

Sundowning and circadian rhythm disorders in dementia

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Abstract

Sleep disorders and disruptive nocturnal behaviours are commonly reported in people with senile dementia and present both a significant clinical problem and a cause of increased stress for caregivers.

Neuronal degeneration of cholinergic Nucleus basalis Meynert (NBM) neurons promote rest-activity disturbance and Sundowning in Alzheimer's disease. NBM neurons modulate the activity of the mainly cholinergic suprachiasmatic nucleus (SCN) and the induction of NONREM sleep. Sundowning might be explained as a syndrome occurring when arousal is to be processed while the neocortex is already turned "off" to (NONREM) sleep. The therapeutic measures should thus primarily be aimed at the stimulation of the circadian system and enforcing "external Zeitgebers". Pharmacologically, application of cholinergic enhancers i.e. cholinesterase inhibitors and melatonin supports and should stabilize the weakened structures.

Key words : Sleep disorder ; old age ; dementia ; neuroleptics ; melatonin ; sundowning ; bright light therapy ; PLMS.

Introduction

Sleep disorders and disruptive nocturnal behaviours are commonly reported in people with senile dementia and present both a significant clinical problem and a cause of increased stress for caregivers. According to a large study in Germany 51% of caregivers experience disruptions of sleep continuity, on average 2.4 per night (Grassel 2000). In fact, many caregivers cite sleep disturbances, including night wandering and confusion, as the main reason for institutionalizing the elderly (Coen *et al.* 1997, Pollak *et al.* 1990). With increasing age qualitative as well as quantitative changes in sleep occur, and approximately 38% of the over-65-year-old report sleep disturbances according to epidemiological studies. 36% suffer from sleep onset disturbances and up to 29% suffer from disturbances of sleep continuity (Foley 1995). Subjectively experienced sleep disturbances correlated negatively with cognitive performance in a 3-year follow-up (Jelicic *et al.* 2002). According to the literature, 34-43% of the patients with Alzheimer's Disease (AD)

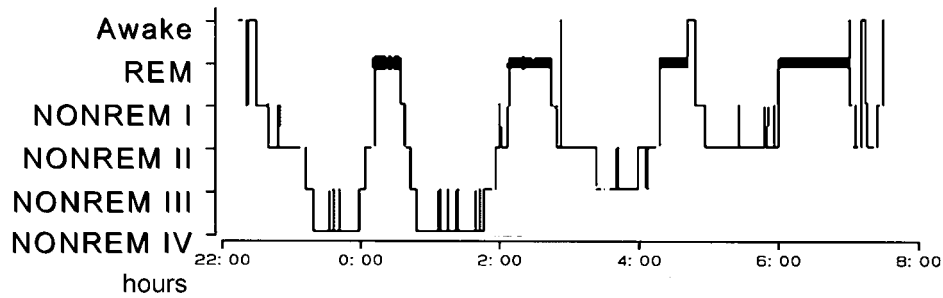
experience sleep disturbances (Cacabelos *et al.* 1996, Tractenberg *et al.* 2003). The extent to which the night sleep is disturbed is said to correlate with severity of dementia (Bliwise *et al.* 1995).

Sleep disturbances in elderly

There are two main types of sleep : rapid eye movement (REM) sleep and nonrapid eye movement (NONREM) sleep, which has four stages. People normally cycle through the four stages of NONREM sleep, usually followed by a brief interval of REM sleep, four or five times every night. Sleep progresses from stage I, during which the sleeper can be awakened easily to stage IV, during which the sleeper can be awakened only with difficulty. In stage IV, blood pressure is at its lowest, and heart and breathing rates are at their slowest. During REM sleep, electrical activity in the brain is unusually high, somewhat resembling that during wakefulness. The eyes move rapidly, and muscles may jerk involuntarily. The rate and depth of breathing increase, but the muscles, except for the diaphragm, are greatly relaxed. The first period of REM typically lasts 10 minutes, with each recurring REM stage lengthening, and the final one lasting up to 40 min (see figure 1). The stage-respective dimensions of sleep change relatively to age. In particular, there is a diminished consolidation of NONREM sleep (see figure 2). Patients with dementia, have lower sleep efficiency, an increase in the length of stage I sleep, a decrease in stage III and stage IV ; more sleep disruptions and awakenings, episodes of nocturnal wandering and an increase in daytime napping.

