Neurodegenerative diseases and sleep disorders

■ **M. Billiard, Y. Dauvilliers**

Federation de Neurologie, Hôpital Gui de Chauliac, Montpellier (F)

Summary

Billiard M, Dauvilliers Y. Neurodegenerative diseases and sleep disorders. Schweiz Arch Neurol Psychiatr 2003;154:384–90.

The interest in sleep disorders associated with neurodegenerative diseases is growing. Indeed, they add up to the clinical features of each of these conditions and may bring insight into their mechanisms. Along this line one of the major findings in recent years has been that REM-sleep behaviour disorder (RBD) has a predilection for synucleinopathies including idiopathic Parkinson's disease, multiple system atrophy and dementia with Lewy bodies, though not for tauopathies. We have reviewed neurodegenerative diseases without dementia (with the exception of idiopathic Parkinson's disease reviewed in another article of the same issue) and neurodegenerative diseases with dementia, in considering clinical features, pathologic patterns, associated sleep disorders and their treatments. *Multiple system atrophy* is characterised by rather severe breathing abnormalities, including obstructive sleep apnoea/hypopnoea syndrome, dysrhythmic breathing and laryngeal stridor, and by REM-sleep behaviour disorder which may precede the onset of clinical features of multiple system atrophy by several years. Insomnia is the most common sleep-related symptom of *progressive supranuclear palsy*. It is generally more severe than in other neurodegenerative diseases. Polysomnography shows the progressive shortening of sleep. Rapid eye movements of REM sleep are abnormal. Sleep disorders have not been systematically investigated in *corticobasal degeneration*. The most efficient therapeutic approaches of these conditions include continuous positive airway pressure (CPAP) in the case of sleep breathing abnormalities and clonazepam for REM-sleep behaviour disorder. *Alzheimer's disease* is the most frequent neurodegenerative disease with dementia. Sleep is both reduced and disorganised. Sleep-related breathing disorders are common. Special features of Alzheimer's disease are "sundowning", an agitation behaviour occurring during the early evening and "episodic nocturnal wandering". In *frontotemporal dementia* sleep disorders are comparable to those of other dementias with aspecific impairment of sleep continuity and architecture. In comparison with other dementias, *dementia with Lewy bodies* leads to more severe sleep disturbances, including more movement disorders whilst asleep, more excessive daytime sleepiness and REM-sleep behaviour disorder characteristic of a synucleinopathy. Current treatments fall into four categories: identifying and treating any medical factor of impaired sleep, using sedative medications as parcimoniously as possible, environmental and circadian manipulations.

Keywords: neurodegenerative diseases; parkinsonism; primary dementias; sleep disorders; synucleinopathy; tauopathy

Introduction

Within the last ten years the interest taken in the sleep of patients with neurodegenerative diseases has greatly increased. There are many reasons for that. First, patients affected with these conditions may complain of various sleep impairments, insomnia, hypersomnia, parasomnia, which find their roots in neurological lesions and may resist conventional treatments. Second, some of these sleep disorders such as severe insomnia, sleep-related abnormal respiratory patterns, REM-sleep behaviour disorder (RBD) may be particular to one or several of these neurodegenerative diseases and help in their positive diagnosis. Third, an improved knowledge of the pathology of each of these conditions opens a window on the anatomical basis

Correspondence:
Michel Billiard, MD
Faculté de Médecine
Hôpital Gui de Chauliac
80, avenue Augustin Fliche
F-34295 Montpellier, Cedex 5
e-mail: mbilliard@wanadoo.fr

of the observed sleep disorders. Last, a recent major progress has been made in considering idiopathic Parkinson's disease, multiple system atrophy and dementia with Lewy bodies as alpha-synucleinopathies and Alzheimer's disease, progressive supranuclear palsy, frontotemporal dementia and corticobasal degeneration as tauopathies [1]. In this article we will concentrate on well-recognised neurodegenerative diseases: idiopathic Parkinson's disease; other neurodegenerative diseases with parkinsonism, multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration; and primary degenerative dementias including Alzheimer's disease, frontotemporal dementia and dementia with Lewy bodies. On the other hand, hereditary disorders like Huntington's chorea, Wilson's disease and Hallervorden-Spatz disease, and primary dystonia which shows no consistent structural abnormality at autopsy, will not be considered. Clinical features, pathologic characteristics and sleep abnormalities of each neurodegenerative disease will be described, while therapeutic approaches will be reviewed for neurodegenerative diseases with and without dementia.

