strongly related to increased traffic accidents and work-related accidents. There is increasing evidence that SBD in patients with neurologic diseases reduces daytime functioning and increases mortality.

Diagnostic procedures and treatment of sleep disorders have developed considerably in recent years. Digital electroencephalography (EEG), audiovisual recording, ambulatory polysomnography (PSG), abbreviated respiratory recordings and actigraphy represent only a few examples of the different sleep recording strategies available.

Treatment modalities have been proposed for many of these disorders including hypersomnia in PD, abnormal motor activity and behavior during sleep, and sleep fragmentation. Important developments have also taken place in the treatment of SBD and include continuous positive airway pressure (CPAP)/auto-adjusted CPAP, variable PAP (VPAP), bi-level-PAP for patients with OSA, barometric or volumetric noninvasive ventilation for patients with weak diaphragm. CPAP treatment reduces the respiratory abnormalities, normalizes sleep abnormalities, and reduces daytime symptoms and cardiovascular and cerebrovascular risks. In patients with severe neurologic deficits like amyotrophic lateral sclerosis (ALS) and multiple system atrophy (MSA) recent data suggest that noninvasive ventilation may improve the quality of life and increase survival.

Although these developments are important and emphasize that sleep alterations have an important role in many neurologic diseases, there is no systematic review of the existing evidence as to how far diagnostic and treatment interventions are beneficial for the management of those neurologic disorders. As 'Management of sleep disorders in neurologic disease' would cover a too widespread an area and, in addition, would overlap with the work of other Task Forces already in progress (RLS, narcolepsy, epilepsy, etc.), the current Guideline will focus on the prevalence, diagnostic procedures, indications and technique for the evaluation and treatment of sleep disorders in only two main areas in which important progress has been achieved in the last few years: *neurodegenerative disorders* and *stroke* with an emphasis on *sleep breathing disorders* in neurologic disease. Therefore, we will not cover here other important areas (sleep and epilepsy, neurooncology, peripheral neuropathies, prionopathies, headache, etc.). In addition, the special problems regarding sleep medicine in children will not be included.

The Task Force will define first the main sleep disorders to be reviewed (insomnia, hypersomnia, parasomnia or circadian sleep disorders) and to what extent they occur in the different neurologic diseases. Secondly, we will describe briefly the different diagnostic techniques used in the evaluation of sleep disorders and finally we will review the evidence supporting any treatment of these disorders in the different neurologic diseases.

The Task Force review the pertinent literature covering three main areas:

1 Taupathies [Alzheimer's disease (AD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD)].
2 Synucleinopathies [PD, MSA and dementia with Lewy bodies (DLB)].
3 Stroke, ALS, myotonic dystrophy, myasthenia gravis and spinocerebellar ataxias.

Search strategy

Several electronic databases were searched including MEDLINE, PubMed, EMBASE, WEB OF SCIENCE, Cochrane, Clinical Trials, National Library of Medicine, and National Guideline Clearinghouse. These were searched until October 2004 or as much of this range as possible looking for the different sleep disorders and symptoms in each of the most frequent or relevant degenerative neurologic disorders and stroke.

Table 1 Occurrences of sleep disorders in neurodegenerative disorders and stroke

	Sleep complaints	Parasomnia (REM behavior disorder)	Insomnia/sleep fragmentation/ circadian disorder	Hypersomnia	Sleep-disordered breathing
Parkinson disease	42–98 [132–135]	30–50 [136]	30–80 [133,134]	15–51 [132,137,138]	20–66 [139,140]
MSA	70 [141,142]	70–100 [78,141,142]	52 [132]	50 [132]	19–69 [30,132]
Alzheimer disease	>25 [143,144]	2 [145]	Common [146]	Common [146]	43–84 [24,147]
Stroke		NR	38 [148]	20–40 [149]	60–70 [149]
Neuromuscular disorders	NR	NR	NR		40–77 [150,151]
PSP	NR	13–27 [152]	40–100 [152,153]	27 [152]	60 [152]
Dementia with Lewy bodies	53 [154]	80–90 [145]	18 [154]	Common [154]	NR

Values are expressed in percentage. REM, rapid eye movement; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; NR, non reported.

Additional articles were sought by handsearching reference lists in standard textbooks and reviews in the field and by contacting academic centers in palliative care and pharmaceutical companies. Language is restricted to European languages.

Selection criteria

Studies considered for inclusion were, when possible, randomized controlled trials of adult patients in any setting, suffering a neurodegenerative disorder (motor neuron disease, PD, MSA, CBD, AD/dementia), myotonic dystrophy, myasthenia gravis or stroke. There had to be an explicit complaint of insomnia, parasomnia or hypersomnia in study participants. We also included observational studies. Sleep disorders have been described in several neurodegenerative diseases, but we have decided not to include them in this review because most are small case series and some lack PSG recordings. An additional literature search was performed in August 2007, but no significant changes in the literature were identified, which substantially changed the conclusion in the report.

Data collection and analysis

Abstracts were selected by the chairmen and independently inspected by individual members of the Task Force; full papers were obtained where necessary. A classification of the different studies according to evidence levels for therapeutic interventions and diagnostic measures will be done in accordance with the guidance [1]. The panel will discuss what possible diagnostic tests and healthcare interventions could be recommended in each particular disease.

