Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis

Pain has been reported to be a leading cause of insomnia in medical illness, where >70% of the patients complain of sleep problems [1, 2]. Most studies of pain and sleep, however, have focused on rheumatic diseases where the prevalence of sleep disturbances has been reported to be very high [3], and many of the daytime symptoms in these patients, such as pain, stiffness and fatigue, may have a close link to the non-restorative sleep pattern associated with the disease [4]. Knowledge of the abnormalities in the sleep process may, therefore, improve our understanding of the disease and lead to a better treatment of the patients.

Especially in fibromyalgia (FM) and rheumatoid arthritis (RA), reports based on objective studies have documented pathological findings during sleep. Pain provoked by injury or disease is the net effect of peripheral nociceptive activation and different biochemical, physiological and psychological mechanisms that involve most parts of the central nervous system. Therefore, pain in these diseases may probably influence the sleep process.

The physiological functions of sleep are partly unknown. Humans alternate in a cycle of sleep and wakefulness called the circadian rhythm. This cyclicity is also seen in other physiological variables, such as many hormones (e.g. growth hormone, prolactin, melatonin), urine secretion, blood pressure, body temperature, etc. [5, 6]. The sleep process itself is also characterized by cyclicity, and the electroencephalogram (EEG), indirectly reflecting the neuronal activity in the brain, is of major importance in the description of the sleep. Traditionally, sleep is divided into non-rapid-eye-movement (NREM) stages 1–4 with increasing depth and rapid-eye-movement (REM) sleep. The belief that sleep is a static condition has been replaced by the assumption that this state is a dynamic form of rest that conserves energy and permits reorganization of cortical neuronal activity, among other functions [7]. The deepest sleep stages especially seem to reflect homeostatic processes for the body and the mind, although this theory cannot explain all aspects of mammalian sleep [8]. In accordance with sleep as a restorative process, anabolic hormones are released mainly during sleep and evidence exists that a boosting of the immune system occurs during the night [9]. Thus, there seems to be a relationship between dynamic changes in sleep and variously cellular, hormonal and immunological functions.

Pain may influence the sleep process and alter these essential parameters, thereby interacting with the course of the disease [3]. On the other hand, sleep disturbances may decrease the pain threshold [10]. Pain and sleep relationships probably reflect the various pathogenetic factors underlying the different diseases. Thus, in patients with FM, the pain is most likely multifactorial and assumed primarily to involve a central pain modulation disorder [11], whereas the pain in RA, however, is probably caused mainly by peripheral nociceptive inputs in joint afferents which show enhanced responsiveness due to the inflammation [12]. Correspondingly, the interaction between sleep and pain probably differs with respect to sensory, physiological and behavioural aspects in the two diseases.

Sleep difficulties, as well as related daytime symptoms such as fatigue and morning stiffness, have been reported in >75% of patients with FM, and the prevalence of awakenings and non-restorative sleep is greater than reported in RA [3]. In several studies, the musculoskeletal symptoms and number of tender points were strongly associated with the non-restorative sleep pattern [13]. An altered chronobiological distribution in symptoms was reported in patients with FM [4] and, correspondingly, a change in the normal diurnal rhythm of cortisol has also been reported [14]. Serotonin metabolism in the central nervous system seems to play a role in the regulation of NREM sleep, pain and affective states [15], and a possible link between sleep disturbances and low levels of brain serotonin has been suggested. Therefore, tryptophan, which is a serotonin precursor, may be important for the symptoms, and lower concentrations of tryptophan and metabolites have been found in the cerebrospinal fluid of patients with FM [16].

The sleep disturbances in FM have also been related to growth hormone secretion and lower levels of growth hormone-related peptide have been found in these patients. As most growth hormone is produced pulsatively mainly during slow-wave sleep (SWS = NREM3 + 4), disturbances of this sleep stage may result in decreased secretion of growth hormone. Although fragmented sleep and other sleep disturbances may theoretically disturb nocturnal hormone secretion, the role of neurotransmitter balance and neuroendocrine axis aberrations in FM is still unclear and the subject awaits further studies.

