Sleep in Neurodegenerative Diseases

32

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Introduction

Neurodegenerative diseases are characterized by progressive neuronal loss in the nervous system and abnormal deposition of some proteins such as alpha-synuclein, tau, or amyloid thought to lead to cell dysfunction. The etiology of most of the neurodegenerative diseases is still unknown. Several sleep disorders including insomnia, rapid eye movement (REM) sleep behavior disorder (RBD), periodic leg movements in sleep (PLMS), restless legs syndrome (RLS), excessive daytime sleepiness (EDS), and nocturnal stridor have been described in patients with neurodegenerative diseases. However, the idea that sleep disorders occur commonly in neurodegenerative diseases is relatively new, although one can find descriptions of sleep problems in the classical descriptions of Parkinson disease (PD), multiple system atrophy (MSA), hereditary ataxias, progressive supranuclear palsy (PSP), and Huntington disease (HD). PD can be considered as a representative neurodegenerative disorder where the main sleep symptoms, namely, insomnia, EDS, and parasomnia, commonly occur.

Parkinson Disease

PD is caused by progressive neuronal loss in many regions of the brain leading to dysfunction of several neurotransmitter systems, particularly the nigrostriatal and mesolimbic dopaminergic systems. The structures that regulate the sleep–wake cycle are also damaged by the disease process. PD is clinically characterized by gait and postural abnormalities, resting tremor, rigidity, and bradykinesia. In addition, patients present nonmotor manifestations such as depression, anxiety, dementia, autonomic impairment, and sleep disturbances [20].

In his monograph written in 1817, James Parkinson first recognized that sleep disturbances are an important component of the condition that he originally termed paralysis agitans [96], particularly in patients in the last stage of the disease. For many years, however, neurologists considered insomnia as the only relevant sleep problem. The presence of sleep disruption was considered a risk for developing levodopa psychosis [87, 111] and likely related to chronic levodopa therapy. This attitude changed completely after the publication of two highly relevant papers: one by Schenck et al. in 1996 [108] describing the development of parkinsonism in patients initially diagnosed with idiopathic RBD, and another by Frucht et al. in 1999 [33] describing sleep attacks in patients taking the dopamine agonists pramipexole and ropinirole (Fig. 32.1).

Sleep complaints in patients with PD are more frequently common than in healthy age-matched controls, can be severe, and in some cases are the initial manifestation of the disease [2, 108], and can have a negative impact on quality of life [30, 65, 70, 77, 119]. Insomnia, sleep fragmentation, nocturia, stiffness, difficulties in turning over in bed, akathisia, nocturnal restless legs, cramps, nightmares, vigorous motor and vocal dream-enacting behaviors, visual hallucinations, confusional awakenings, snoring, witnessed apneas, painful early-morning dystonia, and EDS are some of the sleep problems described in PD. Sleep complaints and polysomnography (PSG) abnormalities found in patients with PD are multifactorial. They are related to damage and functional dysregulation of the brain structures and mechanisms involved in sleep origin and maintenance, the effects of antiparkinsonian drugs on sleep, parkinsonism severity,

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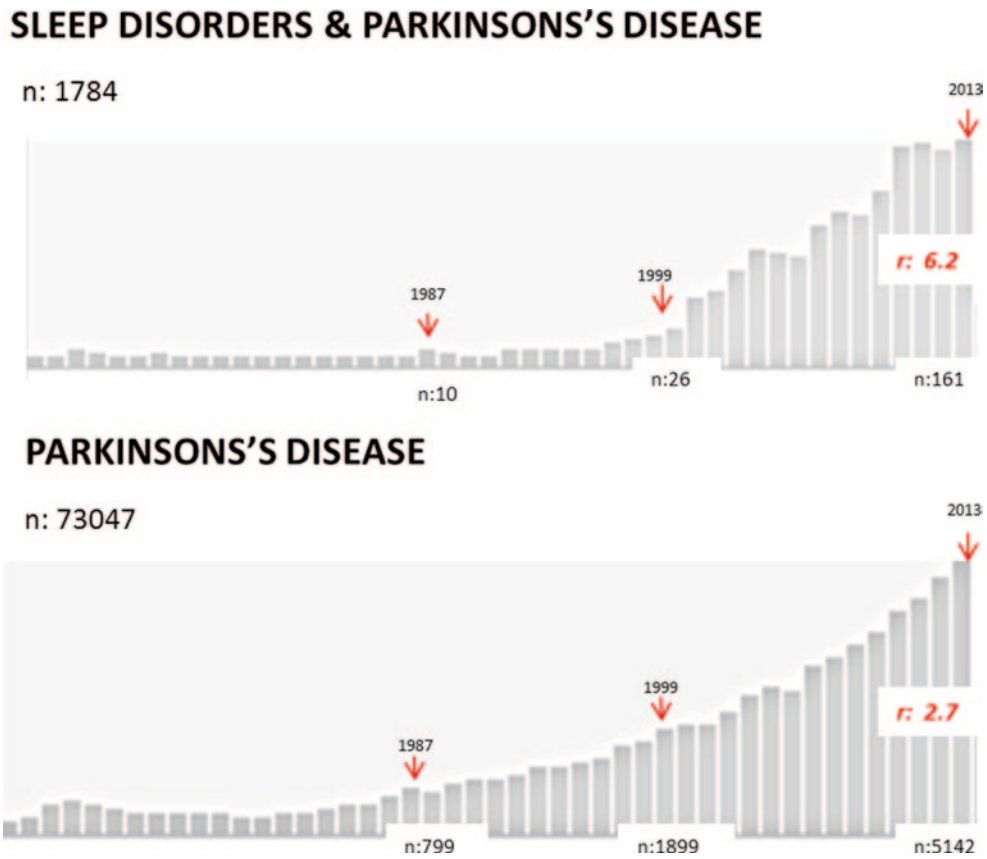