Method for reaching consensus

Where there was uncertainty further discussion was sought by the panel. Data extraction and quality assessments were undertaken independently by the panel reviewers.

Sleep disorders

Classification of sleep disorders

The International Classification, version 2 (ICSD-2) lists 95 sleep disorders [2]. The ISCD-2 has eight major categories:

1 insomnias
2 sleep-related breathing disorders
3 hypersomnias not due to a sleep-related breathing disorder
4 circadian rhythm sleep disorders
5 parasomnias
6 sleep-related movement disorders
7 isolated symptoms
8 other sleep disorders.

In the following only a selected number of the sleep disorders related to neurologic diseases are mentioned.

Insomnia

The insomnias are defined by a repeated difficulty with sleep initiation, duration, consolidation or quality that occurs despite adequate time and opportunity for sleep, and result in some form of daytime impairment. Insomnia complaints typically include difficulty initiating and/or maintaining sleep, and they usually include extended periods of nocturnal wakefulness and/or insufficient amount of nocturnal sleep.

Typical insomnias are acute insomnia and chronic psychophysiological insomnias. Insomnias are often reported in patients with neurologic disorders because of degeneration or dysfunction of the central nervous system areas involved in sleep regulation; motor or sensory symptoms produced by the disease (pain, reduced nocturnal mobility, nocturnal motor activity, etc.) that lower the threshold for arousal from sleep and easily break it and secondary alerting effects of the drugs employed in the treatment of neurologic diseases.

Sleep-disordered breathing

These disorders are characterized by disordered breathing during sleep. A uniform syndrome recommendation was suggested in 1999 by the American Academy of Sleep Medicine [3], which is included in ICSD-2:

1 obstructive sleep apnea syndromes (OSAS)
2 central sleep apnoa-hypopnea syndrome (CSAHS)
3 Cheyne-Stokes breathing syndrome (CSBS)
4 sleep-related hypoventilation/hypoxemic syndromes.

Obstructive sleep apnea syndrome

Obstructive sleep apnea is characterized by recurrent episodes of partial (causing hypopnea) or complete upper airway obstructions (causing apnea) during sleep, often terminated by arousals. Obstructive sleep apnea requires at least five obstructive breathing episodes per hour sleep (apnea-hypopnea index, AHI $\geq$5/h). An apnea is defined by complete cessation of ventilation for a duration exceeding 10 s. A hypopnea is defined as

1 A clear decrease ($>$50%) from baseline in the amplitude of flow signal during sleep.
2 A clear amplitude reduction that does not reach the above criterion, but is associated with an oxygen desaturation of $\geq$3% or an arousal.
3 The event should last 10 s or longer.

Obstructive sleep apnea syndrome is characterized by excessive daytime sleepiness, snoring eventually choking and gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, and/or impaired concentration and insomnia.

Obstructive sleep apnea syndrome is reported in least 2% of females and 4% of males aged more than 30 years [4]. OSAS increases with age. OSAS is more commonly observed in patients with obesity, upper airway and craniofacial abnormalities, cardiac, pulmonary, endocrine (acromegaly, myxedema, diabetes) and cerebrovascular diseases.

Polysomnography findings include oxyhemoglobin desaturations, sleep fragmentation, reduced REM and non-REM stage 3 and 4 sleep.

Central sleep apnea-hypopnea syndrome (CSAHS)

Central sleep apnea-hypopnea syndrome is defined by recurrent apneic episodes during sleep with the absence of obstructive components. A central apnea-hypopnea is defined by:

1 Reduction of airflow of at least 50%.
2 Lack of signs of respiratory drive as determined by respiratory activation.
3 The event should last 10 s or longer.

These episodes may be associated with desaturations, arousals and daytime sleepiness. Central sleep apnea can be divided into normocapnic (idiopathic central sleep apnea, Cheyne-Stokes breathing and high altitude-induced central sleep apnea) and hypercapnic [presenting overlap to sleep hypoventilation syndrome (SHVS)].

Central sleep apnea-hypopnea syndrome is characterized by excessive daytime sleepiness, frequent nocturnal arousals/awakenings, and overnight monitoring documents number of central apneas ≥5/h. The patients should be normocapnic whilst awake.

Predisposing factors are increase in ventilatory response to pCO_2 which may be present in brainstem lesion due to infarction, hemorrhage, demyelination, tumors, etc. Central sleep apnea-hypopnea syndrome is relatively uncommon; precise epidemiological data are not present.

In PSG recording central apneas or hypopneas without respiratory activation in the abdomino-thoracic movements are observed. These episodes may be associated with arousals. Central apneas are more commonly observed in lighter sleep, less frequent in NREM stage 2 and REM, rarely in NREM stage 3 and 4. Central apnea/mixed apneas are sometimes also observed in patients with OSAS.

Cheyne-Stokes breathing syndrome

Cheyne-Stokes breathing syndrome is characterized by cyclic fluctuations in breathing with periods of central apneas or hypopneas alternating with periods of hyperpnea. CSBS occurs in approximately 50% of patients with severe congestive heart failure or neurologic disease/dysfunction; usually acute cerebrovascular episodes. CSBS occurs mostly during sleep, in more severe cases also during wakefulness. Associated features include cardiovascular changes, sleep fragmentation, excessive daytime sleepiness and abnormal response to CO_2. PSG features includes typical respiratory pattern especially during NREM sleep.