Idiopathic Parkinson's disease

Parkinson's disease is characterised by akinesia, rigidity and resting tremor. In addition to these cardinal symptoms, alteration in postural reflexes leading to falls, autonomic symptoms, and neurophysiological and psychiatric changes such as dementia and depression are often observed.

Pathologically Parkinson's disease consists in a neuronal degeneration affecting the pigmented formations of brainstem, substantia nigra whose dopamine neurons project on the striatum, locus coeruleus, dorsal vagal nucleus, the serotonergic raphe nuclei of mesencephalon and pons, as well as other structures which might play an important role, nucleus basalis of Meynert, amygdala and the CA2–3 sector of the hippocampus [2]. Neuronal degeneration is characterised by the presence of intraneuronal inclusions, Lewy bodies and their processes (Lewy neurites), the nature of which remained uncertain for a long time. Today it appears that Lewy bodies and neurites contain ubiquitine which recognises ill-developed proteins, binds to them and leads to their degradation through the proteasome [3] and alphasynuclein [4], a presynaptic protein, which is altered under the effect of ubiquitine, hence the name alpha-synucleinopathy given to Parkinson's disease and other diseases also characterised by altered alpha-synuclein.

Sleep disorders are common in patients with Parkinson's disease. They consist of insomnia, excessive daytime sleepiness, parasomnias, sleep breathing disorders and abnormal movements during sleep. They are described in another article of the same issue.

Other neurodegenerative diseases with parkinsonism

Multiple system atrophy

Multiple system atrophy (MSA) is a degenerative disorder of the central and autonomic nervous system which combines in a variable manner, parkinsonism, cerebellar and pyramidal signs and dysautonomia signs. It is divided into two main clinical and pathologic forms: striatonigral degeneration (MSA-parkinson type) which is often misdiagnosed as Parkinson's disease and sporadic olivopontocerebellar atrophy (MSA-cerebellar type) which may be undistinguishable from idiopathic late-onset cerebellar ataxia at the beginning. The Shy-Drager syndrome is not considered any more as a distinct form as dysautonomia is a quasi universal feature of multiple system atrophy whatever its type.

Characteristic histologic features are neuronal loss and gliosis. In the striatonigral system lesions predominate in the ventral part of substantia nigra, the dorsolateral putamen and the external pallidum. In the olivo-ponto-cerebellar system degeneration involves nuclei ponti and inferior olives, while the dentatus nucleus is relatively spared. Other impaired structures include dorsal vagus nucleus, locus coeruleus, nucleus ambiguous, intermediolateralis cell columns and anterior horn cells of the spinal cord [5]. The discovery of the glial cytoplasmic inclusion helped to define multiple system atrophy as a clinicopathological entity and drew attention to the prominent role played by the oligodendrocytes in the pathogenesis of the condition [6]. Subsequently, glial cytoplasmic inclusions were shown to be positive for alpha-synuclein, providing a link with Parkinson's disease (alpha-synucleinopathy) [7, 8].

The most common sleep disorders in multiple system atrophy result from a variety of sleep-breathing abnormalities including obstructive sleep apnoea/hypopnoea syndrome [9–11], dysrhythmic breathing [10] and laryngeal stridor due to laryngeal abductor paralysis [12, 13] which can cause sudden death. These are probably correlated with direct involvement of the regions of the brain stem that contain the respiratory neurons. REM-

sleep behavior disorder (RBD) is a frequent feature of multiple system atrophy [14–17] as it is for idiopathic Parkinson's disease. It often precedes the onset of MSA features. REM-sleep behaviour disorder is characterised by the intermittent loss of REM-sleep electromyographic atonia and the appearance of elaborate motor activity associated with dream mentation [18, 19]. This syndrome has first been experimentally induced in the cat following bilateral peri-locus coeruleus lesions [20–22]. Loss of neurons has been described in the locus coeruleus and other pontine structures. However, pontine abnormalities may not be a necessary prerequisite for REM-sleep behaviour disorder. Dysfunction of centres and pathways projecting to pontine neurons involved in generation and maintenance of muscle atonia during REM sleep may also lead to REM-sleep behaviour disorder.