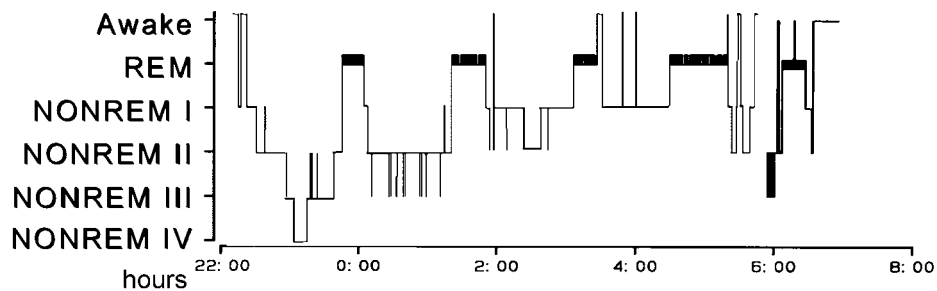
In addition other factors have to be considered causing sleep disturbances in old age like sleep apnea syndrome (SAS), restless leg syndrome (RLS), or nycturia or an enuresis nocturna (Bliwise *et al.* 2004).

Sleep apnea is defined as an absence of air flow at the nose and mouth for at least 10 seconds. Obstructive apnea is defined as the absence of air flow despite respiratory efforts. Central apnea, less common, is characterized by absence of respiratory efforts. Mixed apneas begin centrally, followed



REM : Rapid Eye Movement Sleep ; NONREM I-IV : NON Rapid Eye Movement sleep stage I-IV.

FIG. 1. — Polysomnogram in young adulthood with four sleep cycles



REM : Rapid Eye Movement Sleep ; NONREM I-IV : NON Rapid Eye Movement sleep stage I-IV.

FIG. 2. — Polysomnogram in the elderly

by obstruction. People with SAS may experience waking with gasping, confused wandering in the night, and thrashing during sleep. Among healthy older adults living in community settings, the prevalence of SAS is 28% in men and 20% in women. SAS occurs in 42% of people with dementia who live in nursing homes and correlates with cognitive function (Martin *et al.* 2005). One of the main risk factors for obstructive SAS is obesity, causing an increased size and fat content of the pharyngeal tissues, soft palate and uvula. During the apneas, the oxygen level in the blood falls causing many of the daytime symptoms such as excessive drowsiness. In some cases pulmonary hypertension may develop leading to right sided heart failure or cor pulmonale. Obstructive SAS is also associated with systemic hypertension, cardiac arrhythmia, ischemic heart disease and stroke. Therefore sleep apnea is more often associated with multi-infarct or vascular dementia than with Alzheimer's dementia (Bassetti *et al.* 1996). Weight management and avoiding alcohol and sedatives (which can exacerbate SAS by further relaxing the pharyngeal muscles) at bedtime may relieve SAS. In some individuals continuous positive airway pressure (CPAP) may be required. Patients with AD can also tolerate CPAP but compliance in long-term use may be difficult (Ayalon *et al.* 2006).

Another common cause for sleep disturbances is restless legs syndrome (RLS) with a prevalence of

about 29% in the elderly (Obler 1991). RLS is characterized by unpleasant limb sensations, usually described as a creeping or crawling feeling, sometimes as a tingling, cramping, burning or just plain pain, that are precipitated by rest and relieved by activity. Some patients have no definite sensation, except for the need to move. In up to 50% the arms are affected as well. There is a definite worsening of the discomfort when lying down at night or during other forms of inactivity, including just sitting. About 80% of RLS patients also experience Periodic Limb Movements in Sleep (PLMS). PLMS is characterized by sudden jerking or bending of the legs during sleep ranging from small shudders of the ankles and toes to kicking and flailing of the arms and legs. The periodic jerking often wakes the individual and significantly disturbs their quality of sleep. PLMS can occur independently in up to 45% of elderly (Ancoli-Israel *et al.* 1991). RLS is caused by a functional disturbance in the dopaminergic system (Staedt *et al.* 1995). Treatment of first choice consists of dopaminergic drugs or dopamine agonists such as pergolide or pramipexole (Montplaisir *et al.* 1996, Staedt *et al.* 1998). PLMS is greatly underdiagnosed especially in people with dementia who are unable to describe their symptoms. However, if a deterioration or disruption of sleep is noticed in patients taking antidepressants or neuroleptics, PLMS should be considered, since antidepressants, in particular SSRI and also neuroleptics potentially induce or