Sleep-related hypoventilation/hypoxemic syndrome (SHVS)

Sleep-related hypoventilation/hypoxemic syndrome is defined as hypoventilation related to decreased alveolar ventilation that results in increased $PaCO_2$ and hypoxemia.

Associated features include erythrocytosis, pulmonary hypertension, cor pulmonale, or respiratory failure and excessive daytime sleepiness. Cardiac arrhythmias and systemic hypertension are also observed.

Predisposing factors include morbid obesity (BMI > 35 kg/m^2), chest wall restrictive disorders, neuromuscular weakness or disorders (e.g. ALS), brainstem or high spinal cord lesions, phrenic nerve lesions, acute or chronic polyneuropathies including acute inflammatory demyelynating poly-radiculo-neuropathy, idiopathic central alveolar hypoventilation, obstructive lung disease and myxedema.

Polysomnographic findings include increase in nocturnal $PaCO_2$ and arterial desaturations. Hypoventilations and hypoxemia are more common and severe during REM than in NREM sleep. Arterial pCO_2 and oxygen saturation during wakefulness does not fully reflect sleep-induced hypoventilation.

Hypersomnias not due to a sleep-related breathing disorder

Hypersomnia and/or excessive daytime sleepiness are defined as the inability to stay alert and awake during the day, resulting in unintended lapses into sleep. The most common disorders in this group are narcolepsy, idiopathic hypersomnia, restless legs syndrome (RLS) and periodic limb movements (PLM) during sleep. Hypersomnia is commonly reported in patients with neurologic disease and may be produced by degeneration of sleep/wake centers, sleep fragmentation or medication.

Circadian rhythm disorders

Circadian rhythm disorders are defined as a misalignment between the patients' sleep pattern and the pattern that is desired or regarded as the societal norm. Most of the conditions observed in this group are associated

with external factors like social habits, but in relation to neurologic diseases, conditions that destruct the neural input to the suprachiasmatic nucleus (e.g. complete bilateral retinal, optic nerve, chiasm or hypothalamic lesions) may induce a condition that resembles circadian disorders.

Parasomnias

Parasomnias are undesirable physical or external events that accompany sleep. Parasomnias are disorders of arousal, partial arousal, and sleep stage transition. These disorders do not primarily cause a complaint of insomnia or excessive sleepiness, but frequently involve abnormal behaviors during sleep. Many of the disorders are common in children, but some are also present in adults. The parasomnias are subdivided into the following groups:

1 Disorders of arousal (from NREM sleep): confusional arousal, sleep walking and sleep terror.
2 Parasomnias usually associated with REM sleep: REM RBD, recurrent isolated sleep paralysis and nightmare disorder
3 Other parasomnias, e.g. enuresis, sleep-related groaning (catathrenia).

Of these parasomnias, RBD has a particular relationship to neurodegenerative diseases.

REM sleep behavior disorder

This disorder is characterized by vigorous movements occurring during REM sleep due to lack of inhibition of muscle tone and activity during REM sleep.

Diagnostic criteria are:

1 Presence of REM sleep without atonia: the electromyogram (EMG) finding of excessive amounts of sustained or intermittent elevation of fragmented EMG tone or excessive phasic submental or (upper or lower) EMG twitching.
2 At least one of the following is present:
   (a) Sleep-related injuries, potentially injurious or disruptive behaviors by history.
   (b) Abnormal REM sleep behaviors documented during polysomnographic monitoring.
   (c) Absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder.
   (d) The sleep disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use or substance use disorder.

The patient and sleep partner can be injured. REM behavior disorders are observed in a significant proportion of patients with PD [5]. RBD is also commonly observed in MSA and has been reported in DLB [6–9] and Machado-Josephs disease [10–12]. Patients with isolated RBD have a significant risk of developing PD, DLB or MSA [13]. Occurrence of hallucinations in PD is related to the presence of RBD [5]. Reduced striatal dopamine transporters has been observed in these patients [14]. A confident diagnosis relies on a full PSG recording preferably with synchronized audiovisual recording. A recent study provided a detailed video analysis of RBD. Although a very high number and great variety of motor events during REM sleep were seen in patients with symptomatic RBD due to neurologic disease, most of the events were minor and elaborate or violent behaviors represented only a small fraction of events [15].

Sleep-related movement disorders

Sleep-related movement disorders are characterized by relatively simple, usually stereotypic movements that disturb sleep. PLM, RLS, bruxism, leg cramps, rhythmic movement disorders and other sleep-related movement disorders are classified in this group. Of these RLS and PLM are of particular interest in patients with neurodegenerative disorders. These disorders will not be discussed here as they are the focus of another Task Force [16].

Sleep disorders associated with neurologic disease

Taupathies

Patients with PSP, AD and CBD may complain of significant sleep-related circadian disturbances, sleep/wake and daytime problems [17–24].

1 Sleep/wake disturbances and disruption are commonly observed in AD, with daytime sleep, sleep attack and episodes of micro-sleep (brief, unintended episodes of loss of attention associated with events of sleep).
2 Insomnia (sleep fragmentation, difficulties maintaining sleep) is common as are nocturnal wandering, nocturnal confusion, 'Sundowning' psychosis and nocturia.
3 Excessive daytime sleepiness, sleep attacks and episodes of micro-sleep during daytime may be associated with cognitive problems.
4 Sleep-related disorders such as RBD, RLS, PLM, nocturnal dystonic movements, cramps may occur in PSP, AD and CBD but are more commonly seen in the synucleinopathies.
5 Sleep breathing disorders are common in AD and associated with disease progression and poorer prognosis. OSA is commonly observed in AD, however the clinical significance is questionable.