Progressive supranuclear palsy (PSP)

This is a condition with axial, specially neck rigidity; an erect gait with frequent falls, especially backwards; marked impairment of eye movements including a paresis of vertical downward gaze, slow vertical saccades more than pursuit, staring with widely opened eyes; pseudobulbar signs.

Histologic lesions consist of neurofibrillary degeneration (neurofibrillary tangles), neuronal loss and gliosis of subcortical structures including substantia nigra, superior colliculi, pretectal area, periaqueductal gray, pediculopontine nuclei, internal pallidum, subthalamic nucleus, nucleus dentatus and less constantly locus coeruleus, oculomotor nuclei, red nucleus, medullar olive, median thalamic nuclei and the anterior horn cells of the spinal cord [23, 24]. Abnormal phosphorylated tau proteins are the basic component of neurofibrillary tangles [25] as is the case in Alzheimer's disease, hence the term tauopathy used for these diseases. However, tau proteins do not only accumulate in neurons. They accumulate also in the cell body of the oligodendrocytes [26] and in the astrocytes [27].

Insomnia, the most common sleep-related symptom of progressive supranuclear palsy, appears to be more severe than in other degenerative neurological diseases. Periods of uninterrupted sleep of 1 to 2 hours may be present at the beginning, but as the disease progresses the total amount of sleep decreases, down to no sleep at all in some cases [28–30]. Polysomnography is of great value showing increased fast activity and intrusion of alpha frequency activity, poorly formed sleep spindles and K-complexes. Rapid eye movements of REM sleep are abnormal: vertical eye movements are absent while horizontal eye movements are slower than usual and reduced in number and amplitude. Functional alteration of the median thalamic nuclei may be responsible for the loss of K-complexes and sleep spindles. Absence of vertical eye movements depends on superior colliculi and pretectal area lesions.

REM-sleep behaviour disorder has been reported in a few cases [28, 31–34].

Corticobasal degeneration

Corticobasal degeneration (CBD) is a progressive neurodegenerative disorder typically characterised by akinesia-rigid parkinsonism and apraxia. Importance and persistence of asymmetric symptomatology is of great diagnostic value. Clumsiness of the hand and akinesia are generally the presenting symptoms followed by rigidity and fixed flexion dystonia of the upper limbs. Myoclonus is present in more than half of the cases. The alien hand-limb phenomenon is typical but inconstant.

Pathological features include an asymmetrical cortical atrophy predominating in fronto-parietal and rolandic regions; a neuronal loss and a severe gliosis predominating in the lateral thalamus, striatum, subthalamic nucleus, red nucleus, substantia nigra, locus coeruleus, raphe nuclei and midbrain tegmentum; and the presence of achromatic and swelled neurons (ballooned cells) [35–37]. Corticobasal degeneration is also characterised by the accumulation of abnormal tau protein in neurons and glia [25, 27].

Sleep disorders have not systematically been investigated in corticobasal degeneration. A case of REM-sleep behaviour disorder has been reported with 14 episodes of sleeptalking and singing associated with various movements occurring exclusively during a REM-sleep period without atonia, probably in relation to gliosis in brain stem nuclei [38]. Unilateral periodic limb movements in a case of corticobasal degeneration are of interest in suggesting the role of the loss of inhibitory descending central pathways in the pathogenesis of periodic limb movements [39].

