Neuropathology of Sleep Disorders: A Review

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Abstract
Sleep disorders are important manifestations of neurodegenerative diseases and sometimes are clinically evident well before the onset of other neurological manifestations. This review addresses the neuroanatomical basis and the mechanisms of sleep regulation in humans in relation to the neuropathology of entities associated with sleep disturbances in selected diseases, including Alzheimer disease, progressive supranuclear palsy, Lewy body disorders, multiple-system atrophy, and fatal familial insomnia. This includes abnormalities of circadian rhythm, insomnia, narcolepsy, rapid eye movements sleep behavior disorders, and excessive daytime sleepiness.

Key Words: Insomnia, Narcolepsy, Neurodegenerative diseases, Neuropathology, Prion diseases, REM sleep behavior disorders, Sleep disorders.

INTRODUCTION
The classic neuropathologic studies of encephalitis lethargica and of narcolepsy are milestones in raising clinical awareness on the importance of sleep in neurological diseases. During the past century, progress in the understanding of the neuroanatomical basis of sleep disorders has been slow, perhaps in part because specific clinicopathologic correlations regarding sleep disorders have not been performed. Furthermore, patients with sleep disorders that are believed to have a precise anatomical localization have often been incompletely studied both clinically and neuropathologically.

More than 80 years ago, von Economo (1, 2) showed that patients who had died of encephalitis lethargica had lesions extending from the medulla to the diencephalon. He proposed the concept of a “brain regulatory center,” spreading from the periaqueductal gray at the level of the third nerve nucleus to the posterior and lateral walls of the third ventricle and to the thalamus. In patients with encephalitis lethargica and insomnia, the inflammatory lesions involved mostly the diencephalic regions, including the lateral preoptic area and adjacent forebrain. Patients with hypersonomnia had lesions in the posterior lateral hypothalamus and adjacent midbrain (1, 2).

Subsequent understanding of the neuroanatomical basis of sleep disorders evolved with additional clinicopathologic studies, the application of modern neuropathologic techniques, especially using immunohistochemistry (3), and the expansion of neuropathologic investigations of neurodegenerative diseases (4, 5). Sophisticated methods of clinical and neurophysiologic study at specialized neurological centers became available. They documented a considerably greater prevalence of sleep disorders in patients with degenerative diseases than had been previously suspected (6). New insights into these disorders were gained from genetic analysis (7–12), electrophysiological, pharmacological, and imaging data (13–21). Meanwhile, various animal models have been engineered to elucidate the mechanisms of normal and abnormal sleep (22–27).

Despite such progress, the validity of information derived retrospectively from clinical, neuropathologic, or clinicopathologic studies may be limited because the duration and evolution of illness can vary considerably from case to case (28). Information derived from sleep studies in cats or rodents needs to be correlated to human neuropathologic data with caution because the physiology of sleep may differ among species (29). It is hoped that further development of in vivo imaging studies (14–21) will contribute to the better understanding of sleep disorders in humans.

After a brief review of the neuroanatomy of sleep, we will consider current knowledge about the distribution of lesions associated with the most common sleep disorders in selected neurodegenerative diseases. We will then summarize the postulated pathophysiological mechanisms operating in the disease entities selected for discussion (Table).

Summary of Anatomical and Functional Studies of Sleep
Local processes, neuronal networks, and hormonal influences control various states of consciousness, namely the waking state, non-rapid eye movement (NREM) sleep, and REM sleep. All are regulated by centers in the hypothalamus, including the biologic clock.
The serotonergic neurons in the pontine raphe nuclei (Fig. 1D) projects to the cerebral cortex from the brainstem noradrenergic reticular nuclei (Fig. 1A). The cholinergic system (Fig. 1A, red arrows) arises from the laterodorsal and pedunculopontine tegmental nuclei (Fig. 1D) of the brainstem, the gigantocellular nucleus (not shown in the figure) of the medulla oblongata, and from the magnocellular nuclei of the basal forebrain, including the nucleus basalis of Meynert (Fig. 1D). The cholinergic system stimulates the cortex directly or indirectly (possibly through the hypothalamic tuberomamillary nucleus) and via the aspartate/glutamate (yellow arrow) thalamic intralaminar nucleus, and more diffusely from the laterodorsal and pedunculopontine tegmental nuclei (Fig. 1D) of the brainstem, the gigantocellular nucleus (not shown in the figure) of the medulla oblongata, and from the magnocellular nuclei of the basal forebrain, including the nucleus basalis of Meynert (Fig. 1D). The cholinergic system stimulates the cortex directly or indirectly (possibly through the hypothalamic tuberomamillary nucleus) and via the aspartate/glutamate (yellow arrow) thalamic intralaminar reticular nuclei (Fig. 1A).