Recommendations: Sleep disorders are commonly observed in patients with tauopathies, and there should be increased awareness of these disorders (level C-V). Clearly there is a need for more controlled and intervention studies before definite conclusions can be reached.

Synucleinopathies

Parkinson's disease, MSA and DLB are often associated with major sleep disorders. Patients with these disorders often suffer from a number of significant sleep and daytime-related problems [25–31]:

1 PD-related motor symptoms including nocturnal akinesia, early-morning dystonia, painful cramps, tremor, and difficulties turning in bed.
2 Treatment-related nocturnal disturbances (e.g. insomnia, confusion, hallucinations, and motor disturbances).
3 Sleep-related symptoms such as hallucinations and vivid dreams (nightmares), insomnia (sleep fragmentation, difficulties maintaining sleep), nocturia, psychosis and panic attack.
4 Excessive daytime sleepiness, sleep attacks and episodes of micro-sleep during waking hours.
5 Sleep-related disorders including RBD, RLS, PLM, nocturnal dystonic movements, cramps, and SBD.
6 Laryngeal stridor and obstructive sleep apnea are commonly observed in MSA patients. The presence of stridor in MSA patients is associated with a poorer prognosis.

Recommendations: There is evidence that the majority of patients with synucleinopathies experience one or more sleep disorders. Full PSG recording preferably with audiovisual recording is suggested for the diagnosis especially when RBD and/or SBD are suspected (level C-V). Clearly there is a need for more controlled and intervention studies before definite conclusions can be reached.

Stroke

Patients with strokes, primarily infarctions, may suffer from several sleep disorders and disturbances. Their occurrence and manifestations may vary depending on the specific neurologic deficits [32–41].

1 SBD especially obstructive sleep apnea and nocturnal oxygen desaturations have been found commonly ($>50\%$) in patients with acute stroke. After neurologic recovery SDB may be provoked by stroke, e.g. after damage to the respiratory centers in the brainstem or bulbar/pseudobulbar paralysis due to brainstem. It is possible that sleep apnea prior to stroke may have predisposed the patient as sleep apnea has been suggested as a risk factor for stroke. As sleep apnea is associated with a high incidence of obesity, diabetes, coronary artery disease and hypertension, it remains to be clarified whether it is causative or simply a co-morbid factor. There are several hemodynamic changes in sleep apnea that may play a role in the pathogenesis of stroke development. Stroke and SBD are both common and are associated with significant morbidity and mortality.
2 Patients with stroke may present other sleep disorders such as unilateral periodic limb movement in sleep (PLMS).
3 Post-stroke insomnia is commonly reported.
4 Sleepiness and fatigue are commonly reported, especially in patients with thalamic stroke.

Recommendations: SDB and other sleep disorders are strongly associated with stroke. The relation to stroke outcome, SDB and effect of treatment is incompletely understood. Increased attention should be addressed in patients with stroke specifically identifying SDB and other sleep disorders (level C-III). Clearly there is a need for more controlled and intervention studies before definite conclusions can be reached.

Motor neuron diseases, motor end plate and muscle diseases

Sleep-disordered breathing is observed in several neuromuscular diseases including muscular dystrophy, myotonic dystrophy, myasthenia gravis, ALS, and postpolio syndrome. Although there may be differences, some general observations can be made. Hypoxemia, especially during REM sleep, is commonly found. Severity is correlated with respiratory strength, and sleep-related hypoventilation is usually non-obstructive [42,43].

Patients with ALS and other severe motor neuron diseases have progressive motor deterioration with progressive respiratory insufficiency. This may manifest primarily during sleep where the motor drive is reduced. This is especially true for patients with the bulbar form of ALS or involvement of C3-C5 anterior horn [44,45]. The prognosis is closely related to respiratory muscle strength [46]. Of note, sudden nocturnal death occurs often during sleep. Respiratory indices such as low nocturnal oxygen saturation are associated with poorer prognosis [47,48]. Patients with diaphragmatic involvement may have significantly reduced REM sleep [49]. The primary SBD in patients with ALS – as in other neuromuscular diseases – is therefore a SHVS, whereas OSAS are rare [45].

Management of these patients should therefore include relevant questions regarding symptoms susceptive for SBD. Common symptoms of nocturnal hypoventilations may include fatigue, insomnia, unrefreshing sleep, morning headache and daytime somnolence [50].

Oximetry has been suggested for the identification and screening of sleep-related hypoventilation in patients with ALS [48,51]. Care should be taken because pCO_2 may increase before desaturations are observed, especially in patients with additional chronic obstructive lung disease. Nocturnal oximetry has been suggested to be valuable for screening and evaluation of the treatment effect [48,45]. However, no studies have compared the diagnostic yield between a full PSG, respiratory polygraphy (RP) and nocturnal oximetry in these patients.

Recommendations: PSG with additional CO_2 analysis (transcutaneous or expiratory) should be considered for the identification of sleep-related hypoventilation. The role of oximetry in the identification of sleep-related breathing disorders in neuromuscular diseases is not established)[45,52] (level C).