Different studies regarding sleep architecture in FM have been conducted since the first report by Moldofsky et al. [10]. Various criteria have been proposed for FM
during the last decades. Therefore, the patient materials cannot be regarded as absolutely homogeneous and comparisons must be interpreted with caution. For a review of the studies on sleep macrostructure, see ref. 3. Sleep efficiency was low in most reports with an increase in awakenings and NREM1. Disturbance of sleep physiology with an increase in periodic movements of the legs during sleep (PMLS) and the number of apnoeas was also seen in some studies, but only in selected patients. The major sleep abnormalities have been found in the microstructure, i.e. discrete EEG phenomena not included in the traditional staging of sleep. The alpha-EEG sleep anomaly was first described by Hauri and Hawkins [17], who used the term alpha–delta sleep to characterize a mixture of alpha (8–12 Hz) and delta (0.5–3.5 Hz) waves in a small group of psychiatric patients described as having ‘a general feeling of chronic somatic malaise and fatigue’. A similar sleep anomaly was described by Moldofsky et al. [10] in patients with FM. They described an excess of alpha-EEG not only confined to SWS (dominated by delta waves), but in all NREM stages. As the same researchers subsequently found that the alpha-EEG sleep anomaly, pain and fatigue could be produced experimentally in healthy subjects by selective disruption of stage NREM4, they concluded that the alpha-EEG anomaly during sleep may represent an internal arousal generator interfering with the normal restorative aspects of sleep. Most papers have found that the alpha-EEG sleep anomaly is a consistent feature in patients with FM (see [3] for a review). In one study, the amount of alpha-EEG was correlated to an overnight increase in pain and a decrease in energy [18]. Some studies provided evidence that the alpha-EEG sleep anomaly might lead to more vigilance and arousability during sleep, and the heightened state of perceptual sensitivity may partly explain the subjective complaints of unrefreshed sleep [19, 20].

Most studies on alpha-EEG have been based on visual and hence relatively subjective analysis of the EEG. Using spectral analysis, a quantitative measurement is provided for all existing frequency components, with a resolution only determined by the choice of the method for analysis [3]. Our studies based on frequency analysis basically confirmed the previous findings, as the patients had more alpha-EEG activity in stages NREM2–4 combined in all sleep cycles, and the variability of the alpha power was higher in the patient group [21].

The alpha-EEG anomaly is, however, not specific for patients with FM and it has been described in patients with RA, osteoarthritis and primary Sjögren’s syndrome. The anomaly has also been described in patients without rheumatic disorders, such as in various psychiatric diseases, post-infectious and post-traumatic patients with fatigue and pain, and patients suffering from the chronic fatigue syndrome [3]. The alpha-EEG was also seen in healthy subjects and insomniacs.

Although an excess of alpha-EEG is therefore not specific for FM, it may still be a sensitive marker for a non-restorative sleep pattern. Whether this anomaly represents (1) a primarily central arousal mechanism, (2) a sleep-maintaining process showing enhanced response in some diseases, or (3) reflects peripheral nociceptive stimuli, is still a matter of debate and possibly several mechanisms may play a role in the generation of this phenomenon in clinical settings.

Other frequency components than the alpha band are relevant with respect to the sleep structure and continuity. Power in the lowest frequency range, which probably represents an intensity parameter in the description of the sleep process, may especially be important [3]. We have shown that patients with FM had less power in the two lowest frequency bands [22, 23]. As the low-frequency EEG in NREM sleep may be the best marker for sleep homeostasis, the decrease in the low-frequency components might reflect disturbances of the normal restorative processes during sleep which may probably contribute to some of the daytime symptoms in FM.

As in other patients with rheumatic disorders, sleep problems are frequent in RA. The prevalence of sleep disturbances was 54–70% in most studies. In several papers, pain was reported to be associated with sleep problems [24], but disease activity per se may theoretically be a common factor for eliciting both pain and sleep disturbances, due, for example, to the release of cytokines affecting many neurobiological factors. Sleep disturbances induced by the disease may themselves decrease the pain threshold and, finally, medication may influence the sleep structure. The relationships are, therefore, rather complex.

The polysomnographic studies in RA are not as frequent as those in FM, but generally sleep architecture was found to be normal in most studies (for a review, see ref. 3). However, abnormal sleep physiology was frequently reported with fragmented sleep and an increase in primary sleep disorders. Accordingly, a high prevalence of PMLS was seen in most studies and this may influence the sleep continuity and thus daytime symptoms.

In microstructure, the alpha-EEG sleep anomaly was also found to be frequent in RA, but otherwise no alterations were seen in the different frequency components [24]. Some authors have suggested differentiating between the physiological, transient alpha pattern in RA, which in some reports was associated with arousals, and the more static alpha-EEG seen in FM. Therefore, sleep microstructure disturbances are probably more characteristic in FM than in RA. Hypothetically, this may be related to different pain mechanisms in the two diseases. Thus, RA patients may have nociceptive inputs predominantly from peripheral tissue. As the joints are seldom moved at night, this probably results in only minor interference with sleep structure. On the contrary, the pain in FM may be of a more central origin [16], and reflected mainly in static sleep microstructure abnormalities.