Fig. 32.1 Number of articles published between the years 1966 and 2013 dealing with "Parkinson disease" (PD) and with "sleep disorders and PD." The number of publications on the area of PD in 2013 doubled the number of articles published in 1999, whereas for the area of sleep disorders and PD there were six times more articles in 2013 than in 1999. (Source: Pub Med)

comorbid conditions such as anxiety, depression, and dementia, aging, and genetic individual susceptibility. In general, sleep disturbances gradually worsen with the progression of the disease.

Insufficient and Fragmented Nocturnal sleep

Most patients with PD report insufficient sleep as a result of frequent awakenings, and less commonly, early-onset insomnia and early-morning awakening [65, 70, 77, 119]. In patients with PD, poor and reduced sleep causes severe daytime fatigue and tiredness. Interestingly, as noted in primary insomnia, poor quality and reduced duration of nocturnal sleep in PD are not related to the development of EDS. [6, 103]. Surprisingly, a more robust and continuous sleep architecture has been associated with more severe sleepiness [103]. The main cause of reduced and fragmented sleep in patients with PD is the severity of parkinsonian symptoms. Although muscle tone decreases during sleep, variable degrees of rigidity can be experienced by patients with PD during the different stages of sleep. This rigidity accounts for complaints of stiffness, back pain, and leg cramps. Nocturnal akinesia is responsible, along with stiffness, for poor nocturnal mobility that manifests as difficulties turning over or getting out of bed. This situation can be extremely distressing to patients who need to go to the toilet several times at night. In patients with advanced PD, chronic treatment with bilateral subthalamic stimulation improves subjective sleep quality, something that is thought to be a consequence of increased nocturnal mobility secondary to a an improvement in rigidity and bradykinesia [5, 54]. Patients with PD who also have dementia may exhibit confusional awakenings and visual hallucinations leading to sleep fragmentation and nonrestorative sleep. The main contributors to early-onset insomnia in patients with PD are anxiety, depression, dyskinesias induced by dopaminergic drugs, and the intrinsic effect of several antiparkinsonian drugs such as selegiline and levodopa. Depression and early-morning trunk and foot dystonia cause early awakening. Circadian sleep–wake cycle disruption is another cause of disturbed nocturnal sleep in patients with PD. These individuals have an exaggerated tendency toward an advancement of phase, thereby developing an irregular sleep–wake pattern characterized by early-morning awakening and evening sleepiness. This situation is frequently associated with an advanced disease state, depression, and dementia.

Excessive Daytime Sleepiness

Most of the studies dealing with EDS in PD have been published after 1999, following the paper by Frucht et al. [33]. It is illustrative, as an example, to review the 1998 [90] and 2001 [92] "Algorithms for the management of PD" in the journal *Neurology* to see how EDS was contemplated before and after the Frucht et al. [33] paper was published. In the twentieth century, EDS in PD was considered rare, and usually related to medications. This perception completely changed after the description of "sleep attacks" in PD patients treated with the dopaminergic agonists pramipexole and ropinirole.

The prevalence of persistent EDS in patients with PD ranges from 15.5 to 74% [29, 39, 41, 47, 116, 117, 120, 126]. The main factors contributing to persistent EDS are the intrinsic pathology of PD and the sedative effects of the dopaminergic drugs. In patients with PD, the development of persistent EDS may be related to progressive cell loss in the dopaminergic and nondopaminergic brain structures, and circuits that modulate the sleep–wake mechanisms. In general, persistent EDS is associated with advanced parkinsonism and the use of dopaminomimetics. Other possible causes of persistent EDS should be considered before determining whether EDS is caused by the disease itself or by the effects of dopaminomimetics. Circadian dysrhythmia, obstructive sleep apnea, depression, dementia, and the concomitant use of other sedative drugs such as hypnotics are thought to contribute to persistent EDS.

There is a subgroup of sleepy PD patients with short mean sleep latency and the presence of REM sleep periods on the multiple sleep latency test [6, 103]. In PD, cerebrospinal fluid (CSF) hypocretin levels, however, have been reported to be normal [23] and cataplexy does not occur. In unselected PD patients, autopsies show a loss of 23–62% of hypocretin cells, but CSF hypocretin levels are normal in PD with and without dementia [32, 122] (Table 32.1).