Treatment of sleep disorders in other neurodegenerative diseases with parkinsonism

The approach to diagnosis and management of sleep disorders in these diseases is basically similar to that used for Parkinson's disease. However, because of the risk of serious consequences of disordered breathing in multiple system atrophy,

probably in relation to autonomic dysfunction, polysomnography should be considered systematically in these subjects and nasal CPAP is indicated in all cases of obstructive sleep apnoea/hypopnoea syndrome. In some cases of stridor caused by vocal cord paresis tracheostomy might be necessary [13]. As already pointed out, insomnia, the most common sleep-related symptom of progressive supranuclear palsy, appears to be more severe than in most other neurodegenerative diseases. Unfortunately the drug therapy of insomnia in progressive supranuclear palsy is rather frustrating, as is the drug therapy of progressive supranuclear palsy itself. However, in contrast with most cases of chronic primary insomnia or insomnia associated with mental disorders, subjects with progressive supranuclear palsy sometimes show a surprising tolerance to their major sleep curtailment. Patients with REM-sleep behaviour disorder, whatever the neurodegenerative condition, usually respond to clonazepam, at least initially. This treatment reduces behavioural manifestations and phasic EMG activity without totally restoring REM-sleep atonia. The mode of action of clonazepam is still unclear. Second-line treatments include tricyclic antidepressants, carbamazepine, L-Dopa and dopaminergic agonists.

Primary degenerative dementias

Alzheimer's disease

In Alzheimer's disease the first clinical abnormality is usually subtle memory impairment, often with insight into this progressive abnormality. Naming difficulty and lack of spontaneous convention or other intellectual activity may be evident. Later the features of progressive dementia, with more marked memory disturbance, lack of initiative, disorientation, impaired motor abilities (apraxia), disturbance of speech (aphasia), inability in recognition of perceptions (agnosia), develop. Later still, loss of personal hygiene and social behaviours become disabling problems, and increased muscle tone and hesitant apraxic gait result in immobility followed by emaciation, stupor and death. In the early stages, depression is often an important feature, presumed to be a consequence of the patient's recognition of his or her troubles. Coexisting neurologic features depend on the distribution and nature of the brain lesions. Frontal lobe motor signs as well as extrapyramidal and pyramidal dysfunctions may be present.

At microscopic examination Alzheimer's disease is characterised by three processes: amyloid deposits, neurofibrillary degeneration and neuronal and synaptic loss [40]. The amyloid deposits are made of a 40 to 42 amino-acid long peptide, named Aβ, derived from a large size amyloid protein precursor (APP). Antibodies directed against the Aβ peptide detect amyloid plaques in almost the totality of cerebral cortex, in the hippocampal region and in the wall of arterioles and capillaries. The neurofibrillary degeneration leads to neurofibrillary tangles, the crown of the senile plaque and the neuropil threads which are all characterised by the accumulation of paired helical filaments (PHF) labelled by antibodies directed against the tau protein. In the normal brain there are six major tau isoforms. In Alzheimer's disease the neurofibrillary degeneration is related to the phosphorylation of three tau isoforms. The senile plaque consists of a central core of amyloid deposit surrounded by dystrophic neurites made of abnormal protein tau (crown of the senile plaque). Neuronal loss occurs after neurofibrillary degeneration and could be provoked by the neurofibrillary degeneration itself. Besides tau protein and Aβ peptide several other proteins may be involved: presenelin 1 and 2, apolipoprotein E and even alpha-synuclein present next to Aβ peptide in the senile plaque.

A prominent clinical feature of Alzheimer's disease is disturbed sleep with increased night-time wakefulness, daytime sleepiness and sleep episodes [41]. A more or less random distribution of sleep throughout the 24-hour day is common. In addition, "sundowning", an agitation behaviour that occurs during the early evening either just before or after dinner, and "nocturnal wandering" with disorientation and confusion are often major problems for caregivers. Polysomnographic studies have validated these clinical observations with increased sleep latency and nocturnal awakenings, decreased NREM sleep stages 3 and 4, REM sleep and total sleep time, increased daytime napping. Additionally, sleep-related breathing disorders occur more frequently in patients suffering from Alzheimer's disease than in non-demented subjects, and indexes of severity of sleep-related breathing disorder have been correlated with the importance of cognitive impairment [42]. A single case of REM-sleep behaviour disorder with autopsy-confirmed Alzheimer's disease has been reported [43].

While the neuropathology of dementia can directly disrupt sleep, sleep disturbances in patients with dementia may also depend on multiple causes that require systematic evaluation [44].