Others

Other neurodegenerative disorders of genetic neurologic diseases may cause several sleep disturbances. Subjects with SCA-3 (Machado-Joseph) may also complain of RLS, periodic legs movements, vocal cord paralysis and RBD [10–12,53,54]. In patients with Huntington's disease the involuntary movements tend to diminish during sleep [55]. Sleep disturbances including disturbed sleep pattern with increased sleep onset latency, reduced sleep efficiency, frequent nocturnal awakenings, and more time spent awake with less slow wave sleep have been reported. These abnormalities correlate in part with duration of illness, severity of clinical symptoms, and degree of atrophy of the caudate nucleus [56]. However, other studies have not reported specific sleep disorders in these patients [57].

Recommendations: Some studies suggest that sleep disorders occur in genetic neurologic diseases (level C-V). Clearly there is a need for more controlled and intervention studies before definite conclusions can be reached.

Diagnostic techniques in sleep disorders

Diagnostic procedures for sleep diagnosis include: PSG, partial time PSG, partial polygraphy (or RP) and limited channel polygraphy: oximetry determining SaO_2 pulse and actimetry. Daytime sleep may be evaluated with the multiple sleep latency test (MSLT) or maintenance of wakefulness test (MWT) and standard EEG. An overview of these tests is presented in Table 2.

Attended versus unattended monitoring

The nocturnal diagnostic procedures may be performed in the following settings.

Attended monitoring

In this group of techniques trained personnel are physically present throughout the recording session. The advantages are that patients are continuously monitored, interventions are possible, patients with physical or mental handicaps can be recorded, and it is possible to record multiple recordings. The disadvantages are that it is time and staff demanding, expensive, require hospital beds and extensive equipments.

Unattended portable monitoring

In this group of techniques trained personnel are not physically present throughout the recording session. These recordings are typically performed ambulatory or in-hospital. The patients are instructed and/or mounted in the afternoon the recording is performed at home or in the hospital. The data are analyzed the next day. The advantages are that it is less staff and time demanding; the disadvantages are the risk of data loss. Interventions and video recording are not possible, and in practice the number of physiological variables is limited. In addition, the technique requires that the patients understand and are able to respond to the information and can handle the technique.

Recording techniques

Polysomnography

The PSG is the 'gold standard' for diagnostic procedures in sleep medicine [58–61]. By definition PSG includes measures of sleep staging. PSG includes the following procedures.

Routine PSG

The standard PSG recording includes electroencephalogram (EEG), electro-oculogram (EOG) and chin EMG to measure the presence and depth of sleep, but also includes the RP variables and EMG of the anterior tibialis muscles.

Extended PSG

In addition to the routine setting this includes additional leads for recording EMG, EEG, intra-esophageal pressure, $PaCO_2$ of other physiological measures.

Video-PSG

Audiovisual recording synchronized with the polygraphic signals is obtained in addition to the test.

Full EEG and PSG

In particular cases a complete 21-channel EEG or more may be obtained in addition to the PSG signals. This can further be supplied with video recordings.

Table 2 Different methods for the diagnosis of sleep disorders in neurologic diseases

Type	Definition	Indication	Advantage/ disadvantage
PSG			
Routine PSG	Multi-channels EEG, EOG, submental EMG, ECG, respiration, ±tibial EMG	Routine screening for sleep disorders: SBD, PLM, chronic insomnia	Golden standard. May be performed inside or outside hospital. Standard method. Moderate expensive, time consuming, staff-demanding
Extended PSG	Routine PSG + extra physiological channels e.g. EMG, intraesophageal pressure, CO_2	Special indications: esophageal reflux, myoclonias, etc. Depends on selected channels	
Video-PSG	PSG + video recording	Motor and behavioral phenomena during sleep	A video signal is present. Full physiological recording is obtained. The difference between the methods is primarily the number of EEG channels. Expensive, time consuming, staff-demanding.
Full EEG-PSG	Full EEG (21 channels) + PSG	Motor and behavioral disturbances, differential diagnosis epilepsies	
Partial channel polygraphy			
Respiratory polygraphy	Monitoring of respiration + SaO_2 ± cardiac measures, e.g. pulse	OSAS	Easy, inexpensive. Moderate-good sensitive and specificity for OSAS, the validity for other SBD is not present
Oximetry	Monitoring of SaO_2	Monitoring or screening for severe SBD	Easy, inexpensive. Low sensitive and specificity for SBD
Actigraphy	Determination of motor activity (days–months)	Sleep–wake disturbances	Inexpensive, limited clinical usefulness

PSG, polysomnography; EEG, electroencephalography; EOG, electro-oculogram; EMG, electromyogram; OSAS, obstructive sleep apnea syndrome; SBD, sleep-related breathing disorder.

Partial polygraphy

Partial polygraphy includes selected measures, but without recording the sleep stages, as defined by EEG, EOG and EMG. Typically a surrogate measure of sleep is obtained (e.g. lack of movement artifact, snoring, questionnaire information). Therefore the limitations of these methods are that information regarding sleep-wake and sleep stages is not obtained.