FIG. 3. — PAM-RL records leg movements continuously for up to 72h differentiating between standing and lying position using an integrated position sensor. Somnomedics®.

exacerbate PLMS (Horiguchi *et al.* 1999, Kraus *et al.* 1999, Wetter *et al.* 2002, Yang *et al.* 2005). PLMS can be easily diagnosed by actigraphy placed on the ankle of each leg (Ancoli-Israel *et al.* 2003, King *et al.* 2005, Sforza *et al.* 2005). Actigraphy is highly tolerated even in severely demented patients and makes home recordings more accessible, permitting the evaluation of patients in their natural sleeping environment and minimizing laboratory effects likely to alter the patient's typical sleep patterns (see figure 3).

Circadian rhythm disorders in dementia

Circadian rhythmicity, regulated by the suprachiasmatic nucleus (SCN), is observed in secretion of several hormones such as melatonin, body temperature and heart rate among other physiological functions. Specific ganglion cells in the inner retinal layer project light information to the SCN via the retinohypothalamic tract. From here, messages are transmitted via a neural pathway to the pineal gland which secretes melatonin – the chemical circadian pacemaker. Melatonin secretion is suppressed by light but increased at night during sleep, and is a sensitive marker of light shift changes in circadian rhythm. The SCN is also involved in the regulation of arousal level or sleep-wake rhythm via projections to the anterior and posterior hypothalamus (Miller 1993). Circadian disorders, such as sleepwake cycle disturbances, are associated with aging, and even more pronounced in dementia. Many studies have reported disrupted melatonin production and rhythms in aging and in AD that are taking place as early as in the very first preclinical AD stages (neuropathological Braak stage I-II) (Wu and Swaab 2005). Since an Alzheimer pathology underlies approximately 70% of dementing diseases (Neuropathology Group of the MRC CFAS 2001), the potential impact of the neurophysiological changes of Alzheimer's dementia on the rest-activity regulation should be discussed. Neuronal degeneration in the Nucleus basalis Meynert (NBM) is one of the most prominent features (McGeer *et al.* 1984, Reinikainen *et al.* 1988). The NBM could be defined as a cholinergic nuclear area which belongs

to the ascending reticular activation system (ARAS) and which innervates the neocortex. There, acetylcholine reduces the resting/voltage-dependent potassium membrane potential and thus increases neuronal excitability (reagibility). NBM neurons show a bursting and a tonic firing pattern. Whereas the latter might be associated with NONREM sleep, faster release of acetylcholine might underlie wakefulness (Nunez 1996). During the wake phase cholinergic pathways also inhibit the nuclei reticulares thalami (Steriade 2004). During the sleep phase this inhibitory influence disappears and the nuclei reticulares thalami induce a GABA-modulated NONREM sleep synchronization. Thus it is understandable that in Alzheimer's dementia an increasing cholinergic deficit produces EEG frequency decelerations which complicate the differentiation of the sleep-wake EEG with increasing severity of dementia. Accordingly, an extremely low cell density in the NBM and a low activity of the choline acetyltransferase in the cortex of patients with the highest delta activity is found (Riekkinen *et al.* 1990). The decreasing activity of the SCN and the synthesis of melatonin that diminishes in accordance with the progression of the illness (as determined by the Braak stages) (Wu *et al.* 2003) facilitate the disturbed rest-activity rhythm in AD along with reduced so-called "external zeitgebers" (physical activity, social isolation, low light intensity in living areas). While napping may be an expression of a disrupted sleep-night-structure, it has been shown to induce changes in the circadian rhythm when performed in the evening hours (Yoon *et al.* 2003).