Sudden onset of sleep episodes (SOS), or sleep attacks, are less common than persistent EDS in patients with PD [50]. Among patients with PD treated with dopaminergic drugs, the prevalence of SOS is estimated to range from 0 to 32% [29, 47, 117, 120]. Episodes of SOS are considered to be the result of a dopaminergic class effect; that is, they have been shown to be associated with the use of virtually all dopaminergic drugs, occur several days or months after the introduction of the dopaminergic drug, and usually resolve or decrease after its withdrawal, reduction, or replacement. The most common variables associated with SOS episodes are therapy with dopamine agonists, duration of parkinsonism, elevated Epworth Sleepiness Scale scores, age, and sex [83, 91, 97]. In PD, modafinil [49] and sodium oxybate [94] may improve EDS.

Sleep-Disordered Breathing

Several studies have shown that sleep-disordered breathing is common in patients with PD, especially in those individuals complaining of sleepiness. However, it is not significantly more prevalent in patients with PD than in age-matched populations [10, 26, 27, 89, 123] (Table 32.2). In PD, the frequency of an apnea–hypopnea index greater than 5 is 27–54%, and the frequency of greater than 30 is 4–15%. The number of apneas does not change across consecutive nights and is not modified by the introduction of a dopaminergic agent. The number of apneas per hour in PD is not associated with age, gender, body mass index, the occurrence of RBD, oxyhemoglobin saturation at night, scales that assess sleepiness, and parkinsonism severity. Therefore, it seems that PD itself does not confer an increased risk of obstructive apneas and that the frequent presence of this condition in PD is a reflection of aging or reduction of the upper airway space. Nevertheless, patients with PD who experience EDS should undergo routine PSG to identify the potential for obstructive sleep apneas. In these cases, correct treatment of this condition with continuous positive airway pressure (CPAP) can help them greatly.

Table 32.1 Comparison between Parkinson disease with narcolepsy with cataplexy and with narcolepsy without cataplexy

	Narcolepsy with cataplexy	Narcolepsy without cataplexy	Parkinson disease
Hypersomnia	+	+	+
Sleep attacks	+	+	+
Cataplexy	+	-	-
Hallucinations	+	+	+
Sleep paralysis	+	+	-
REM sleep behavior disorder	+	+	+
HLA DQB1*0602	>90%	60%	30%
Sleep onset REM periods in the multiple sleep latency test	+	+	+/-
Absent hypocretin in cerebrospinal fluid	>90%	10%	0%
Loss of hypocretinergic cells in the hypothalamus	90%	30%	23–62%

Table 32.2 Obstructive sleep apnea in Parkinson disease

Author Year	Country	Patients (*n*)	Mean age (years)	Mean AHI (*n*)	AHI > 5 (%)	AHI > 10 (%)	AHI = 5–15 (%)	AHI > 15 (%)	AHI = 15–30 (%)	AHI > 30 (%)
Rye et al. 2000 [103]	USA	27	68	11	–	–	–	–	–	–
Arnulf 2002 [6]	France	54	68	10	47	14	28	20	11	9
Stevens et al. 2004 [116]	USA	19	60	9	–	–	–	–	–	–
Iranzo et al. 2005 [57]	Spain	45	65	16	–	–	–	–	–	–
Diederich 2005 [27]	Luxemburg	49	65	8	43	–	20	22	8	15
Baumann 2005 [10]	Switzerland	10	69	11	–	–	–	–	–	–
Trotti and Bliwise2010 [123]	USA	55	64	7	44	–	29	15	11	4
Noradina 2010 [89]	Malaysia	46	64	7	54	–	27	27	18	9
De Cock 2010 [26]	France	100	62	10	27	–	6	21	11	10

AHI apnea–hypopnea index (number of apneas and hypopneas per hour of sleep).

REM Sleep Behavior Disorder

RBD is a parasomnia first described in five patients in 1986 by Schenck et al [106], who expanded the following year [107] the observation to ten new patients, involving predominantly older men (half of whom had a major neurologic disorder including parkinsonism). Since that time, RBD has taken an increasingly important role in understanding sleep in PD. Before the description of RBD, episodes of nocturnal agitation were considered a variant of somnambulism, and thought to appear out of deep nonrapid eye movement (NREM) sleep and probably induced by levodopa (Scharf et al 1978).

RBD is characterized by dream-enacting behaviors, fearful dreams, and REM sleep without atonia. RBD may be idiopathic or associated with neurodegenerative diseases [60]. Studies from three different groups have shown that patients with idiopathic RBD develop the classical motor and cognitive symptoms of PD, dementia with Lewy bodies, and MSA with time [58, 61, 101, 108, 109].