Respiratory polygraphy or cardio-respiratory monitoring

A recording that typically measures a combination of variables including: respiratory effort (thoracic and/or abdominal), airflow, pulse oximetry, electrocardiography and snoring. The main application for RP is the diagnosis of OSAS, whereas the use of RP in the diagnosis of other SBD has not been evaluated. Meta-analysis of RP applied in patients without neurologic diseases suggests that the sensitivity and specificity in the diagnosis of OSAS when compared with the gold standard, PSG, is moderate, ranging between 82–94% and 82–100% respectively (class I). There are currently no studies comparing the use of RP to the PSG in patients with neurologic diseases.

Oxymetry

Oxymetry records the oxyhemoglobin saturation (SaO_2) with a sensor usually placed over one finger or ear that stores values typically obtained during sleep.

The use of oximetry may be subdivided into the following categories:

1 For the identification of OSAS in patients without neurologic diseases, the diagnostic value is poor, the sensitivity and specificity ranging between 36–100% and 23–99%, respectively. Only in the identification of moderate sleep apnea (AHI exceeding 10/h), oximetry provides a moderate sensitivity (92%) and specificity (97%).
2 Oximetry alone cannot differentiate between obstructive and central sleep apnea.
3 Oximetry is insufficient for the identification of stridor in MSA, as these patients rarely present desaturations unless there is the presence of sleep apnea.

4 The use of oximetry in the diagnosis of alveolar hypoventilation has been subject to evaluation. The use of nocturnal trendings in SaO_2 has been recommended routinely (evidence class II) for the identification of hypoventilation and for the treatment indication of noninvasive positive pressure ventilation (NIPPV) in patients with ALS [48]. A consensus established in 1999 by the European Respiratory Society recommended initiating nocturnal NIPPV in patients with neuromuscular diseases (including ALS) when one of the following markers was reached:

(a) Symptoms (fatigue, dyspnea, morning headache, orthopnea, etc.) and
(b) one of the following:

(i) $PaCO_2 \geq 45$ mmHg;
(ii) nocturnal oximetry demonstrating oxygen saturation ≤88% for 5 consecutive minutes;
(iii) for progressive neuromuscular disease (this is not the case of ALS), maximal inspiratory pressures < 60 cmH_2O; or
(iv) forced vital capacity $< 50\%$ predicted [62].

Later other criteria have been proposed in order to increase the sensitivity for the identification of respiratory failure in ALS, for example a mean nocturnal SaO_2, ≤93%, which presents a three time shorter survival than others, suggesting this threshold could be of interest to start a treatment [47], or combination of desaturations, AHI and symptoms [63].

The use of oximetry for screening for SBD in patients with neurologic diseases is thus complex. The diagnostic value of oximetry in the identification and differentiation between of OSA and CSA is poor-moderate, is insufficient for the identification of stridor. On the other hand, the need for a simple screening device for identification of alveolar hypoventilation is present. Oximetry present relation to disease severity (desaturation) [48], but there is a further need for documentation for the application of oximetry in neurological diseases.

Actimetry

In this recording a device consisting of a movement sensor that is placed in one limb, usually the non-dominant arm, records the presence and intensity of movements for relatively long periods of time, typically weeks. This allows measurement of the patterns of activity (wakefulness) and inactivity (sleep) throughout that period [64–66]. Actimetry has a minor role in the diagnosis of primary sleep disorders in patients with neurologic diseases, but it may be valuable in patients with disturbances in sleep/wake cycle or in the evaluation of motor disturbances. Furthermore, some actimetry devices may be useful for the detection of leg movements [67].

Number of recording nights

The number of nights needed to identify or exclude sleep disorders is poorly characterized. In the diagnosis of SBD there are no or little group differences between night 1 and night 2. Only few patients change the diagnosis between the two observations. This suggests that for the diagnosis of SDB, a positive finding is useful, but care should be taken when the results are negative, especially if sleep is very disturbed by the recording procedure [68]. In contrast, there is limited information regarding the number of nights needed to identify other sleep disorders in patients with neurologic diseases, e.g. nocturnal motor and behavioral disorders like PLM, RBD, or nocturnal epileptic seizures. In general these patients need a longer recording and observational period, at least two nights or even more.

Daytime recordings

Daytime recordings in patients with sleep disorders may include daytime PSG, MSLT/MWT and a standard EEG.

Daytime PSG

The aim of this measure is to replace the more complicated and expensive nocturnal PSG with a daytime PSG. The test is typically performed during a partial daytime sleep period. This requires that the patients sleep during the test. The sensitivity in the diagnosis of OSAS in patients without neurologic diseases is poor to moderate with a sensitivity between 66% and 100% and a specificity ranging between 66% and 100% (class II). There are currently no data regarding the value of daytime PSG in patients with neurologic diseases. There is currently no available evidence suggesting that a daytime test may replace the nocturnal test for the diagnosis of other sleep disorders in patients with neurologic diseases. The evidence for the use of daytime PSG in patients with neurologic diseases relies on weak evidence and is not recommended

Multiple sleep latency test and maintenance of wakefulness test

These tests measure the time it takes for a patient to fall asleep when placed in a highly soporific situation. In the MSLT the subject lies in bed in a dark and silent room with the instruction not to oppose sleep. In the MWT the room is dimly illuminated and the subject lies in a semi-reclined position with the instruction to resist sleep. In both tests sleep onset is defined by EEG criteria and the protocol consists of four to five naps performed at 2 h intervals, typically starting at 9:30–10:00 h after a nocturnal PSG. The MSLT appears to measure the ability to fall asleep whereas the MWT appears to measure the ability to remain awake, which may not always be

closely related, perhaps explaining why the correlation between MSLT and MWT is poor (0.41–0.52) [69]. The criteria for sleep onset and duration of each sleep period as well as the normative values for the MSLT are not unanimous, although a mean latency of < 5 min is considered abnormal. Normative values for the MWT are better established: in the 20-min variant latency shorter than 11 min is abnormal [69] (class III).