The monoaminergic system (Fig. 1A, blue arrows) projects to the cerebral cortex from the brainstem noradrenergic locus coeruleus (Fig. 1D), histaminergic neurons of the hypothalamic tuberomamillary nucleus, and more diffusely from the serotonergic neurons in the pontine raphe nuclei (Fig. 1D) (47, 48).

The Hypothalamic Orexin/Hypocretin System (Hormonal)

Neurons of the lateral and posterior hypothalamus secrete orexin/hypocretin, a highly excitatory hormonal neuropeptide (Fig. 1A, green square–ended line) capable of stimulating selected brain nuclei, principally via norepinephrine, histamine, acetylcholine, dopamine (49), and GABAergic systems. The orexin/hypocretin system stabilizes wakefulness (29, 46–48) and exerts control over breathing and muscle tone during the different stages of sleep and wakefulness. Data on other systems (serotonergic and dopaminergic) can be found in references 3, 16, and 29, 46–48.

### Waking State

Arousal and alertness arise from depolarization of thalamocortical systems (Fig. 1A) and enhanced excitability of cortical pyramidal cells under the effect of the ascending activating system (neuronal) and the hormonal orexin/hypocretin system (14, 46–48).

### The Ascending Reticular Activating System (Neuronal)

The ascending activating system projects to the cerebral cortex (Fig. 1A, D).

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### NREM AND REM SLEEP

#### NREM Sleep

Sleep begins upon cessation of ordinary sensory inputs. Neuronal interactions in corticothalamic systems induce rhythmic activity and hyperpolarization of layer V of the cerebral cortex (14). The activity of the ascending reticular activating and the orexin/hypocretin systems progressively decreases. This is caused by the inhibiting action of GABAergic cells in the basal forebrain and in the median/ventrolateral preoptic hypothalamus (Fig. 1B, yellow arrows), which become highly active and to the end of the stimulating action of orexin/hypocretin (Fig. 1B) (14, 47–48, and below).

There are fewer recent studies on NREM sleep than on REM sleep. Slow oscillations (<0.1 Hz) involve the default mode network (19, 21), which includes mainly the posterior cingular cortex, the precuneus, the medial and dorsolateral prefrontal cortex, and the ventral anterior cingular cortex. It is thought to correspond to task-independent brain activity (concerned with multiple cognitive functions, including attention, prospection, memory, or self) operating when the task-positive network is not activated. One investigation that correlates electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) demonstrates that the slow oscillations characteristic of NREM sleep do not indicate a state of brain quiescence (19). Rather, they are a manifestation of an active state during which fMRI brain activity is synchronized to slow oscillations in frontal areas, inducing a decoupling with posterior areas of the default mode network during deep sleep. This occurs in the presence of preserved activity levels in the individual network components, suggesting that it is not activity per se but rather the coherent activation of all parts within the network that leads to a conscious experience (19). It has been suggested that the brain responses synchronized by slow oscillations restore the microarousal activity patterns that facilitate neuronal interactions (18). Little

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**Table 1: Sleep Disorders Associated With Selected Degenerative and Prion Diseases**

<table>
<thead>
<tr>
<th>Sleep Disorders/Neurological Diseases</th>
<th>Insomnia and Biologic Clock Dysfunction</th>
<th>Symptomatic Narcolepsy</th>
<th>REM Sleep Behavior Disorders</th>
<th>Excessive Daytime Sleepiness</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>+++ (6, 30, 31)</td>
<td></td>
<td>++ (late) (32, 33)</td>
<td>++ (4, 6)</td>
<td>Apneas and autonomic dysregulation (34)</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
<td>++++ (34–37)</td>
<td></td>
<td></td>
<td>+++ (9, 34, 37)</td>
<td>RLS and periodic limb movements (34)</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>+++ (38, 39)</td>
<td>+++ (40, 41)</td>
<td>++++ (33, 42)</td>
<td>+++ (31, 39)</td>
<td>RLS and periodic limb movements (39)</td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>+++ (6, 38, 39)</td>
<td>+++ (40, 41)</td>
<td>++++ (33, 42, 44)</td>
<td>+++ (31)</td>
<td>Apneas (31, 39)</td>
</tr>
<tr>
<td>PSP</td>
<td>++ (6, 38, 39)</td>
<td>++ (41)</td>
<td>++++ (6, 33, 44)</td>
<td>+++ (31, 39)</td>
<td>Apneas, RLS (39)</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>++ (6, 38, 39)</td>
<td>++ (45)</td>
<td>++++ (6, 33, 42, 44)</td>
<td>++ (31, 39)</td>
<td>Autonomic dysregulation (6, 45)</td>
</tr>
</tbody>
</table>

Scale from ++++: very frequent to ±: mild or infrequent symptom; PSP, progressive supranuclear palsy; REM, rapid eye movement; RLS, restless legs (or limbs) syndrome.
morphological data are available in this area. In this regard, however, NREM sleep might have an important role in synapticogenesis (13, 46).