RBD occurs at least in one-third of patients with sporadic PD [34, 105] and is also frequent in patients with PD secondary to mutations in the *parkin* gene [71]. RBD occurs in PD patients untreated or treated with dopaminergic agents. RBD is more common in the rigid-akinetic clinical subtype of the disease than in the tremoric subtype [72]. For reasons not yet known, RBD is more common in male patients with PD than in female patients. Of note, up to 29% of patients with PD with confirmed RBD by video-PSG are unaware of their abnormal motor and vocal sleep behaviors, and up to 13% do not recall dreaming [57]. In these cases, history suggestive of RBD can be obtained only from the bed partner. On the other hand, hallucinations, somnambulism, confusional awakenings, and severe obstructive sleep apneas may mimic RBD symptoms in PD [52]. The sensitivity of specialized interviews for identifying RBD in patients with PD varies from 33 to 95%. There is some evidence that RBD in PD is associated with dementia [128], age, and disease duration [115]. However, the occurrence of RBD in nondemented PD subjects with early stages of the disease is not uncommon. When comparing patients who have PD and RBD with patients who have idiopathic RBD and MSA with RBD, there are few differences in RBD-related clinical and sleep measures [57]. The pathophysiology of RBD in patients with PD is thought to result from the degeneration or dysfunction of the brainstem structures that modulate REM sleep [60]. Such areas include the medial medulla, pedunculopontine, and subcoeruleus mesopontine regions, and their anatomic connections with the substantia nigra pars reticulata, basal ganglia, hypothalamus, and limbic system. Postmortem studies examining the brains of patients with PD have shown that the degenerative process begins in the lower brainstem and advances upward through the pons before reaching the midbrain where the substantia nigra is located [17]. This might account for the observation that RBD precedes the onset of parkinsonism. However, an alternate sequence of neuropathologic events may take place to account for the more common finding of parkinsonism preceding RBD. RBD in PD, and associated with any other condition including the idiopathic form, responds to low doses of clonazepam at bedtime. Melatonin can be a therapeutic alternative in those few cases that do not respond to clonazepam or do not toler-

ate this drug. In refractory cases, methods of self-protection from injury during episodes of RBD may be necessary. Pramipexole does not improve symptoms of RBD in patients with PD [73], a finding suggesting that dopamine dysfunction does not play a central role in the pathogenesis of RBD.

Restless Legs Syndrome

RLS is a sensorimotor disorder characterized by an urge to move the legs. This impulse is caused by unpleasant sensations that begin during periods of inactivity at night and is relieved by movement. RLS is a condition that affects up to 5–15% of the general population over 60 years of age and may interfere with sleep initiation and maintenance. Iron and dopaminergic dysfunction in the diencephalo-spinal system are believed to play a critical role in the pathogenesis of RLS because patients with RLS dramatically respond to dopaminergic drugs. Although the description of RLS is several centuries old, the description that levodopa improved their symptoms [3] pointed out the role of the dopaminergic system in RLS and the possible relationship between RLS and PD.

There is no evidence, however, that idiopathic RLS predisposes to develop PD [59] (Table 32.3). On the one hand, patients with idiopathic RLS do not progress to PD [132]. On the other hand, while it had been suggested that there is an association between PD and RLS, the evidence is still limited to few studies with methodological problems that have reported conflicting results [18, 44, 66, 69, 75, 76, 79, 88, 93, 98, 118, 129]. When PD patients are compared with a control group, there is no difference between the rate of RLS between the two groups [2, 19, 42]. It should be noted that RLS must be carefully distinguished by clinical history from other uncomfortable sensations commonly experienced by the PD subjects (stiffness, pain, tingling, heat, cramps) which may be related to parkinsonian features and not to RLS (rigidity, tremor, central pain, off periods, dystonia, and dyskinesias). Like in idiopathic RLS, PD patients with true RLS have low serum ferritin levels. In most of the PD cases with comorbid RLS, parkinsonism precedes the onset of RLS and severity of RLS is mild. This is probably because dopaminergic agents improve both RLS and parkinsonism. However, PD and RLS may be coexistent because they are both prevalent in the elderly. If true RLS is bothersome or prevents the PD patient from sleeping, the evening dose of dopaminergic agents can be increased or a standard formulation can be prescribed. Alternatively, other nondopaminergic drugs that are effective for RLS such as gabapentin and pregabalin can be used.

Periodic Leg Movements During Sleep

PLMS are repetitive, stereotyped leg movements that are 0.5–10 s in duration and are separated by an interval of more than 5 s but less than 90 s. The occurrence of PLMS is thought to be related to the impairment of central dopaminergic function because PLMS decrease in frequency with the use of dopaminergic medications. Moreover, PLMS in PD increase after chronic treatment with bilateral subthalamic stimulation probably because this type of surgery facilitates the reduction or withdrawal of dopaminergic drug treatment [54]. PLMS are more frequent in untreated patients with mild to moderate PD than in healthy individuals [135]. Most patients with PD who experience PLMS are unaware of these leg movements because PLMS are generally not associated with awakenings. Therefore, PLMS in PD may be not considered a main contributing factor for developing insomnia, sleep fragmentation, and EDS.