Frontotemporal dementia

Frontotemporal dementia is the second cause of degenerative dementia after Alzheimer's disease. It is characterised by behavioural disturbances, affective symptoms, difficulty in verbal expression, preservation of spatial orientation and praxis. Physical signs are tardive including archaic reflexes, pyramidal signs, parkinsonism, hypotension and tension variations.

Neuropsychological examination reveals disorders of the executive functions.

The clinical syndrome occurs with either of three histologic types: prominent microvacuolar change without specific histological features (aspecific frontotemporal lobe degenerative-type), severe astrocytic gliosis with or without ballooned cells and inclusion bodies (Pick-type), aspect identical to aspecific frontotemporal lobe degeneration-type, plus spinal motoneuron degeneration (motoneuron disease type) [45, 46]. Abnormal tau protein is present in frontotemporal dementia [47]. However, electrophoretic profiles of the abnormal tau protein differ in aspecific frontotemporal dementia and Pick's disease [48].

Sleep disorders are comparable to the other dementias with aspecific impairment of sleep continuity and architecture [49]. REM-sleep behaviour disorder has not been reported.

Dementia with Lewy bodies

Characteristic features of dementia with Lewy bodies (DLB) are progressive dementia, moderate parkinsonism, myoclonus, marked fluctuation of alertness and cognitive performances, precocious and elaborated visual hallucinations, and depression.

The pathology includes cortical Lewy bodies and Lewy body-related neurites. The cortical Lewy bodies are slightly different from those encountered in the brainstem, but they retain their antigenic characteristics: they are stained by the antiubiquitin antibodies and the antisynuclein antibodies [50]. Thus dementia with Lewy bodies is part of the alpha-synucleinopathies together with Parkinson's disease and multiple system atrophy.

The level of sleep disturbances in dementia with Lewy bodies is high. In comparison with Alzheimer's disease, DLB patients have more overall sleep disturbances, more movement disorders whilst asleep and more abnormal daytime sleepiness [51]. However, the most typical sleep disorder associated with dementia with Lewy bodies is REM-sleep behaviour disorder [52–55], to the extent that it is regarded as a supportive feature for the diagnostic of dementia with Lewy bodies [56]. Worth mentioning is the fact that most patients described by Boeve et al. [55] began REM-sleep behaviour disorder years, sometimes decades, before the cognitive symptoms evolved.

Treatment of sleep disorders in dementias

Current treatments for improving sleep in dementias fall into four categories: identifying and treating any treatable factor of impaired sleep, pharmacology, environmental manipulations and circadian therapies.

Medications that could have an adverse effect on sleep and breathing during sleep should be reduced in dose or discontinued. Associated conditions that could interfere with sleep, such as pain due to arthritis or other diseases, should be treated. Agitated depression is not uncommon and responds well to drugs such as trazodone. Frequency of urination may result from infection or enlarged prostate and should be treated.

Due to the limited number of controlled trials demonstrating the efficacy of sedating medications in demented patients and the frequent adverse effects of those, their use should be as parcimonious as possible. Sedating antidepressants such as trazodone may be of benefit in those subjects with depression and low doses of haloperidol in case of uncontrollable agitation.

Physical restraints should be avoided. Providing a wandering area available at night in institutions may allow demented persons with increased hyperactivity at night not to be forced to stay in bed. The use of a night light may decrease the disorientation that occurs in the dark. Finally, caregivers need to be trained to give reassurance and reality orientation. Staying with a patient for a quarter of an hour or more is usually more efficient than giving medications.

In addition, it is important attempting to reduce frequent naps during the day and encouraging the person to go to bed later. Exercise programs during the day act in the same direction. Evening light exposure is useful in reducing disruptive night-time activity [57]. More recently, the role of low-intensity dawn-dusk simulation, a "naturalistic" form of light therapy designed to embed sleep in its accustomed phase, has been underlined [58]. Melatonin has been shown to improve sleep and suppress "sundowning" in subjects with Alzheimer's disease [59].