Sundowning

The synopsis of these neuropathological changes in the SCN and the NBM makes the occurrence of rest-activity disturbances more easily understandable. The most spectacular disturbance is "sundowning". This term describes a delusional and often delirious state which occurs at twilight or during early night (Bliwise 1994). People with dementia may become more confused, restless and insecure, hallucinations may occur. It can be worse after a move or change in the person's routines. Data on the prevalence are varying from 10 to 25% in institutionalized patients (Evans 1987, Martin *et al.* 2000) and even higher numbers in Alzheimer's patients living at home reaching up to 66% (Gallagher-Thompson *et al.* 1992). A decrease of the activity of the SCN, the so-called "internal zeitgeber", could play a major role for the occurrence of sundowning. In favor of this assumption is the fact that sundowning usually occurs at twilight with reduced light intensity and the fact that rays of light have a stimulating effect on the SCN via the glutamatergic retinohypothalamic tract (Belenky and Pickard 2001). The reduced lightmediated

activation of the SCN could thus negatively influence the arousal level and induce a desynchronization of the rest-activity rhythm. In line with the latter assumption, sundowning intensity increases with reduction and phase delay of the temperature amplitude (Volicer *et al.* 2001).

To our opinion, the sundowning in AD, is pathophysiologically based on a cortical activation (arousal reaction) with concurrently reduced indirect SCW mediated base activation which is additionally enhanced by the cholinergic deafferentiation of the cortex and the reduced cholinergic inhibition of the nuclei reticulares thalami. Putting it more simply, sundowning is characterized by an arousal (e.g. fear due of impaired visual orientation, vocalizations of other residents) whereas the neocortex is "turned off", programmed toward NONREM sleep. Because of the cholinergic deafferentiation of the cortex the patient is then not able to build up the attentional capacity necessary for the processing of arousal. As a consequence, the stimulus causing the arousal cannot be processed and agitation persists or even augments. In this line disruptive vocalizations of elderly demented typically occurs more often during the afternoon and evening hours (Burgio *et al.* 2001).

Interestingly, patients with dementia with Lewy bodies (DLB) are especially sensitive to anticholinergic agents, indicating marked cholinergic dysfunction.

Post-mortem studies of brain tissue from patients with DLB revealed a severe depletion of the NBM with 75% to 80% loss of large cholinergic neurons (in AD 50% to 70% loss of cholinergic neurons) (Jellinger 2000), and a severely reduced cholinergic activity in the reticular thalamic nucleus associated with hallucinations and fluctuating consciousness (Perry *et al.* 1997).

Sedative psychotropic medication applied in the treatment of sundowning and nocturnal agitation is to be considered problematic since benzodiazepines or neuroleptics further weaken the already instable sleepwake rhythms and further decrease neuronal metabolic activity. Furthermore, the possibility that low-dose antipsychotic treatment and treatment with benzodiazepine is associated with increased risk of cerebrovascular events in elderly patients with dementia has been raised (Finkel *et al.* 2005). Anyhow, others suggested that preexisting cerebrovascular risk factors might interact with some atypical antipsychotics increasing the risk of events (Liperoti *et al.* 2005). It seems therefore plausible that sedative psychotropic medication on the one hand increase duration of hospitalization (Yuen *et al.* 1997) and on the other hand promotes confusion, impaired cognition and excessive sedation with danger of falling (Ancoli-Israel and Kripke 1989, Stoppe *et al.* 1999). Consequently, substances physiologically stimulating the circadian timing system in a specific way should be applied.

Pharmacological candidates are cholinesterase inhibitors and melatonin.

Cholinesteraseinhibitors are the therapy of choice for the treatment of AD and have also shown efficacy in other forms of dementia (McKeith *et al.* 2000, Samuel *et al.* 2000, Feldman *et al.* 2001, Aarsland *et al.* 2002, Erkinjuntti *et al.* 2002, Black *et al.* 2003, Kurz *et al.* 2003, Moretti *et al.* 2003, Wilkinson *et al.* 2003, Bullock 2004, Burns *et al.* 2004, Malouf and Birks 2004). Metaanalysis showed that they also influence non-cognitive symptoms and reduce psychotic symptoms, especially in Lewy body dementia (McKeith *et al.* 2000, Trinh *et al.* 2003). They should be applied at daytime in demented patients, especially when disturbances of circadian rhythms or sundowning occur.