Table 32.3 Restless legs syndrome in Parkinson disease

Author Year	Country	Patients (*n*)	Mean age (years)	RLS in PD (%)	RLS in controls (%)
Lang 1987 [75]	Canada	100	62	0	NE
Ondo 2002 [93]	USA	303	67	21	NE
Khan and Sahota 2002 [66]	USA	26	NE	38	NE
Tan et al. 2002 [117]	Singapore	125	65	0	NE
Krishnan et al. 2002 [69]	India	126	57	8	1
Braga-Neto 2004 [18]	Brazil	86	65	52	NE
Nomura 2006 [88]	Japan	165	68	12	2
Gómez-Esteban 2007 [44]	Spain	114	69	22	NE
Loo 2008 [79]	Singapore	200	65	3	0.5
Lee et al. 2009 [76]	Korea	447	64	16	NE
Calzetti 2009 [19]	Italy	118	69	13	6
Peralta et al. 2010 [98]	Austria	113	67	24	NE
Verbaan et al. 2010 [129]	Holland	269	61	11	NE
Angelini 2011 [4]	Italy	109	67	6	4
Gjestard et al. 2011 [42]	Norway	200	65	12	7

NE not evaluated

Multiple System Atrophy

Historically, what is now considered a single disease was first described as three separate entities: striatonigral degeneration, olivopontocerebellar atrophy, and Shy–Drager syndrome [133, 134]. The characteristic pathologic findings, however, are the same and consist of neuronal loss and abnormal intracytoplasmic glial inclusions of alpha-synuclein in widespread areas of the central nervous system most frequently involving the substantia nigra, locus ceruleus, putamen, inferior olives, pontine nuclei, and cerebellar Purkinje cells. There are two main clinical presentations of MSA: the parkinsonian and the cerebellar subtypes, with dysautonomia occurring in both presentations. The disease affects both sexes, usually starts in the sixth decade, and in general progresses invariably with death occurring after an average of 6–9 years [133, 134]. Death during sleep is not infrequent [86, 105, 113].

Multiple central neurotransmitter systems are impaired including dopaminergic, cholinergic, serotonergic, adrenergic, noradrenergic, and glutamatergic. Insufficient and fragmented sleep, stridor, sleep-disordered breathing, and RBD are common among MSA subjects. RBD and stridor are considered red flags of the disease [40].

Insufficient and Fragmented Nocturnal Sleep

MSA patients commonly report sleep onset and maintenance insomnia [36, 130]. Polysomnographic studies in MSA patients frequently demonstrate marked sleep fragmentation and reduced sleep efficiency. Urinary dysfunction related to both urinary incontinence and retention is also a major contributor for reduced and fragmented sleep in subjects with MSA. In some instances, sleep onset insomnia can be associated with anxiety or with agitated depression. Early awakenings may be a sign of depression. Like in PD, the intrinsic pathology in MSA itself is likely to be an important factor for the development of sleep impairment, because early and untreated MSA patients exhibit disturbed and poor sleep. Sleep fragmentation in MSA is more common than in PD, particularly in advanced cases, reflecting the more severe clinical condition and the more diffuse underlying pathological process in MSA. Sleep-related structures such as some brainstem nuclei and basal ganglia are damaged in MSA. The occurrence of sleep complaints in subjects with MSA is related to longer disease, disease severity, and depression. Like in PD, treatment strategies in MSA patients with difficulties in initiating and maintaining sleep need to be highly individualized.

Excessive Daytime Sleepiness

The occurrence of EDS in MSA has not been systematically addressed by either subjective or objective means until recently [84] . It appears to be as frequent as in PD, since approximately a quarter of the patients with moderate disease present this symptom. The underlying cause of hypersomnia may be multifactorial due to obstructive sleep apneas, depression, reduced nighttime sleep, and the effect of some medications such as antidepressants, benzodiazepines, and dopaminergic agents that can even cause sleep attacks [48]. A few patients may show mild reduced mean sleep latency in multiple sleep latency tests and the presence of multiple sleep onset REM periods. Despite the finding that in MSA there is some degree of hypocretinergic cell loss in the posterior hypothalamus [11], the hypocretin-1 levels in the CSF are normal [80].

Sleep-Disordered Breathing and Stridor

There are two different causes of sleep-disordered breathing in MSA. One is central hypoventilation due to degeneration of the pontomedullary autonomic respiratory center. The other is obstructive sleep apnea as a result of upper airway obstruction, mainly at the level of the larynx.

Central Hypoventilation In MSA, many of the areas involved in the automatic control of respiration (nucleus tractus solitarius, pre-Bötzinger complex, medullary raphe, and arcuate nucleus) have severe cell loss [12]. This results in central sleep apneas, Cheyne–Stokes respiration during sleep and during wakefulness in both supine and erect positions, dysrhythmic breathing patterns such as cluster breathing with periods of apneas during wakefulness and sleep, apneustic breathing, periodic inspiratory gasps manifested by a short inspiratory time and prolonged expiratory time, and diminished ventilatory response to both hypercapnia and hypoxemia [21, 22, 78, 124]. These breathing abnormalities occur particularly during sleep and in most of the cases they are subclinical. In a few cases, however, central hypoventilation may manifest as severe dyspnea and respiratory failure. Central sleep apneas are commonly found in later stages of MSA, but in a few cases may be the presenting feature of the disease [24, 43]. In some patients with MSA, failure to increase ventilation in response to hypoxia and hypercapnia may cause sudden death during sleep, particularly in subjects with comorbid untreated obstructive sleep apneas.