**REM Sleep**

The onset of REM sleep (Fig. 1C) is characterized physiologically by activation of electrical cortical activity in a desynchronized pattern, as occurs in the waking state (48). It is first associated with suppression of muscle tone (“tonic REM sleep”), followed by the onset of rapid eye movements (“phasic REM sleep”). There is activation principally of the centrencephalic, paralimbic, and unimodal sensory regions. Areas that normally participate in the highest order analysis and integration of neural information, namely, the dorsolateral prefrontal cortex, are not activated (15, 50). Rapid eye movement sleep occurs under the influence of the hypothalamus and upper brainstem nuclei (see later). The use of fMRI with simultaneous polysomnographic recordings upon acoustic stimulation has shown that during phasic REM sleep, and not in tonic sleep, the active thalamocortical network includes the basal forebrain, limbic, and parahippocampal areas (50).

The brainstem mechanisms controlling the onset and cessation of REM sleep are of interest in relation to neuropathologic studies of patients with sleep disorders, but limited data on human and other primates are available.

In the rat, mutually inhibitory (“flip-flop switch”) GABAergic neurons (“REM-on”) (Fig. 1C, 5-pointed star) have been described in the sublaterodorsal nucleus and the prelocus-coeruleus located in the pontine tegmentum and “REM-off” neurons (Fig. 1B, 4-pointed star) located in the ventrolateral periaqueductal gray matter and lateral pontine tegmentum (51). Human “REM-on” neurons might reside in the region of the sublaterodorsal and precoeruleus nuclei, and the location of “REM-off” neurons is postulated to be in the ventrolateral and lateropontine periaqueductal gray matter (6, 43, 44) (Fig. 1C, D). Glutamatergic “REM-on” neurons (Fig. 1C, brown arrows) are believed to project to the basal telencephalon, setting off electrical cortical activity there. In the human brainstem, ponto-geniculo-occipital sharp waves preceding and occurring during REM sleep are believed to originate from the ventromedial tegmentum (52).

In the rat, glutamatergic “REM-on” neurons (Fig. 1C) also project to the ventromedial medulla and to spinal interneurons, thereby inhibiting muscular tone. They activate neurons with cholinergic receptors in the locus coeruleus/subcoeruleus and glycineric receptors in the magnocellular reticular nucleus of medulla oblongata. A restricted region within the ventromedial medulla contains glutamatergic neurons that project to the spinal ventral horn and regulates REM and motor atonia. Similar mechanisms are postulated to occur in humans (44). The cholinergic system acts as a modulator of REM sleep (14, 44). Functional imaging studies with positron emission tomography during REM sleep have shown that the human cholinergic system is active as in the waking state, whereas monoaminergic systems are silent in both REM and NREM sleep (16).

In summary, lesions of the brainstem involving regions in close proximity to the sublaterodorsal nucleus and prelocus-coeruleus areas and the mesopontine nuclei may affect the organization of REM sleep. Lesions of similar regions close to the locus coeruleus/subcoeruleus and the pedunculopontine nuclei and laterodorsal tegmentum affect muscle tone during REM sleep (6, 44).

**THE HYPOTHALAMIC ORGANIZATION (HORMONAL AND NEURONAL) OF SLEEP AND THE BIOLOGIC CLOCK**

The hypothalamus modulates all of the aforementioned systems (14, 46, 47, 53–59). The neuronal and hormonal systems that control the waking state are mainly the histaminergic nerve cells of the hypothalamic tuberomamillary nucleus and the orexin/hypocretin neurons, which form a compact lateral and posterior cluster, the ventrolateral preoptic area, that is bordered by more sparsely aggregated neurons in the intermediate region of the hypothalamus (Fig. 1D1) (47).

Conversely, selected GABAergic and galaninergic neurons in the ventrolateral preoptic area and the tuberal hypothalamus inhibit wake-promoting regions in the hypothalamus and brainstem and participate in the generation of NREM sleep (Fig. 1B). The posterior hypothalamus also contains melanoconcentrating hormone (MCH) neurons (Fig. 1A–C, pink square-ended lines) that are often colocalized with orexin/hypocretin neurons and innervated by neurons expressing exclusively orexin/hypocretin. In rats, MCH neurons fire during wakefulness, occasionally during NREM sleep, and maximally during REM sleep. The MCH neurons discharge in a mutually reciprocal manner to orexin/hypocretin neurons across the sleep-wake cycle (57). Hypothalamic orexin/hypocretin and acetylcholine neurons of the mesopontine tegmentum exert opposing influences on reticulospinal neurons and modulate muscle tone in rats (25).