Melatonin is believed to predominantly inhibit the activity of the SCN via Mel_{1a,b} receptors (Liu *et al.* 1997, Jin *et al.* 2003). Exogenously administered melatonin possesses a circadian-phase-dependent hypnotic property (Wyatt *et al.* 2006) improving sleep only when endogenous melatonin is absent. Melatonin should be given after light therapy at 8 p.m.

Results of a functional MRI study demonstrate that melatonin modulates brain activity in a manner resembling actual sleep although subjects are fully awake. Furthermore, the fatigue inducing effect of melatonin on brain activity is essentially different from that of sleep deprivation thus revealing differences between fatigues related to the circadian sleep regulation as opposed to increased homeostatic sleep need (Gorfine *et al.* 2006). However, placebo-controlled studies on the application of melatonin showed contradictory results. Asayama *et al.* (2003) found a significant decrease in nocturnal activity, a prolongation of sleep and an improvement of cognition after 4 weeks of administering melatonin (3 mg), whereas Serfaty *et al.* (2002) did not find an amelioration of sleep after the administering of 6 mg of melatonin over a period of 2 weeks. Singer *et al.* (2003) found after two months of administration of either 2.5 mg sustained-release melatonin, 10 mg melatonin or placebo, no statistically significant differences in objective sleep measures for any of these groups although non-significant trends for increased nocturnal total sleep time and decreased wake after sleep onset were observed in the melatonin groups relative to placebo. Trends for a greater percentage of subjects having more than a 30-minute increase in nocturnal total sleep time in the 10 mg melatonin group and for a decline in the day-night sleep ratio in the 2.5 mg sustained-release melatonin group, compared to placebo, were also seen. On subjective measures, caregiver ratings of sleep quality showed improvement in the 2.5 mg sustained-release melatonin group relative to placebo.

Thus, melatonin might need a longer time to exert an effect on sleep and other relevant

symptoms of dementia. This supports the study of Cardinali *et al.* (2002), who found a positive influence on sundowning and sleep under the application of 6 mg of melatonin in the 4-month follow-up.

Another interesting aspect in this context is the fact that music therapy increases the melatonin levels in AD patients and possibly has a soothing effect by means of the latter mechanism (Kumar *et al.* 1999).

In general, after exclusion of sleep disturbances due to PMLS and before applying other drugs, non-pharmacological approaches in order to physiologically stimulate the chronobiological and homeostatic regulation of rest-activity rhythms should be primarily used. The remaining dynamic usedependent neuronal processing/connecting capacity should be reinforced by sufficient light exposure a well-directed day-structure with meals, stimulating coffee and physical activity on a regular basis. The caregivers should be asked for a description of the daily routine and given the respective advice (Teri *et al.* 2002).

However, studies provide evidence that in some nursing home environments only a light intensity of a median of 54 lux was measured, and the residents only spent approximately 10 minutes in light of more than 1000 lux (Shochat *et al.* 2000). In comparison with that we reach 300-500 lux in our illuminated workspaces. Even on cloudy days during winter the light intensity reaches 3000-4000 lux outdoors. The positive effect of daylight on sleep could be proven in a study on elderly with sleep disorders (Mishima *et al.* 2001). In this study an exposure to daylight for two hours in the morning and for two hours in the afternoon resulted in increased melatonin levels and sleep amelioration. In demented patients light therapy during the evening hours reduces nocturnal motoric agitation (Satlin *et al.* 1992, Haffmans *et al.* 2001), but light therapy during the morning hours is also effective (Okumoto *et al.* 1998, Lyketsos *et al.* 1999) and even an amelioration of cognition in the Mini Mental State Examination can be achieved (Yamadera *et al.* 2000, Graf *et al.* 2001). Also indirect light therapy with increased light intensity in the living room stabilizes the sleep-wake cycle (van Someren *et al.* 1997). Stimulation exerted by sunrise and sunset also had positive effects on sleep onset latency, nocturnal agitation states and sleep duration in elderly patients with advanced dementia (Fontana Gasio *et al.* 2003). According to the available data and the routines of (nursing) homes, we recommend for demented patients a 30-minute light therapy of 10,000 lux which in consideration of the load on the time schedule can be easily fitted into the ward routine. Alternatively 2500 lux can be applied for two hours. However, it has to be noted that severely demented patients with substantial degeneration of the SCN can only benefit to a limited extent (Ancoli-Israel *et al.* 2003).

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