Obstructive Sleep Apneas and Stridor In MSA, obstructive sleep apneas are more common than central hypoventilation. It is usually the result of upper airway obstruction at the level of the larynx. PSG with synchronized audiovisual

monitoring discloses laryngeal stridor during sleep in up to 36–42% consecutive unselected MSA patients [56, 57, 130]. Detection of stridor in MSA is very important because this condition is associated with life-threatening episodes of respiratory failure, nocturnal choking episodes, sudden death during sleep, and short survival [86, 113, 137]. Nocturnal stridor occurs in all clinical stages of MSA and in few cases it may be the initial symptom of the disease [43]. Between patients with and without stridor, there are no differences in age, sex, body mass index, duration and severity of the disease, and the MSA subtype. Compared to subjects without stridor, patients with stridor have a higher apnea–hypopnea index, oxyhemoglobin desaturations, and vocal cord abnormalities on laryngoscopy [56]. It should be noted that nocturnal stridor and snoring may coexist. The severity of nocturnal stridor increases with the passage of time and invariable worsening of the disease. Stridor during wakefulness follows nocturnal stridor. Daytime stridor reflects marked laryngeal obstruction and potential severe respiratory failure.

In unselected MSA subjects, laryngoscopy may show asymptomatic partial vocal cord abduction restriction. In patients with stridor, laryngoscopy during wakefulness detects normal adduction of the vocal cords in phonation, and partial or complete abduction restriction of the vocal cords during inspiration. This abduction restriction may be unilateral or bilateral. Subjects with complete unilateral vocal cord abduction restriction do not present severe dyspnea because the glottic space is relatively wide during inspiration. Subjects with complete bilateral abduction restriction usually have both diurnal and nocturnal stridor, and are at a high risk of developing episodes of subacute respiratory insufficiency [56]. In some patients with mild stridor, movements of the vocal cords during wakefulness seem to be normal, but flicker-like movements may be seen during inspiration reflecting the possible earliest stage of vocal cord abduction dysfunction that can be detected by direct laryngoscopy. In these subjects, laryngoscopy during anesthesia with propofol or diazepam discloses paradoxical movements of the vocal cords (adduction on inspiration and abduction on expiration) or partial vocal cord abduction [64]. Vocal cord abductor restriction is exacerbated during sleep, and partial abduction limitation during wakefulness may become total during sleep [68]. This is because the vocal cord abductor muscles, like other muscles of respiration, have a reduced tone during sleep.

The origin of laryngeal obstruction in MSA is unclear, but it is thought to be related to a combination of factors including denervation of the vocal cord abductors and abnormal overactivation of the vocal cord adductors [46, 51, 62]. In patients with parkinsonism, the occurrence of vocal cord paralysis indicates underlying MSA and not PD [63]. Management of laryngeal narrowing in MSA is complex. Laryngeal surgery (vocal cord lateralization, cordectomy) is associated with an increased risk of aspiration. Experience with botulinum toxin is limited to a very few patients [82]. Botulinum toxin therapy may increase the risk of bronchial aspiration, aggravate dysphonia, and dysphagia, and requires electromyographic guidance and repeated injections.

CPAP is an effective noninvasive treatment for eliminating stridor and obstructive sleep apneas in MSA [37, 53, 56]. In patients at early stages of disease, CPAP is an effective long-term therapy for the management of obstructive sleep apneas and nocturnal stridor. Adaptation to the CPAP machine can be difficult in advanced cases. CPAP abolishes stridor because it eliminates the abnormal activity of the vocal cord adductors during inspiration, thereby reducing the laryngeal resistance and increasing the glottic aperture. While untreated stridor is associated with short survival, it has been shown that median survival time is similar between subjects without stridor and those with stridor treated only with CPAP. When CPAP is not tolerated after intensive support, tracheostomy should then be considered. In subjects with daytime stridor, elective tracheostomy should be advised since this condition leads to dramatic subacute episodes of respiratory failure.

Central apneas without important desaturations may appear after tracheostomy and CPAP therapy because of possible unmasking of central apneas after correction of obstructive apneas. Despite the elimination of stridor with tracheostomy some patients have died while sleeping, presumably due to respiratory arrest of central origin or cardiac arrest related to autonomic failure.

REM Sleep Behavior Disorder

The vast majority of patients with MSA have RBD with a prevalence of 90–100% [56, 100]. The finding that in MSA brainstem cell loss is consistently widespread and severe may explain the high prevalence of RBD in this disease. RBD in MSA is unrelated to age, disease severity, disease duration, clinical subtype (parkinsonian or cerebellar), or to any other demographic or clinical feature. In about half of the patients, RBD antedates the onset of parkinsonian, cerebellar, or autonomic symptoms by a mean of 7 years [57].