Lastly, the hypothalamic biologic clock in the suprachiasmatic nucleus regulates these systems with regard to circadian rhythms and ambient light. The neurons of this pacemaker have clock genes with synchronized cadenced expression (54, 55). There are 2 populations of neurons in the rat: 1) the dorsomedial neurons with clock genes that have mostly an approximate 24-hour rhythm that can persist during darkness; and 2) the ventrolateral neurons with light-sensitive gene expression modulated by the retinohypothalamic tract, originating from retinal ganglion cells (53). These neurons send GABAergic projections to the sleep-promoting ventrolateral preoptic nucleus and glutamate-thyrotropin–releasing hormone projections to the wake-promoting orexin/hypocretin neurons in the lateral hypothalamic area.

The ventrolateral suprachiasmatic nucleus relays this information to the pineal gland via the well-known pathway that includes the medial forebrain bundle, the intermedialateral cell column of the upper thoracic spinal cord, and the superior cervical ganglion (59).

Melatonin, which is secreted by the pineal gland, is implicated in numerous physiological processes, including circadian rhythms, stress, and reproduction. A large number of nuclei (including suprachiasmatic, supraoptic, paraventricular, infundibular, and tuberomamillary nuclei; mamillary bodies; the basal forebrain; thalamic ventromedial, dorsomedial, and paraventricular nuclei) show immunoreactivity for
the melatonin receptor MT1. These neurons may regulate the sensitivity to stimuli that set the biologic clock in phase with the environment (48). A GABAergic mechanism couples the ventrolateral and dorsomedial regions of the suprachiasmatic nucleus. This nucleus also projects to hypothalamic neurons secreting orexin/hypocretin and expressing melanin-concentrating hormone (58) and to the locus coeruleus (59) (Fig. 1B, C, yellow arrows).

SUMMARY OF STUDIES DESCRIBING BRAIN LESIONS ASSOCIATED WITH SLEEP IN SELECTED NEURODEGENERATIVE DISEASES AND FATAL FAMILIAL INSOMNIA

Disruption of the Circadian Rhythm and Insomnia

Insomnia is believed to occur under 3 sets of circumstances: 1) the suprachiasmatic nucleus fails to induce sleep, 2) the thalamocortical systems are impaired, and 3) the anatomical centers responsible for wakefulness are damaged or are not inhibited.

Disruption of this system in many neurodegenerative disorders and is part of the clinical picture of a wide range of neuropathologic processes with varied anatomical localizations, making strict clinico-pathologic correlations difficult. Furthermore, multiple factors (e.g., organic, psychic, cognitive, or therapeutic) may act synchronously to induce insomnia. Two paradigmatic mechanisms, that is, dysfunction of the biologic clock in Alzheimer disease (AD) and thalamic impairment in fatal familial insomnia (FFI) have been thoroughly studied.

Dysfunction of the Suprachiasmatic Nucleus: Biologic Clock Fails to Induce Sleep

The main alterations of sleep patterns in AD are reduced sleep efficiency, increased numbers of awakenings, and sleep-wake rhythm disturbances (Table). A direct correlation has been noted between the severity of some sleep disorders and the clinical stage of dementia. Swaab’s group used post-mortem samples soon after death derived from the Netherlands Brain Bank and showed that, in 68 control pineal glands, the clock genes (hBmal1, hCry1 and hPer1) are rhythmically expressed (30). Interestingly, the level of expression is related to the time of death during the course of the day. In advanced AD (Braak stages V–VI for neurofibrillary tangles) and even in preclinical stages (Braak stages I–II), rhythmic expression of clock genes is no longer found. Surprisingly, hCry1 mRNA is increased in AD. A reduction of hypothalamic neurons that express melatonin MT1 receptors, vasopressin, and vasoactive intestinal peptide is seen in AD patients with Braak stages V–VI. In distinction, in aged controls (Braak stage 0) and in patients with early AD (Braak stages I–II), the only affected neurons are those that express melatonin receptors (30). The authors suggest that there is a functional disconnection between the suprachiasmatic nucleus and the pineal gland in AD. Similar results have been documented in the de-afferented pineal gland in rats (30). Melatonin seems to inhibit neurons possessing MT1 receptors, thereby regulating neuronal sensitivity to stimuli that set the biologic clock in phase in response to environmental influences (14, 30).

