

Sleep Disorders in Neurological Diseases

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Introduction

Sleep disorders are an important accompaniment of most neurological diseases but are often overlooked in the wake of overwhelming motor and cognitive abnormalities. The review presents an overview of these disorders and their mechanism followed by a practical approach to their diagnosis and management. Primary sleep disorders like narcolepsy, fatal familial insomnia, restless leg syndrome, etc are beyond the scope of this discussion.

Synucleinopathies

The prevalence of EDS in Parkinson's Disease (PD) is found to be higher in PD when compared to age matched controls[1,2,3]. This is an important issue because of its impact on the daily functioning of the patient and risk of falling asleep while driving. Disruption of nocturnal sleep due to motor symptoms like bradykinesia and rigidity, adverse effects of drugs like vivid and distressing dreams is the most common cause. Sleep disordered breathing due to stridor, obstructive or central sleep apnea could be the cause in patients with multiple system atrophy (MSA). A primary form of hypersomnia due to deficiency of hypothalamic hypocretin is also observed especially in advanced PD and multiple system atrophy [4,5]. The 4 year cumulative prevalence of somnolence in a cohort of Parkinsonian subjects (mean age of 61.2 years and mean UPDRS total score of 31) was 35%. The clinical predictors of this outcome identified in this

study were initial treatment assignment to pramipexole, UPDRS mental subscore, male gender and presence of more than 5 co-morbid illnesses[6]. In another study where 235 patients with PD were objectively assessed for excessive daytime sleepiness using the Stavenger Sleepiness Questionnaire and the Epworth Sleep Scale, the prevalence was 54.2% at 8 years. Association of EDS with clinical variables like age, male gender and use of dopamine agonists at baseline was observed on multivariate analysis[7].

REM Sleep Behavioral Disorder (RBD) results from a failure to switch-off the brainstem responses causing muscle atonia during REM sleep that restrain an individual from drifting into the virtual reality of his dreams. This leads to embarrassing and at times dangerous enactment of the dream content like crying, punching, talking, leaping, and injuring oneself and the bed partner. The clinical phenomenology of synucleinopathy associated RBD is similar to that of idiopathic RBD but self-reported severity has been observed to be higher in the latter. Diagnosis requires 1) history of dream-enactment behaviors and 2) VPSG evidence of increased tonic or phasic electromyographic (EMG) activity during REM sleep associated with abnormal behaviors. The best evidence for this association has come from long term follow-up of patients with idiopathic RBD. In a 5 year follow up of 44 patients with RBD, it was found that 45% of patients without any evidence of neurodegenerative disorder at baseline manifested clinical features of a synucleinopathy, most commonly PD. [8]. In an earlier study, 38% with RBD went on to develop a Parkinsonian syndrome after 5 years of follow up[9]. In a cross-sectional assessment of 93 patients with PSG confirmed diagnosis of RBD, 57% had an associated neurodegenerative disorder of which 43% had PD and related disorders. RBD symptoms predated the classical symptoms of the PD in as many as 52% cases by a median of 3 years (range, 1-30 years)[10]. Plazzi et al reported clinical features and polysomnographic findings

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consistent with RBD in 69.7% and 90% of patients in his series of 39 patients with MSA[11], albeit none of them fulfilled the diagnostic criteria for RBD. Motor manifestations and sleep talk were present in most of the patients. MSA patients with RBD when compared to PD exhibited shorter disease duration, a greater percentage of REM sleep without atonia, higher PLMS index, and less total sleep time.

Braak et al demonstrated that Lewy bodies start inhabiting the brainstem structures much before the extrapyramidal structures thus explaining the tendency for RBD to predate parkinsonian symptoms in synucleinopathies [12]. Severe loss of cholinergic neurons in the pedunculopontine (PPT) and laterodorsal (LDT) tegmental nuclei has been observed in Parkinsonian syndromes most notably in MSA and PSP followed by DLBD and PD. These neurons through their midbrain connections are involved in regulation of REM-sleep associated phenomena [13]. But the correlation of these pathological phenomena with clinical manifestations of RBD is not established.