Huntington Disease

HD is a genetic autosomal dominant neurodegenerative disorder characterized by progressive dementia, chorea, and psychiatric disturbances linked to expanded cytosine–adenine–guanine (CAG) repeats in the Huntington gene. Pathological studies demonstrate severe atrophy of the putamen and caudate, and, to a lesser extent, of the cortex [13].

Sleep disorders are common among patients with HD, particularly in advanced stages. Patients usually report poor sleep quality, sleep fragmentation with frequent awakenings at night, EDS, and the circadian rhythm sleep disorder of the advanced phase type resulting in early-morning awakening [8, 121, 131]. Interestingly, a transgenic model of HD in mice has a disrupted circadian rhythm that worsens as the disease progresses, suggesting a progressive impairment of the suprachiasmatic nucleus in the hypothalamus [85]. In a community survey study with 292 patients, sleep problems were reported by 87% and were rated as important by 62%. Sleep problems, in rank order, were restless limb movements, periodic jerky movements, waking during the night, hypersomnia, and early awakening [121]. In one study involving 25 patients, 64% complained of insomnia, advanced sleep phase occurred in 40%, and hypersomnia in 32% [8].

Overall, PSG studies show reduced sleep efficiency, increased wake time after sleep onset, increased percentage of light sleep, increased REM sleep latency, and reduced percentage of deep sleep and REM sleep [8, 45, 114, 136]. In HD, sleep complaints and PSG abnormalities increase with disease severity and duration. PSG studies have shown a low incidence of sleep apneas in patients with HD [9, 16] and RBD [8]. Multiple sleep latency tests were performed in only one study showing a reduced sleep latency in 4 of 25 patients (16%) and no REM sleep periods [8].

In a pathological study, a mean reduction of hypocretin cells of 27% was observed in five HD brains [99]. However, HD patients do not have a narcoleptic phenotype because cataplexy is absent [8], the multiple sleep latency does not detect sleep onset REM periods [6], and hypocretin-1 level in the cerebrospinal has been found to be normal in 22 alive patients [81] and in samples from ten postmortem patients [35]. Thus, it can be speculated that surviving hypocretinergic neurons in the hypothalamus still provide sufficient hypocretin to prevent the occurrence of hypersomnia and narcoleptic features.

REM Sleep Behavior Disorder

RBD was investigated by clinical history and PSG in one study that involved 25 patients. Three (12%) had video-PSG confirmed RBD. Two were aware of their abnormal behaviors at night, but these behaviors were considered clinically mild. In an additional patient, video-PSG showed RBD but the patient was not aware of displaying dream-enacting behaviors or having unpleasant dreams. Patients were two women and one man aged 41, 45, and 65 years, respectively. One had mild HD and two moderated HD severity [7]. In another study of 30 HD patients, 7 (23%) patients and bed partners reported symptoms suggestive of RBD but PSG was not performed [131].

Restless Legs Syndrome

In a series of 25 patients, only one (4%) had RLS and a PLMS index greater than 15 was found in six (24%) [6]. PLMS did not fragment sleep. In contrast, one study with six patients found a high mean PLMS index of 123 that fragmented sleep [16]. A 55-year-old man developed RLS 3 years prior the onset of the classical symptoms of HD. PSG demonstrated high indices of periodic leg movements during sleep (index of 58) and wakefulness (index of 79). RLS symptomatology and sleep quality improved dramatically with gabapentin [104]. RLS was described in one family with HD. All five family members affected by RLS were also affected by HD, but some family members with RLS did not have HD suggesting that there may have been the independent occurrence of RLS in this family [28].

Progressive Supranuclear Palsy

PSP is a tauopathy involving the brainstem, basal ganglia, and many other brain areas. It is characterized by dementia, poor levodopa responsive parkinsonism, vertical gaze palsy, and falls. PSG studies show a decreased REM sleep percentage and other features also seen in PD such as decreased total sleep time and reduction in sleep spindles and K complexes. Sleep complaints include insomnia and symptoms suggestive of RBD. The first reported case of RBD linked to PSP was a 70-year-old woman presenting with inhibition of speech during wakefulness and intelligible somniloquy at night due to RBD [95]. Parkinsonism developed one year before the onset of RBD. In a series of 15 patients who underwent PSG, two had clinical RBD, and four exhibited REM sleep with increased tonic electromyographic activity [7]. Clinical manifestations of RBD were severe in one patient, but none of the patients were aware of their abnormal sleep behaviors. The finding that RBD may be found in a tauopathy such as PSP argues against RBD as an exclusive feature of the synucleinopathies (PD, dementia with Lewy bodies, and MSA). Sleep-disordered breathing and RLS are not major complications in PSP.

Hereditary Ataxias

Hereditary ataxias are inherited neurodegenerative disorders that in most cases result from mutations in genes. Modes of inheritance in hereditary ataxias are autosomal dominant (e.g., spinocerebellar ataxias), autosomal recessive (e.g., ataxia telangectasia, Friedreich ataxia), and X-linked (e.g., fragile X tremor ataxia syndrome). These diseases affect the spinocerebellar tracts, cerebellum, brainstem, and many other structures in the brain. They are clinically characterized by progressive ataxia and a wide variety of other neurological symptoms and signs such as polyneuropathy and parkinsonism in addition to nonneurological symptoms including cardiomyopathy and cutaneous telangectasia [67]. Occurrence and clinical relevance of sleep disorders have recently received attention, particularly RBD and RLS.