Conclusion

Neurodegenerative diseases are associated with a wide variety of sleep disorders which range from a disorganisation of sleep continuity and architecture in all dementias to more specific disorders in neurodegenerative diseases without dementia. An increasing knowledge of the pathology of these diseases and the associated neurotransmitter deficits opens a window on the understanding of the brain mechanisms involved in the occurrence of these sleep disorders. A major breakthrough of the last years was the observation that REM-sleep behaviour disorder has a predilection for alpha-synucleinopathies including Parkinson's disease, multiple system atrophy and dementia with Lewy bodies, not for tauopathies such as Alzheimer's disease, progressive supranuclear palsy, frontotemporal dementia and CBD, and that REM-sleep behaviour disorder may precede by several years the development of the disease itself, a fact of major clinical relevance. Yet, the site of degeneration causing REM-sleep behaviour disorder remains unclear; brainstem proton magnetic resonance spectroscopy in idiopathic REM-sleep behaviour disorder did not detect any brainstem abnormality [60]. Moreover, a few cases of REM-sleep behaviour disorder have been described in subjects with progressive supranuclear palsy, CBD or Alzheimer's disease. Thus further investigations are indicated to elucidate the relationship between REM-sleep behaviour disorder and alpha-synucleopathy. Also a common methodology should be observed in polysomnographic evaluations of subjects with neurodegenerative diseases so that results obtained by different authors can be compared. Unfortunately, except for REM-sleep behaviour disorder, there is no current hope for more efficacy in the treatment of associated sleep disorders than in the treatment of the neurodegenerative diseases themselves.

References

1 Litvan I. Recent advances in atypical parkinsonian disorders. Curr Opin Neurol 1999;12:441–6.

2 Duyckaerts C, Verny M, Hauw JJ. Données récentes sur la neuropathologie des syndromes parkinsoniens. Rev Neurol (Paris) 2003;159:3S11–3S18.

3 De Martino GN, Slaughter CA. The proteasome, a novel protease regulated by multiple mechanisms. J Biol Chem 1999;274:22123–6.

4 Spillantini MG, Schmidt ML, Lee VMY, Trojanowski JQ, et al. Alpha-synuclein in Lewy bodies. Nature 1997;388:839–40.

5 Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, et al. Clinical features and natural history of multiple system atrophy. J Neurol Neurosurg Psychiatry 1995;58:160–6.

6 Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striato-nigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 1989;94:79–100.

7 Arima K, Ueda K, Sunohara N, Arakawa K, et al. NACP/alpha-synuclein immunoreactivity in fibrillary components of neuronal and oligodendroglial cytoplasmic inclusions in the pontine nuclei in multiple system atrophy. Acta Neuropathol (Berl) 1998;96:439–44.

8 Dickson DW, Liu W, Hardy J, Farrer M, et al. Widespread alterations of alpha-synuclein in multiple system atrophy. Am J Pathol 1999;155:1241–51.

9 Guilleminault C, Tilkian A, Lehrman K, Forno L, et al. Sleep apnoea syndrome: states of sleep and autonomic dysfunction. J Neurol Neurosurg Psychiatry 1977;40:718–25.

10 McNicholas WT, Rutherford R, Grossman R, Moldofsky H, et al. Abnormal respiratory pattern generation during sleep in patients with autonomic dysfunction. Am Rev Respir Dis 1983;128:429–33.

11 Sadoaka T, Kakitsuba N, Fujiwara Y, Kanai R, et al. Sleep-related breathing disorders in patients with multiple system atrophy and vocal cord palsy. Sleep 1996;19:479–84.

12 Hughes RG, Gibbin KP, Lowe J. Vocal fold abductor paralysis as a solitary and fatal manifestation of multiple system atrophy. J Laryngol Otol 1998;112:177–8.

13 Blumin JH, Berkc GS. Bilateral vocal fold paresis and multiple system atrophy. Arch Otolaryngol Head Neck Surg 2002;128:1404–7.

14 Manni R, Morini R, Martignoni E, Pacchetti C, et al. Nocturnal sleep in multisystem atrophy with autonomic failure: polygraphic findings in ten patients. J Neurol 1993;240:247–50.

15 Tison F, Wenning G, Quinn N, Smith S. REM sleep behavior disorder as the presenting symptom of multiple system atrophy. J Neurol Neurosurg Psychiatry 1995;58:379–80.