Epilepsy

The relevance of sleep disorders in epilepsy was first recognized when OSA was observed in a subset of patients with frequent seizures. In a cross-sectional study of 124 consecutive patients with epilepsy, EDS was found in 16.9%, OSA in 28.2%, and insomnia in 24.6% patients[14]. In another case-control study, there was no significant difference between the groups for prevalence of EDS, but insomnia of sleep-maintenance type was more frequent in patients with epilepsy [15]. Patients with NFLE when compared with controls had an increased frequency subjective sleep related symptoms like "tiredness after awakening" and "spontaneous mid-sleep awakenings" but not in EDS (Vignatelli et al). Thus far, OSA remains the most accepted association in epilepsy. Weatherwax et al reported OSA in 45% of patients with epilepsy who underwent polysomnographic evaluation while Malow et al evaluating a group of patients with intractable epilepsy found OSA in one third of patients of which 13% had severe OSA[17,18]. The factors predisposing to OSA in epilepsy are older age, male sex and presence of nocturnal seizures. The Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) is a useful instrument for prediction of OSA in epilepsy with a higher sensitivity in males compared to females [17]. A single case series demonstrated improvement of

seizure control with effective management of OSA [19]. This observation needs to be confirmed in future studies. The efficacy and tolerability of CPAP is also unclear.

Stroke

The prevalence of sleep disordered breathing (SDB) is considerably higher in stroke victims than in the general population. While the prevalence of OSAS (OSA + EDS with AHI ≥ 5) in Wisconsin study by Young et al was 4% in men and 2% in females, the prevalence of OSA (AHI ≥ 10) in stroke patients varies from 44% to as high as 96% depending on the methodology of the study. The term SDB encompasses three entities namely sleep apnoea, snoring-upper airway resistance syndrome and obstructive sleep apnea syndrome. SDB is now recognized to be an independent risk factor for stroke as well as TIA and also contributed indirectly by increasing the risk of hypertension[20-23]. A declining trend is sometimes noted with increasing duration of stroke which is most prominent for positional sleep apnoea which refers to sleep apnoea directly related to the positioning of the patient[22,23]. Existing literature does not support a significant association between sleep apnoea and stroke severity or outcome.[20,23,25]. Sleep apnea refers to temporary respiratory pauses during sleep. To be of significance it should be 10 seconds or more. Sleep apnea can be obstructive, central or mixed. In obstructive sleep apnea there is cessation of airflow through nose or mouth, but with continuing respiratory effort as evidenced by diaphragmatic and intercostal muscle activities. In central apnea, there is no respiratory effort at all. Mixed apnea begins as central apnea with cessation of airflow and respiratory effort, but appears as obstructive apnea towards the end with appearance of respiratory effort, while nasal and mouth airflow show continuing restriction. Sleep hypopnea is defined as 30% or more airflow limitation associated with 4% or more oxygen desaturation. Sleep apnea and hypopnea are combined together in an index called Apnea-hypopnea or Respiratory disturbance index (AHI or RDI) defined as number of apneas or hypopneas per hour of sleep. Normal AHI is less than 5. In Upper airway resistance syndrome there is no airflow limitation significant enough to cause apnea-hypopnea and oxygen desaturation, but subtle flow limitation causes recurrent arousals and resultant sleep fragmentation. The airflow limitation in UARS cannot be identified by usual PSG recording of respiration using

ronasal themistor, but requires nasal pressure monitoring using nasal cannula or better still, by the gold standard, intraoesophageal balloon manometry. Patients with UARS exhibit all the clinical manifestation and consequences of obstructive sleep apnea. Obstructive sleep apnea syndrome (OSAS) refers to the PSG demonstrated OSA with its clinical manifestation of excessive daytime sleepiness.

Dementia

A disrupted night time sleep, excessive day time sleepiness and circadian rhythm disturbances are sleep disturbances commonly described in patients with dementia which can impact the cognitive abilities and functioning of the patient as well as indirectly increase the caregiver burden. Behavioral symptoms like irritability, agitation, hallucinations and anxiety contribute to insomnia while the severity of dementia and degree of functional disability is related to the occurrence of excessive daytime sleepiness[26-28]. Degeneration of the nucleus basalis of Meynert in dementia especially AD leads to a dysregulation of its vital connections with the biological clock (suprachiasmatic nucleus) which in turn regulates the switch between activity and NREM sleep[29]. Circadian gene regulation defects are also identified in dementias like DLBD[30]. Pineal melatonin secretion and pineal clock gene oscillations are found to be affected in AD[31]. This contributes to the phenomenon of sun-downing in patients with dementia. Encouraging good sleep hygiene, cutting down on sleep-disrupting medications and environmental interventions form the first-line management of these patients [32,33].