REM Sleep Behavior Disorder

In one study in spinocerebellar ataxia type 3 (SCA3 or Machado Joseph disease), 53 patients reported more symptoms suggestive of RBD, RLS, obstructive sleep apneas, and insomnia than controls [25]. One study described the presumed presence of RBD in 12 of 22 (56%) SCA3 patients of Portuguese or Azorean origin. Diagnosis was based on a questionnaire, patients were not interviewed by the authors, and PSG was not performed [31]. In a SCA3 patient with clinically suspected RBD video-PSG showed normal REM sleep atonia and non-REM sleep episodes of complex nonrhythmic behaviors lasting more than 10 min [38]. The first reported SCA3 patient with confirmed RBD was a 51-year-old Portuguese man with violent sleep behaviors leading to injuries. PSG showed increased electromyographic activity in the limbs and chin associated with kicking, thrashing, and yelling [74]. We described the presence of video-PSG confirmed RBD in five of nine (55%) consecutive Spanish SCA3 patients, four men and one woman, with a mean age of 48 years and a mean ataxia duration of 14 years. In two patients, RBD preceded the ataxia onset by 10 and 8 years. Clinical RBD severity was mild or moderate [55].

One study evaluated eight patients with SCA2 from five German families with sleep interviews and video-PSG. All but one reported good quality of sleep. None of the patients and bed partners reported symptoms suggestive of RBD such as nightmares, frequent vocalizations, and aggressive sleep behaviors. Video-PSG, however, showed subclinical RBD (increased submental electromyographic activity not associated with abnormal behaviors) in three patients, normal REM sleep in two, and REM sleep was not observed in three [125]. In another study, four of five SCA2 patients of three different Austrian families had increased electromyographic activity during REM sleep in the video-PSG. These four patients exhibited a mild form of RBD consisting of prominent myoclonic jerks in absence of complex and elaborate behaviors [14]. In one study, RBD was not detected in five patients with SCA type 6 [15].

Restless Legs Syndrome

Several studies have evaluated the occurrence of RLS in subjects with SCAs [1, 14, 15, 55, 102, 110, 127]. Studies found RLS in patients with SCA1, SCA2, SCA3, and SCA6 who were not treated with dopaminergic or antidopaminergic drugs (Table 32.4).The highest frequency of RLS has been

Table 32.4 Studies evaluating the frequency of restless legs syndrome in hereditary ataxias

Author year (Country)	SCA1 patients studied (*n*)	RLS in SCA1 (%)	SCA2 patients studied (*n*)	RLS in SCA2 (%)	SCA3 patients studied (*n*)	RLS in SCA3 (%)	SCA6 patients studied (*n*)	RLS in SCA6 (%)	RLS in controls (%)
Schöls et al. 1998 (Germany) [110]	6	0	11	18	51	45	21	5	NA
Abele et al. 2001 (Germany) [1]	13	23	22	27	23	30	NA	NA	10
Iranzo et al. 2003 (Spain) [55]	NA	NA	NA	NA	9	55.5	NA	NA	0
Boesch et al. 2006b (Austria) [15]	NA	NA	NA	NA	NA	NA	5	40	NA
Boesch et al. 2006a (Austria) [14]	NA	NA	5	0	NA	NA	NA	NA	NA
Reimold et al 2006 (Germany) [102]	4	25	4	25	2	100	NA	NA	NA
D'Abreu et al. 2008 (Brazil) [25]	NA	NA	NA	NA	53	20.7	NA	NA	4.7

RLS restless legs syndrome, *SCA1* spinocerebellar ataxia type 1, *SCA2* spinocerebellar ataxia type 2, *SCA3* spinocerebellar ataxia type 3, *SCA6* spinocerebellar ataxia type 6, *NA* not available

found in SCA3, ranging from 30 to 55 % of the cases [1, 55, 110, 127] a higher figure than what is found in general population based studies. RLS symptoms were mild, moderate, or severe, and RLS was diagnosed only upon specific questioning when the studies were conducted. PSG in SCA1, SCA2, SCA3, and SCA6 showed a high number of PLMS in patients with or without RLS [14, 15, 55, 102, 110]. Most SCA patients were unaware of their leg movements and PLMS were usually not associated with arousals.

Sleep-Disordered-Breathing

PSG studies in patients with autosomal dominant SCAS and ataxia telangiectasia have shown that obstructive sleep apneas are not a common finding, except in one study where an apnea–hypopnea index greater than 5 was detected in four of five patients with SCA6 (range, 6–15) [15]. However, patients with SCA1 [112] and SCA3 [55] may show vocal cord abductor palsy, probably due to neuronopathy of the nucleus ambiguous impairing the recurrent laryngeal nerve fibers that mainly innervate the posterior cricoarytenoid muscle.

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