Despite these limitations, neurophysiologic tests can be performed in neurologic patients (level C). However, most of the evidence-based recommendations that have been elaborated before have so far not included patients with neurologic disorders. There is a need for studies evaluating these techniques in patients with neurologic disorders.

Standard EEG

A standard EEG has limited use in the diagnosis of sleep disorders in patients with neurologic diseases, aside from the indication of epilepsy (level C).

Management of sleep disorders

Treatment of SDB in neurologic diseases

Treatment of OSAS

1 Continuous positive airway pressure is a well-documented treatment for moderate and severe obstructive sleep apnea (AHI ≥15/h) and improves nocturnal respiratory abnormalities, daytime function, and cognitive problems [70–72] (level A). There is no significant difference regarding treatment effect or changes in subjective variables between fixed pressure CPAP or auto-adjusted CPAP [73] (level A). In some patients, for example neuromuscular disorder patients, CPAP may be difficult to accept and bi-level PAP may be used [74] (level B).
2 Continuous positive airway pressure and bi-level PAP is potentially useful in patients with SBD in stroke [75], but the evidence as to whether this influences quality of life, daytime symptoms, rehabilitation, morbidity, and mortality is limited. Recent studies suggests that CPAP treatment in post-stroke patient with sleep apnea may reduce the risk of new vascular events [76]; however a controlled study suggests that the effect is limited aside from symptomatic patients [77] (level C).
3 Severe SBD including laryngeal stridor in patients with MSA may be treated with CPAP/bi-level CPAP. Recent studies suggest that treatment with CPAP in MSA patients with laryngeal stridor showed high CPAP tolerance, no recurrence of stridor, no major side effects, subjective improvement in sleep quality, and increased the survival time to MSA patients without stridor [78,79]. CPAP is therefore an effective noninvasive long-term therapy for nocturnal stridor (level C).
4 There is limited evidence that suggests oral appliance (OA) use improves subjective sleepiness and sleep-disordered breathing compared with controls in patients with OSAS without neurologic diseases (level B). nCPAP is apparently more effective in improving sleep-disordered breathing than OA use (level B). There are no data regarding the use of OA in patients with neurologic diseases. Until there is more definitive evidence on the effectiveness of OA, caution should be exercised in the use of OA in patients with OSAS. If used it should only be tried in patients who are unwilling or are unable to comply with nCPAP therapy [80,81] (level C).
5 Although surgical treatment may be valuable in selected patients, there is a limited number of controlled trials documenting an effect of surgery in the upper airway against OSAS [82] (level C). There are no studies suggesting that surgery in the upper airway has any effect on OSAS in patients with neurologic diseases (level C), and is likely to be contradicted.
6 Medical treatments have no positive effect on OSAS [83] (level A). There are no studies available indicating that medication has any treatment effect of OSAS in patients with neurologic diseases (level C).
7 Although some patients with OSAS present increased weight and a negative lifestyle profile (tobacco, alcohol, physical activity) no controlled studies have evaluated the effect of intervention against these factors [84] (level C). No studies have addressed the effect of lifestyle interventions on OSAS in patients with neurologic diseases (level C).

Treatment of central sleep apnea-hypopnea syndrome

Case series have shown that CPAP treatment does not influence the CO_2 response in CSAHS, despite a reduction in apneas, increase in PaO_2, and reduction in subjective sleepiness [85–87] (class IV). Probably due to the rareness of the disease, there are no randomized studies regarding CSAHS and treatment. Medical treatment with acetazolamide and theophyllin have furthermore been suggested [88], but the evidence for their use is poor (level C).

Treatment of Cheyne-Stokes breathing syndrome

Initially CPAP was used in patients with central apnea/CSBS and cardiac insufficiency [89–92], but during recent years adaptive ventilation has been found effective probably by an increased preload in patients with significant cardiac failure and reduce the respiratory

abnormalities [93] (class IV). A recent randomized controlled study suggests the use of noninvasive adaptive ventilation may improve daytime function, respiratory and cardiac measures [94] (class II). The experience with the use of adaptive ventilation, CPAP or bi-level CPAP in patients with Cheyne-Stokes respiration due to central respiratory failure, e.g. brainstem lesions, is sparse and the evidence level is poor (level C).

Treatment of sleep hypoventilation syndrome
Treatment includes NIPPV with bi-level PAP (bi-PAP, variable PAP-VPAP), noninvasive volumetric ventilation, and eventually invasive ventilation under control of nocturnal respiratory parameters [95] (class IV). CPAP is not the primary treatment, as the motor effort mostly is reduced in these patients, which may lead to worsening of the SBD. NIPPV may reduce sleep disturbances, increase cognitive function, and prolong the period to tracheostomy [96,97] (class IV). Treatment of these condition requires a specialized team and ethical aspects should be addressed in the patient's management, especially regarding timing and need for tracheotomy (level C).