16 Plazzi G, Corsini R, Provini F, Pierangeli G, et al. REM sleep behavior disorder in multiple system atrophy. Neurology 1997;48:1094–7.

17 Tachibana N, Kimura K, Kitajima K, Shinde A, et al. REM sleep motor dysfunction in multiple system atrophy: with special emphasis on sleep talk as its early clinical manifestation. J Neurol Neurosurg Psychiatry 1997;63:678–81.

18 Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 1986;9:293–308.

19 Schenck CH, Bundlie SR, Patterson AL, Mahowald MW. Rapid eye movement sleep behavior disorder: a treatable parasomnia affecting older adults. JAMA 1987;257:1786–9.

20 Jouvet M, Delorme F. Locus coeruleus et sommeil paradoxal. C R Soc Biol 1965;159:895–9.

21 Sastre J, Jouvet M. Le comportement onirique du chat. Physiol Behav 1979;22:979–89.

22 Hendricks JC, Morrison AR, Mann GL. Different behaviors during paradoxical sleep without atonia depend on pontine lesion site. Brain Res 1982;239:81–105.

23 De Bruin VM, Lees AJ. Subcortical neurofibrillary degeneration presenting as Steele-Richardson-Olszewski and other related syndromes: a review of 90 pathologically verified cases. Mov Disord 1994;9:381–9.

24 Hauw JJ, Daniel SE, Dickson D, Horoupian DS, et al. Preliminary NINDS Neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 1994;44:2015–9.

25 Mailliot C, Sergeant N, Bussière T, Caillet-Boudin ML, et al. Phosphorylation of specific sets of tau isoform reflects different neurofibrillary degeneration processes. FEBS Lett 1998;433:201–4.

26 Arima K, Nakamura M, Sunohara N, Nishio, et al. Ultrastructural characterization of the tau-immunoreactive tubules in the oligodendroglial perikarya and their inner loop processes in progressive supranuclear palsy. Acta Neuropathol (Berl) 1997;93:558–66.

27 Komori T. Tau-positive glial inclusions in progressive supra-nuclear palsy, corticobasal degeneration and Pick's disease. Brain Pathol 1999;9:663–79.

28 Laffont F, Autret A, Minz M, Beillevayre T, et al. Polygraphic sleep recording in 9 cases of Steele-Richardson's disease. Rev Neurol (Paris) 1979;135:127–42.

29 Perret JL, Jouvet M. Etude du sommeil dans la paralysie supra-nucléaire progressive. Electroencephalogr Clin Neurophysiol 1980;49:323–9.

30 Aldrich MS, Foster NL, White RF, Bluemlein L, et al. Sleep abnormalities in progressive supranuclear palsy. Ann Neurol 1989;25:577–81.

31 Shimizu T, Sugita Y, Iijima S, Teshima Y, et al. Sleep study in patients with spinocerebellar degeneration and related diseases. In: Koella WP, editor. Sleep 1980. Basel: S. Karger; 1981. p. 435–7.

32 Pareja JA, Caminero AB, Masa JF, Dobato JL. A first case of progressive supranuclear palsy and pre-clinical REM sleep behavior disorder presenting as inhibition of speech during wakefulness and somniloquy with phasic muscle twitching during REM sleep. Neurologia 1996;11:304–6.

33 Sforza E, Krieger J, Petiau C. REM sleep behavior disorder: clinical and physiopathological findings. Sleep Med Rev 1997;1:57–69.

34 Olson E, Boeve B, Silber M. Rapid eye movement sleep behavior disorder: demographic, clinical, and laboratory findings in 93 cases. Brain 2000;123:331–9.

35 Gibb WR, Luthert PJ, Marsden CD. Corticobasal degeneration. Brain 1989;112:1171–92.

36 Riley DE, Lang AE, Lewis A, Resch L, et al. Cortico-basal ganglionic degeneration. Neurology 1990;40:1203–12.

37 Rinne JO, Lee MS, Thomson PD, Marsden CD. Cortico-basal degeneration: a clinical study of 36 cases. Brain 1994;117:1183–96.