Some studies have found a relationship between sleep parameters and disease activity in RA. We used a graphical chain model for the multivariate statistics, this being appropriate in the evaluation of the complex
correlations between the variables [24]. Although the relationships between disease activity parameters and sleep variables were somewhat complex, an association between pain scores and morning stiffness on the one hand, and time spent awake and in stages NREM2, REM and SWS on the other, was found. Such findings may improve our knowledge of the disease process and possibly contribute to the development of supplementary treatment alternatives in RA.

Sleep problems have also been reported in other rheumatic disorders and were found in patients with systemic lupus erythematosus, primary Sjögren's syndrome, osteoarthritis, low back pain and ankylosing spondylitis [3]. Disturbances of sleep, however, seem to be common in most diseases with pain as a dominant complaint and are frequent in, for example, coronary heart disease and in patients suffering from headache, duodenal ulcer disease, oesophagitis and non-specific chronic pain.

Experimental studies have shown that sleep deprivation causes sleepiness, fatigue, negative mood and impaired intellectual functions [25]. Agnew et al. [26] conducted one of the first selective NREM4 deprivation studies, resulting in the subjects becoming physically uncomfortable with changes in bodily feeling. These results were reproduced by Moldofsky et al. [10], who deprived six healthy subjects of NREM4 sleep. The subjects displayed increasing morning tenderness during the three nights and, coincidentally, they complained of musculoskeletal aching, stiffness, generalized heaviness and unusual somatic fatigue, symptoms which subsided over the following recovery nights. It was concluded that the alpha-EEG induction, together with a decrease in NREM4 sleep, was able to induce FM-like symptoms in healthy subjects. In subsequent studies, however, the musculoskeletal symptoms following SWS deprivation could not be reproduced ([27, 28], A. M. Drewes et al., 1999, unpublished) and it is up to future studies to address these very important aspects.

Several physiological and psychological factors with the potential to influence sleep exist in rheumatic diseases, and the EEG findings described above may not necessarily be related to pain. However, experimental studies, where different pain stimuli were given during sleep in healthy subjects, resulted in EEG alterations comparable to those seen in the patient groups [29], thus confirming the importance of the different EEG phenomena as markers of pain in rheumatic patients.

As sleep disturbances are frequent in medical diseases, the treatment must often focus on the nightly complaints. Although the treatment at night may be directed against e.g. stiffness and arousals related to cognitive and psychiatric components of the disease, nightly medication is frequently prescribed for pain and/or sleep complaints. The diurnal distribution of analgesics is unknown, but the consumption of hypnotics is probably high in patients with pain, and in rheumatic diseases 15–70% regularly took these drugs [30–32]. The treatment of pain during the night and sleep problems have many aspects. Obviously, pain relief is a major treatment goal, but also treatment of restless sleep has been shown to enhance the quality of life in patients with chronic illness [33]. For treatment of pain, simple analgesics are often prescribed. Acetaminophen, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are among other factors known to inhibit prostaglandin synthesis in the central nervous system, and therefore they may interact with body temperature and sleep/wake functions, for example. In healthy subjects, acetaminophen may not alter sleep structure, whereas aspirin and NSAIDs probably have more negative effects [3]. In patient groups, results may be different and, in RA, NSAIDs do not seem to give objective sleep changes, whereas subjective feeling of sleep may improve [34]. During amitriptyline and opiate treatment, a negative sleep profile may be induced, which can limit the use of these drugs in patients with pain [3].

As sleep problems are frequently reported in patients with pain, treatment with hypnotics may also be of value. Furthermore, as sleep disturbances may theoretically have a negative impact on homeostatic aspects and lead to a decrease in the pain threshold, a pharmacological modulation of sleep continuity may be a therapeutic supplement, also with respect to daytime symptoms. Third-generation hypnotics may be of some value in patients with FM [35, 36], as improvement in sleep and daytime energy are crucial to these patients. Pain, however, was not affected and additional treatment must frequently be recommended. In RA, daytime sleepiness, morning stiffness and sleep score were improved in one study following treatment with a hypnotic [37], whereas we were only able to confirm the effect on the subjective assessment of sleep [38]. Medication supposed to have more selective receptor subtype specificity or experimental substances may turn out to be useful in future studies. It should be stressed, however, that ordinary sleep hygiene arrangements, such as an undisturbed room with pleasant humidity and temperature, often may improve sleep sufficiently.

In summary, evidence for an intimate relationship between different sleep parameters and physiological, hormonal and immunological functions exists, and correspondingly sleep disturbances may be related to morbidity and influence the outcome in medical illness. Sleep problems are frequent in rheumatic diseases and epidemiological as well as clinical studies have given support for a strong association between pain and sleep disturbances. Most studies have included patients with FM and RA, but sleep fragmentation and disturbances of sleep structure may also aggravate the pain in other patient groups and contribute to the daytime symptoms. The clinician should be aware of these interactions, as treatment of the nightly complaints may also improve the daytime symptoms.

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