The Thalamocortical Systems Are Damaged

Severe insomnia and autonomic dysfunction (“agrypnia excitata”) typically occur in the rare prion disease FFI (9–11, 34–37, 60–63). Fatal familial insomnia is an autosomal dominant disease mainly linked to a D178N/V129 mutation at codon 178 of PRNP, the prion protein (PrP) gene, aligned on the same allele with a methionone codon at position 129 of a common polymorphism of this gene in some populations (34, 37). Rare sporadic cases have been reported, called MM2-thalamic-type sporadic Creutzfeldt-Jakob disease (61). Transgenic D178N/V129 mice develop EEG abnormalities and alterations in sleep-wake patterns comparable to those seen in patients with FFI and show pathological features reminiscent of Creutzfeldt-Jakob disease (CJD) (27). Ninety-six percent of patients with FFI have severe insomnia associated with alterations of the sleep-wake cycle and sometimes hypersomnia (9); less frequently, periodic limb movements and central apneas may also be seen (34). Early in the course of the disease, these sleep disturbances may occur in combination with severe autonomic dysfunction, such as excessive perspiration and salivation, tachycardia, hypertension, fever, and impotence (83%). Signs and symptoms in common with CJD are also observed: cognitive/memory deficits and psychiatric symptoms (87%), myoclonus (70%), and other symptoms including late pyramidal/extrapyramidal signs (34). Polysomnography recordings show a variable range of the proportion of NREM sleep.
and REM activities, including episodic fluctuations between NREM and short-lasting REM sleep (35), reduction of NREM activity, and REM sleep (34), and sometimes even the absence of NREM and REM sleep (36). In the terminal stages of FFI, imaging studies show cerebral atrophy. Positron emission tomography scans performed on carriers of the D178N mutation of PRNP as early as 13 months before the onset of clinical manifestations show a mild hypometabolic state in the thalamus, first extending to the mesial frontal lobes and then involving the entire cerebrum, including the basal ganglia (10). Magnetic resonance spectroscopy combined with the measurements of apparent diffusion coefficient of water in different brain areas has shown a metabolic pattern compatible with thalamic gliosis confirmed by the pathological study (62). Indeed, severe thalamic neuronal loss and gliosis are characteristically seen in postmortem studies of FFI, usually without concomitant spongiform change, except in very advanced stages of the disease (9, 35–37, 62). The most severely affected thalamic nuclei are the anteroventral, mediodorsal nuclei, and the pulvinar (37). Morphometric investigations have shown a 90% loss of neurons in association nuclei and in motor nuclei and a 60% loss in limbic-paralimbic, intralaminar, and reticular nuclei (63). PrP immunohistochemistry and, more frequently, Western blotting are diffusely positive in the regions of the brain characteristically involved in CJD, especially in the thalamus, but less so in limbic structures and brainstem. Atrophy of the inferior olive with neuronal loss and gliosis is also commonly observed. With reference to sleep disorders, there is also gliosis of the hypothalamus and periaqueductal area and serotonergic neurons are selectively lost in the raphe nuclei (37).

The persistence of REM sleep in a few patients with FFI may be explained by the preservation of relevant pontine areas. Hypovigilance and sleepiness are caused by the lesions of the thalamic nuclei, including those with limbic connections and of the intralaminar nuclei. The disorganization of multiple thalamic circuits necessarily results in disruption of the sleep-wake rhythms (63). In summary, the thalamus and thalamocortical systems are always involved in fatal insomnia, and thalamic lesions seem likely responsible for the reduction or loss of both NREM and REM sleep.

The Anatomical Centers Responsible for Wakefulness Are Not Inhibited or Are Impaired: Involvement of the Ascending Activating System

Damage to the ascending activating system may lead to insomnia and/or excessive daytime sleepiness in neurodegenerative diseases. In Lewy body disorders, intralaminar thalamic nuclei (64) and numerous other components of the ascending activating system (medullary magnocellular nucleus and locus coeruleus complex) are involved by the synucleinopathy at “preclinical” stage 2 of Braak for Parkinson disease (PD). At stage 3, there is involvement of the nucleus basalis of Meynert, the pedunculopontine and the tuberomamillary nucleus, and the substantia nigra contributing in motor disorders (5). This is also the case in AD, in which several structures implicated in the ascending activating system are involved. These include the basal nucleus of Meynert, the locus coeruleus, the upper raphe nuclei, the tegmentopontine reticular nuclei, and adjacent areas (4). In progressive supranuclear palsy (PSP), the thalamic intralaminar nuclei (64) are often involved, and the laterodorsal and pedunculopontine tegmental nuclei, basal nucleus of Meynert, locus coeruleus, raphe nuclei (65), and nigrostriatal pathways (66) are severely damaged. The range of clinical and pathological presentations of PSP and its variants share similar histopathologic, biochemical, and genetic features with typical PSP (67).

The involvement of thalamic and hypothalamic nuclei is implicated in arousal (Table). In PD, it must also be stressed that there is marked neuronal loss in the thalamic nuclei with limbic connections (68) and that the hypothalamic ventromedial nucleus is affected at late stages of Braak (5). This is also the case in AD, in which the thalamic nuclei with limbic connections are severely affected; neurofibrillary changes occur in the anteroventral nucleus and, to a lesser extent, in the adjoining reticular nuclei (69). Lesions of the thalamic nuclei with limbic connections have also been reported in PSP (70).