Follow-up
Although there is no evidence when and how follow-up of treatment with CPAP and NIPPV should be executed, we recommend regular follow-up of the treatment with control of compliance and treatment effect (level C).

Ethical aspects
Treatment of patients with severe neurologic diseases like ALS and MSA with NIPPV include medical and ethical problems which should be addressed. Adequate involvement of the patients and family, and the treatment, its use, and limitations should be carefully discussed. It is important to clarify the limitations of the treatment and there should be careful discussion regarding whether such treatment should be offered, initiation and discontinuation. There are serious ethical problems, e.g. when to initiate, discontinue and whether invasive ventilation should be offered [63,98].

Medical treatment

Treatment of excessive daytime sleepiness in neurologic diseases
Several groups of patients with neurologic diseases commonly complain of excessive daytime sleepiness. The etiology may be secondary to the disease, medication (dopaminergic or benzodiazepine drugs), sleep disorders such as sleep apnea, nocturnal motor phenomena, etc. In patients where these factors cannot be modified the wake-promoting agent modafinil may be used. Modafinil was primarily introduced to treat excessive daytime sleepiness (EDS) in narcolepsy [99–104]. Case studies [105,106] and double-blind controlled studies [107,108] suggest that modafinil reduces excessive daytime sleepiness in Parkinson's patients (class B-II). Modafinil has also been suggested in ALS [109], post-stroke depression [110,111] but no controlled studies are present (class IV). Furthermore, modafinil has been used for the treatment of hypersomnolence in OSAS without neurologic co-morbidity [112]. There are no studies evaluating whether other central-acting drugs like methylphenidate may have similar effects.

Other treatment of sleep disorders in neurologic diseases
Treatment of sleep disorders in neurodegenerative diseases is often complex and may involve different strategies. Management of some nocturnal disturbances in patients with PD may worsen nocturnal symptoms due to other causes and may increase EDS. PD-related motor symptoms can be treated with long-acting Dopamin agonists (DA) to obtain continuous DA receptor stimulation during the night. Both treatment-related nocturnal disturbances and psychiatric symptoms may be related to drug treatment, and therefore, in both cases, drug reduction or discontinuation should be considered.

As patients with taupathies suffer from a variety of sleep problems and have major motor and cognitive deficits, inpatient polysomnographic assessment is preferable to investigate their sleep symptoms fully. However, this often poses severe practical problems.

Some sleep disorders, such as RLS and PLMS, may be controlled by DA agents, and others, such as insomnia and EDS, may be improved by reducing dopaminergic stimulation (level C).

Clonazepam or donepezil, possibly prescribed with melatonin, have been suggested based on case series for the treatment of REM behavior disorders. No controlled studies are available [28,113].

Patients with dementias often present circadian disturbances which may be relieved by melatonin and/or phototherapy [114–131].

In selected cases treatment with hypnotics may be useful, but there is no evidence for its use, there is a potential risk for chronic use and additional risk for worsening of SBD if present.

Clearly there is a need for more controlled and intervention studies before definite conclusions can be reached.

Recommendations

1 Patients with neurologic diseases often have significant sleep disorders which may affect both nocturnal sleep and daytime function with increased

morbidity and even mortality. Many of these disorders are potentially treatable. Therefore, increased awareness should be directed toward sleep disorders in patient with neurodegenerative, cerebrovascular and neuromuscular diseases. Despite that, there are practically no grade A or B studies in this area.

2 A PSG is usually a diagnostic minimum for the diagnoses of the most commonly reported sleep disorders in patients with neurologic diseases.

3 In patients with nocturnal motor and/behavior manifestations, a full video-PSG/video-EEG-PSG should be considered.

4 Respiratory polygraphy has a moderate sensitivity and specificity in the diagnosis of OSAS without neurologic diseases, but its value for diagnosis of other SBD or in patients with OSAS with neurologic diseases has not been evaluated compared to gold standard PSG.

5 Limited channel polygraphy oximetry has a poor to moderate sensitivity-specificity for the identification of OSAS in patients without neurologic diseases. Oximetry cannot differentiate between obstructive and central sleep apnea or is insufficient to identify stridor. It is possible that oximetry has a role for the screening of hypoventilation in patients with neuromuscular weakness. Furthermore, oximetry may be useful for the control of CPAP treatment.

6 Patients with sleep-disordered breathing and muscle weakness and/or cardiac or pulmonary co-morbidity may present a SHVS, which manifests early as increased CO_2, hence $PaCO_2$ should be considered and controlled in such cases during sleep recordings.

7 Fixed pressure CPAP/auto-adjusted CPAP is the most effective treatment of OSAS. This probably also includes patients with OSAS and neurologic diseases. However, there is a need for further evaluation of the effect of CPAP in patients with OSAS and neurologic diseases.

8 Bi-level PAP/variable PAP, NIPPV and volumetric ventilation is useful for SBD-like central apneas, Cheyne-Stokes breathing, and alveolar hypoventilation.

9 There is a clear need for further studies focusing on the diagnostic procedures and treatment modalities in patients with sleep disorders and neurologic diseases.

Conflicts of interest

None reported.

References

The references are available at: http://blackwell-synergy.com/doi/abs/10.1111/j.1468-1331.2007.01965.x