Meningitis

Insomnia can occur as a long term complication of bacterial and viral meningitis. The risk of suffering from insomnia is probably not linked to the causative organism. The proposed mechanism is a release of excitatory amino acids like quinolic acid and glutamate and a decreased concentration of tryptophan leading to impaired serotonin synthesis. In a cross-sectional assessment of 89 subjects with a history of bacterial or viral meningitis a year back and 42 age-matched healthy controls using the Pittsburgh Sleep Quality Index (PSQI) and the Schlafragebogen B (sleep questionnaire B; Sf-B), significant differences were observed in sleep quality and in the frequency of sleep disturbances. Severe sleep

disturbance indicated by PSQI score ≥ 5 was seen in 58% of patients with meningitis[34]. In another questionnaire survey of 505 cases of meningitis two years after illness and an equal number of age-matched healthy controls, insomnia was more frequently reported by relatives of patients with meningitis (OR2.31, 95%CI.1.17-4.82)[35].

Spinocerebellar Ataxia Type 2

SCA 2 shares pathological features with PD and MSA in that the pontine neurons regulating REM sleep are critically involved. Polysomnography supports this finding with varying degrees of REM sleep abnormalities observed in different studies[36,37,38]. Tuin et al has proposed a classification of these abnormalities into a prodromal stage (I) of nonspecific sleep disturbance with increased nocturnal wakefulness and reduced light sleep, possibly together with RBD or an inconspicuous reduction in REM sleep stage (II) after SCA2 manifestation with REM density reduction, RWA, increased wakefulness, and sparse dream recall a stage (III) with REM density reduction, RWA, increased wakefulness, lack of dream recall, and increased REM latency ; and a stage (IV) with REM loss, lack of dream recall, and increased SWS[38]. Since this classification was based on a short case series, future studies are required for better characterization of sleep abnormalities in this disorder. Osario and Daroff were the first to demonstrate absence of REM in sleep records of patients with SCA-2[39]. These abnormalities are the result of early involvement of pontine and later involvement of the thalamic neurons regulating REM sleep. The midbrain raphe neurons are relatively spared thus explaining the preserved slow wave sleep in these patients.

Myotonic dystrophy

Sleep disturbances are seen in about 30-40 percent patients with myotonic dystrophy. Excessive daytime sleepiness (EDS) was the most commonly observed disturbance in a series of 157 patients with genetically proven MD, which correlated with severity of muscle weakness but not with other demographic, disease or genetic parameters[40]. Rubinzstein et al in their evaluation of 36 patients with myotonic dystrophy found that 39% of patients had idiopathic hypersomnolence while 6% had mixed sleep apnoea and hypersomnolence.

[41] Polysomnographic studies have demonstrated decreased mean sleep latency, sleep onset REM periods and decreased levels of sleep, findings similar to narcolepsy. EDS could rarely be the presenting manifestation in MD[42] Although factors like apathy, depression, respiratory muscle weakness and sleep apnoea may contribute, neurochemical disturbances are thought to play an important role in the genesis of sleep disturbances in this disorder. A decreased level of hypocretin 1 in the CSF was demonstrated in one study when compared to age-matched controls; but no correlation was seen with the severity of the sleep disorder [43]. A recent study which tested this hypothesis did not reveal significant difference in hypocretin levels with respect to controls [44]. This lends support to the alternate theory that neuronal accumulation of the mutant transcripts in MD leads to a dysregulation of alternate splicing in the sleep regulatory networks in the brain; which ultimately results in reversion to a neonatal sleep pattern[45].

Multiple Sclerosis

Insomnia can result from spasticity, pain, flexor spasms, pain, immobility, nocturia or drugs. A narcolepsy like sleepiness phenomenon can haunt a subset of patients with multiple sclerosis. A dysfunction of the hypocretin system in the hypothalamus consequent to a demyelinating lesion is suggested as the probable cause [46]. There are case reports of patients with MS developing RBD secondary to critical lesions in the brainstem.[47].