In summary, there are combined lesions of the ascending system and of the biologic clock in neurodegenerative diseases (especially in AD); involvement of some thalamic and hypothalamic nuclei may contribute to insomnia.

Narcolepsy

Narcolepsy is a symptom complex comprising sudden and uncontrollable sleep attacks, episodes of skeletal muscle paralysis, and atonia induced by emotional stress or laughing (cataplexy). Whole-body paralysis occurs before falling asleep or upon awakening (sleep paralysis) and may be accompanied by hallucinations when falling asleep (hypnagogic hallucinations) (38). The disease is divided into 3 subtypes: idiopathic narcolepsy (with or without cataplexy) and narcolepsy secondary to a medical condition (symptomatic narcolepsy). Additional new entities have been recently proposed (71, 72). Narcolepsy is characterized by the intrusion of REM sleep during wakefulness. Hypothalamic lesions of primary narcolepsy include a massive loss of hypocretin neurons (with relative sparing of MCH neurons) and gliosis in the lateral hypothalamic area (73, 74). These abnormalities have been presumed to be secondary to a burnt-out chronic autoimmune process. The lesions extend to the targets of the hypocretin system, namely, tuberomamillary nuclei, dorsal, and central raphe. In distinction, the thalamus and mammillary bodies are normal (73). Although not part of the defining criteria (71), more than 90% of patients with narcolepsy-cataplexy carry HLA-DQB1*0602. Linkage studies show associations of primary narcolepsy with various regions of chromosomes 17, 4, and 21 (8). Most cases of narcolepsy, whether primary or symptomatic, seem to be attributable to disorders of hypothalamic hypocretin neurons. In rare cases of symptomatic diseases (Table), lesions have been demonstrated in either the hypothalamus or in targets of the hypothalamic hypocretin system (40).

For example, affected neurons may be seen in the hypothalamus in Lewy body disorders (5). Hypocretin neuronal loss, as shown by immunohistochemistry, starts at Braak stage 1 for PD (23%) and is maximal at Braak stage 5 (62%). There is also significant hypertrophy and reduction in the
In patients with PD and Lewy body dementia experiencing RBD, neuropathologic examination was at first focused on substantia nigra and locus coeruleus lesions. However, these regions were severely affected in 4 autopsy cases of pallido-ponto-nigral atrophy (tau N279K mutation) without evidence of RBD. It should be noted that the locus coeruleus is silent during REM sleep (6, 44). Furthermore, RBD was the single polysomnographically proven symptom in a case studied at postmortem in which a very extensive synucleinopathy was not especially associated with a correspondingly significant involvement of the substantia nigra or the locus coeruleus. The general topography of the lesions in that patient, however, was consistent with the notion that the human equivalent of the rat’s sublaterodorsal and precoeruleus nucleus and ventrolateral lateropontine periaqueductal gray matter are the anatomical sites involved in human REM sleep (44). Braak’s scheme of development of lesions in PD may explain why RBD often precede motor signs (5, 75). At stage 1, α-synuclein immunohistochemistry reveals lesions of the dorsal IX/X motor nucleus and/or the intermediate reticular zone of medulla oblongata. At Braak stage 2, the inferior raphe nuclei, magnocellular reticular formation, including the gigantocellular nucleus of medulla, and the coeruleus-subcoeruleus complex are affected. The substantia nigra and ventral tegmental area, central limbic nucleus, and central subnucleus of the amygdala are involved only from Braak stage 3.

In conclusion, the precise identification of a distinct anatomical structure responsible for RBD in Lewy body disorders has not been possible, but case studies have shown that important sites of involvement are the sublaterodorsal and locus coeruleus–precoeruleus areas (6, 43, 44) (apparently not the locus coeruleus alone) in association with the ventrolateral and lateropontine periaqueductal gray matter (44).

In MSA, RBDs are very frequent and often precede other signs and symptoms (42). The monoaminergic deficit in striatum, without thalamic concomitant cholinergic deficit, observed in MSA (79) does not seem to explain RBD by itself. The mechanism of RDB in MSA is likely to involve much more complex and as yet poorly understood mechanisms (3, 45, 79–81). There have been a few systematic neuropathologic studies of this disorder, but neither a correlation with sleep disorders nor a temporospatial study of the lesions has been performed. In addition to the lesions seen in the lateral reticular nuclei, accessory olive, pontobulbar and arcuate nuclei, glial cytoplasmic inclusions are seen in central tegmental tract, and to a lesser degree, corticopontine, corticomedullary, corticospinal, spinoreticular, olivocerebellar tracts (81, 82). Few preclinical cases have been studied in

number of neurons expressing MCH from 12% at Braak stage 1 to 74% at Braak stage 5 of PD (75). There is a remarkably good correlation between loss of hypothalamic neurons and the clinical score using the Hoehn and Yahr Scale for PD (76). By contrast, the correlation between substantia nigra neuronal loss and Hoehn and Yahr clinical score is less strong (75).