38 Kimura K, Tachibana N, Aso T, Kimura J, et al. Subclinical REM sleep behavior disorder in a patient with corticobasal degeneration. Sleep 1997;20:891–4.

39 Iriarte J, Alegre M, Arbizu J, de Castro P. Unilateral periodic limb movements during sleep in corticobasal degeneration. Mov Disord 2001;16:1180–3.

40 Davous P, Delacourte A. Maladie d'Alzheimer. Encycl Méd Chir (Elsevier, Paris), neurologie 1999; 17-056-A-10:1–15.

41 Vitiello MV, Prinz PN. Sleep/wake patterns and sleep disorders in Alzheimer's disease. In: Thorpy MJ, editor. Handbook of Sleep Disorders. New York: Marcel Dekker; 1990. p. 703–18.

42 Reynolds CF 3rd, Kupfer DJ, Taska LS, Hoch CC, et al. Sleep apnea in Alzheimer's dementia. Correlation with mental deterioration. J Clin Psychiatry 1985;46:257–61.

43 Schenck CH, Garcia-Rill E, Skinner RD, Anderson ML, et al. A case of REM sleep behavior disorder with autopsy-confirmed Alzheimer's disease: postmortem brain stem histochemical analyses. Biol Psychiatry 1996;40:422–5.

44 Vitiello MV, Borson S. Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment. CNS Drugs 2001;15:777–96.

45 Brun A, Englund E, Gustafson L, Passant U, et al. Clinical and neuropathological criteria for fronto-temporal dementia. J Neurol Neurosurg Psychiatry 1994;57:416–8.

46 Robert PH, Lafont V, Snowden JS, Lebert F. Diagnostic criteria for fronto-temporal lobe degeneration. Encephale 1999;25:612–21.

47 Vermersch P, Bordet R, Ledoze F, Ruchoux MM, et al. Mise en évidence d'un profil particulier de protéines T pathologiques dans des cas de démences fronto-temporales. CR Acad Sci 1995;318:439–45.

48 Delacourte A, Buée L. Normal and pathological Tau proteins as factors for microtubule assembly. Int Rev Cytol 1997;171:167–224.

49 Pawlak C, Blois R, Gaillard JM, Richard J. Sleep in Pick disease. Encéphale 1986;12:327–34.

50 Verny M, Duyckaerts C. Dementia with Lewy bodies. Ann Med Interne (Paris) 1998;149:209–15.

51 Grace JB, Walker MP, McKeith IG. A comparison of sleep profiles in patients with dementia with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry 2000;15:1028–33.

52 Uchiyama M, Isse K, Tanaka K, Yokota N. Incidental Lewy body disease in a patient with REM sleep behavior disorder. Neurology 1995;45:709–12.

53 Negro P, Faber R. Lewy body disease in a patient with REM sleep disorder [letter]. Neurology 1996;46:1493–4.

54 Turner RS, Chervin RD, Frey KA, Minoshima S, et al. Probable diffuse Lewy body diseases presenting as REM sleep behavior disorder. Neurology 1997;49:523–7.

55 Boeve BF, Silber MH, Ferman TJ, Kokmen E, et al. REM sleep behavior disorder and degenerative dementia: an association likely reflecting Lewy body disease. Neurology 1998;51:363–70.

56 McKeith IG, Galasko D, Kosaka K, Perry EK, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–24.

57 Satlin A, Volicer L, Ross V, Herz L, et al. Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. Am J Psychiatry 1992;149:1028–32.

58 Fontana Gasio P, Krauchi K, Cajochen C, Someren E, et al. Dawn-dusk simulation light therapy of disturbed circadian rest-activity cycles in demented elderly. Exp Gerontol 2003;38:207–16.

59 Cardinali DP, Brusco LI, Liberczuk C, Furio AM. The use of melatonin in Alzheimer's disease. Neuroendocrinol Lett 2002;23(Suppl 1):20–3.

60 Iranzo A, Santamaria J, Pujol J, Moreno A, et al. Brainstem proton magnetic resonance spectroscopy in idiopathic REM sleep behavior disorder. Sleep 2002;25:867–70.