Migraine

Migraine is associated with sleep onset and maintenance type of insomnia in about fifty percent cases [48]. Deprivation of sleep in turn precipitates migraine episodes in most of them and such attacks usually show a circadian variation with one peak in the morning hours and one peak after noon[49].

Huntington's disease

Nocturnal sleep may be disturbed by depressed mood, anxiety and choreic movements. The maintenance phase is predominantly affected with decreased sleep efficiency without frank arousals. REM sleep abnormalities like increased latency of REM onset and decreased

percentages are also reported.[50] .Circadian rhythm disturbance have also been reported in a mouse model[51].

Special Investigations

Polysomnographic recordings with special electrodes for upper limb and lower limb EMG recording need to be done in patients with RBD, RLS and unusual nocturnal motor symptoms. Special requirements may need to be provided in stroke patients who have OSA to make sure that they are stable during the recording. In patients where the differential of epilepsy with parasomnia exists extended EEG channels should be put with an EEG montage. Video PSG facility should be available for patients where motor movements are nocturnal. Sound recording should also be available for recording any vocalizations.

Management

When encountering a patient with a neurological disorder and sleep disturbance, one needs to ascertain the underlying cause in order to successfully manage this problem. The factors responsible could be:

The factors contributing to disturbed sleep vary according to the disease entity. For example, several symptoms both motor and non-motor can disturb sleep in the PD patient. This includes wearing off, axial rigidity, nocturia, freezing, dystonia, dyskinesias, akathisia, restlessness, tremor, nocturnal pain and cramps, depression, neuropsychiatric symptoms or obstructive sleep apnoea. Improvement of these symptoms by appropriate measures would produce a proportionate benefit in the sleep efficiency. In dementia neuropsychiatric disturbances and urinary problems are the key culprits. In stroke, positioning of the patient may be detrimental. Whichever factor is responsible needs to be modified accordingly.

Disease related Drugs: Anti-Parkinsonian drugs especially when taken in the evening hours can significantly affect the quality of sleep. Levodopa, anticholinergics, amantidine and seligiline can adversely affect sleep. The offending drug should be stopped or reduced whenever suspected to be the cause of poor sleep quality or insomnia. When this cannot be ascertained, drugs should be sequentially withdrawn starting with anticholinergics followed by amantidine and then

dopaminergics. Drugs used for treatment of dementia like donepezil and galantamine can occasionally cause insomnia. Drugs used for other neurological disorders as well as those administered for concurrent problems can also cause sleep problems.

Definitive

EDS

In neurological diseases, EDS is usually secondary to poor night time sleep or due to disease or drug related factors which need to be corrected as a firstline measure. Modafinil a wake promoting compound acting on the hypothalamus, ideally suited for disorders like narcolepsy where EDS is the primary problem can be tried in selected cases [52]. Armodafinil, the R-enantiomer of modafenil is an equally effective and safe option with the added advantage of a longer half-life [53].

RBD

The management doesn't differ from that of idiopathic RBD. The drug of choice is clonazepam which produces benefit in about 90% of cases. Treatment is started at a dose of 0.5 mg and subsequently increased to 1-2 mg. In patients prone to falls or associated OSAS, melatonin (3-9 mg) is preferred. Dopaminergic drugs and cholinesterase inhibitors may reduce RBD associated motor phenomena but do not have a consistent predictable effect [54]. Patients should be instructed to avoid drugs causing/aggravating RBD like MAO inhibitors and serotonergic anti-depressants

SDB

CPAP remains the best option for the therapy SDB, but its acceptance and feasibility is yet to be established in these patient subgroups [55] (Hui et al). Wake promoting drugs like modafinil can be used to improve the associated EDS.

Circadian rhythm disturbances

Melatonin in a dose of 10 mg daily and light therapy with 5000-10,000 lux bright light produce modest effects in abnormal sleep-wake cycles seen in neurodegenerative disorders especially AD [56, 57].

Conclusion

Sleep abnormalities like insomnia, EDS, RBD and circadian rhythm disturbances form a part of the clinical spectrum in most neurological diseases. A good clinical interview supplemented by PSG will enable one to classify and treat these disorders.

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