In other neurodegenerative diseases, such as multiple systems atrophy (MSA), the 3-fold reduction of hypocretin/orexin neurons in the posterior hypothalamus (45) and the presence of abundant concomitant glial cytoplasmic inclusions labeled by anti-ubiquitin antibodies may be the pathological substrates that underlie the sleep disorders such as hypersonomnia, symptomatic narcolepsy, and dysfunction of autonomic regulation in these patients. On the other hand, precise clinicopathologic correlation is problematic because patients with long-standing disease have also lesions involving widespread areas of the basal ganglia and brainstem. The same is true for PSP, in which the hypothalamus has been less studied but has been found to be involved in a postmortem study in a case with frontotemporal atrophy (77). Clinically, patients with PSP have low orexin levels in the cerebrospinal fluid (41).

Interestingly, a few reports of patients with symptomatic narcolepsies and lesions in the mesencephalon or medial pons shown by radiological imaging have indicated that some cases of narcolepsy and REM sleep behavior disorders (RBDs) (as described in the following paragraph) may be related to lesions in comparable anatomical sites. Of particular interest is the report of a 30-year-old patient who had hypersonomnia, sleep paralysis, hypnagogic hallucinations, and RBD and was found to have an acute, apparently focal, inflammatory process in the medial tegmentum. Cerebrospinal fluid hypocretin and leptin dosages were normal. The patient did not have the characteristic human leukocyte antigen type found in narcolepsy (40). However, these results must be viewed critically because they were not autopsy controlled, and the patients described might have had idiopathic narcolepsy (40).

**REM Sleep Behavior Disorders**

The RBDs encompass abnormalities extending from simple limb jerks to complex integrated, sometimes violent, body movements in which patients seem to be unconsciously acting out their dreams. The systems controlling muscular tone and cerebral electrical activity during REM sleep are independent, but some dissociation between them can exist (6, 43, 44, 78). The RBDs occur when physiological motor inhibition during REM fails to be initiated.

Boeve et al (44) analyzed the imaging findings of 5 previously published cases of symptomatic narcolepsy and RBDs associated with focal lesions in the brainstem; neuropathologic examination was not performed. The periaqueductal area, floor of the fourth ventricle, and paramedian territory of the upper pons were involved, but specific anatomic structures affected could not be ascertained. In a retrospective clinicopathologic study (1990–2006) of REM sleep disorders including 36 patients with degenerative diseases followed at the Mayo Clinic, the authors found 31 cases of Lewy body diseases, 4 cases of MSA, and 1 case of PSP (44). In a more recent study of the cases from the Mayo medical records presenting from 2002 to 2006 and meeting the criteria of idiopathic RBD at onset, the sleep disturbances occurred long before other clinical symptoms in some cases; 27 patients experienced isolated RBD for at least 15 years before evolving into PD, PD dementia, dementia with Lewy bodies, or MSA. The time interval between RBD and the onset of clinical manifestations ranged up to 50 years, with a median of 25 years (42).

In patients with PD and Lewy body dementia experiencing RBD, neuropathologic examination was at first focused on substantia nigra and locus coeruleus lesions. However, these regions were severely affected in 4 autopsy cases of pallido-ponto-nigral atrophy (tau N279K mutation) without evidence of RBD. It should be noted that the locus coeruleus is silent during REM sleep (6, 44). Furthermore, RBD was the single polysomnographically proven symptom in a case studied at postmortem in which a very extensive synucleinopathy was not especially associated with a correspondingly significant involvement of the substantia nigra or the locus coeruleus. The general topography of the lesions in that patient, however, was consistent with the notion that the human equivalent of the rat’s sublaterodorsal and precoeruleus nucleus and ventrolateral lateropontine periaqueductal gray matter are the anatomical sites involved in human REM sleep (44). Braak’s scheme of development of lesions in PD may explain why RBD often precede motor signs (5, 75). At stage 1, α-synuclein immunohistochemistry reveals lesions of the dorsal IX/X motor nucleus and/or the intermediate reticular zone of medulla oblongata. At Braak stage 2, the inferior raphe nuclei, magnocellular reticular formation, including the gigantocellular nucleus of medulla, and the coeruleus-subcoeruleus complex are affected. The substantia nigra and ventral tegmental area, central limbic nucleus, and central subnucleus of the amygdala are involved only from Braak stage 3.

In conclusion, the precise identification of a distinct anatomical structure responsible for RBD in Lewy body disorders has not been possible, but case studies have shown that important sites of involvement are the sublaterodorsal and locus coeruleus–precoeruleus areas (6, 43, 44) (apparently not the locus coeruleus alone) in association with the ventrolateral and lateropontine periaqueductal gray matter (44).

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MSA, and the occurrence of a sleep disorder is not specifically mentioned (83).

In PSP, lesions of the locus coeruleus, central pontine nuclei (found in more than 50% of reported cases), and pedunculopontine nuclei are frequent, but clinicopathologic correlations with sleep disorders have not been performed (65).

The onset of RBD is a late occurrence in AD (Table) (32). The tegmentopontine reticular nuclei and, more generally, regions of superior and dorsal brainstem, but also the locus coeruleus (4, 84, 85), are frequently affected.

The RBDs, especially when early or preceding the other signs, are more frequent in synucleinopathies than in most tauopathies or other degenerative disorders. This is likely caused by the topography of the lesions because RBDs are frequent in some tauopathies such as Guadeloupean parkinsonism (86).

Excessive daytime sleepiness, characterized by need for sleep during the day, is a common symptom in patients with sleep disorders and frequently accompanies AD, Lewy body disorders, PSP, MSA (31, 39), and normal aging. It may result from lesions of the ascending activating system (as previously described), but may also be seen in patients with mood disorders, sleep deprivation, sleep apnea syndrome, restless leg syndrome, or as a pharmacological side effect. It might also be the consequence of other lesions involving the default-mode system.

DISCUSSION

Insomnia caused by organic causes is a rare phenomenon. In most cases, it can be attributed to dysfunction of the biologic clock, thalamocortical lesions, and/or to alterations of the ascending activating system modulated by the hypothalamus. Idiopathic narcolepsy is almost always caused by hypothalamic lesions of the hypocretin system; this is also the case for symptomatic narcolepsy, which can likely occasionally be caused by alterations in the targets of the same system. In some degenerative disorders, such as PD and Lewy body dementia or MSA, the onset of RBD may precede other clinical signs by many years. In this regard, we would emphasize the neuropathologic importance of the mutually inhibitory system of GABAergic neurons “REM-on” likely located in the region of the sublaterodorsal nucleus and precoeruleus area of the pontine tegmentum and “REM-off” in the ventrolateral gray matter and lateral pontine tegmentum. Some dissociation can occur between systems independently controlling REM muscular atonia and cerebral electrical activity, leading patients to “live out their dreams” in RBD. This should direct future research on the early involvement of these areas in sleep disorders in patients with neurodegenerative diseases.

Other symptom complexes such as central apnea (Table), which are frequent in MSA and less so in PD and Lewy body dementia and in PSP (3, 31, 39), have not been discussed in this review. We have chosen to confine this review to a discussion of the clinicopathologic correlations of selected human sleep disorders and to deal principally with dysfunction of the most important systems: the biologic clock, the thalamocortical system, the multiple arousal system, the orexin/hypocretin system, and REM sleep. Other systems might certainly also be implicated in human degenerative diseases. We would like to emphasize that EEG and fMRI correlative studies have demonstrated that slow oscillations (<1 Hz), characteristic of NREM sleep, indicate an active state during which fMRI brain activity is synchronized to these oscillations in specific cerebral regions. The partial overlap between the response patterns related to these oscillations and the waking default mode network, a brain circuit that is highly active in the absence of overt behavior (17–19, 87), seems a potentially fruitful area for future investigation because it is affected in a number of brain disorders. As briefly mentioned, the areas involved include portions of the medial temporal lobe, the medial prefrontal cortex, and the posterior cingulate cortex, along with the adjacent precuneus (88) and the medial, lateral, and inferior parietal cortex (19, 88).

Interestingly, unified oscillations of NREM sleep have an important role in synaptic plasticity, linking NREM sleep, electrocortogenesis, fMRI brain activity, and morphological findings (14). Using fMRI, dysfunction of this system has been described in AD (89) and in the behavioral variant frontotemporal dementia (90), where the sleep disorders are more frequent in the temporal form of the disease than in the frontal form of the disease (90). They are also more common than in AD (89) or PD (91).

CONCLUSIONS

Selected neuropathologic studies of patients with degenerative and prion diseases with sleep disorders have shown that the topography of the lesions goes a long way to explain the clinical manifestations, but more often than not, such correlations are only statistical or imprecise. These studies indicate that the anatomical localization of lesions is of fundamental importance rather than the underlying nature of the pathological process (i.e. synucleinopathy vs tauopathy vs PrP deposits). The pathophysiology of human sleep disorders remains far from clear. This is hardly surprising as the understanding of mechanisms governing normal human sleep is still quite incomplete. Furthermore, a number of topics remain to be explored, including epigenetic modulations in gene expression and molecular modifications within the waking state, REM sleep, and NREM sleep in normal and diseased patients. Prospective clinicopathologic studies, including systematic analyses of polysomnography, the use of modern neuromaging, genetic and biochemical techniques, and detailed morphological and topographic documentation of lesions in degenerative and prion diseases are needed.

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