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CNS SPECTRUMS The International Journal of Neuropsychiatric Medicine

The Significance, Assessment, and Management of Nonrestorative Sleep in Fibromyalgia Syndrome

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Needs Assessment: More than 90% of patients with fibromyalgia syndrome (FMS) describe poor quality of sleep in which sleep is perceived to be light and unrefreshing. Patients with FMS often experience restlessness with kicking and involuntary leg movements, or have a sleep-related breathing disorder such as loud snoring and interruptions to breathing. It is important for clinicians to recognize the relationship between nonrestorative sleep and the pain, fatigue, and cognitive and emotional symptoms experienced by patients with FMS.

Learning Objectives:

- Explain the relationship between nonrestorative sleep and the often perplexing features of fibromyalgia syndrome (FMS), such as myalgia and tender points.
- Identify some methods of assessing nonrestorative sleep in FMS.

Target Audience: Primary care physicians and psychiatrists.

CME Accreditation Statement: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: February 15, 2008. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

To receive credit for this activity: Read the five articles in this supplement, reflect on the information presented, and then complete the CME posttest and evaluation. To obtain credits, you should score 70% or better. Early submission of this posttest is encouraged. Please submit this posttest by March 1, 2010, to be eligible for credit. The estimated time to complete all five articles and the posttest is 4 hours. Release date: March 1, 2008. Termination date: March 31, 2010.

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Abstract

People with fibromyalgia syndrome (FMS) experience unrefreshing sleep, aches, hypersensitivity, and cognitive and emotional difficulties. Although no specific causative factor or biological agent is known to account for all of the features of FMS and these related diagnoses, the generalized hypersensitivity of the body is considered to be affected by disturbances in central nervous system (CNS) functions. Such CNS disturbances are intrinsic

to the sleeping-waking brain, where the common symptom elements in all these illnesses are poor quality of sleep, nonspecific pain, fatigue, and psychological distress in the absence of known disease pathology.

Introduction

People with fibromyalgia syndrome (FMS) typically complain of unrefreshing sleep, generalized aching in their bodies, and fatigue that interfere with their day-to-day functioning. They describe hypersensitivity to various noxious tactile, environmental, and food stimuli, as well as cognitive and emotional difficulties including anxiety and depression. Such symptoms are common in medical practice where they may be found in patients with a variety of perplexing painful syndromes where no specific physical pathology can be identified. These syndromes attract diagnostic labels that reflect the beliefs and specialized interests of various medical disciplines. For psychiatrists, these symptoms may be considered aspects of a somatoform pain disorder or an underlying major depressive disorder. For infectious disease specialists, they may be associated with the label chronic fatigue syndrome (CFS). For rheumatologists, such patients, who were initially diagnosed with fibrositis, are now considered to have fibromyalgia because there is no inflammatory connective disease pathology. Indeed, patients with FMS are more likely than controls to meet lifetime symptom and diagnostic criteria for these and other diagnostic labels, eg, irritable bowel syndrome or temporomandibular joint pain disorder.[1] Although no specific causative factor or biological agent is known to account for all the features of FMS and these related diagnoses, the generalized hypersensitivity of the body is considered to be affected by disturbances in central nervous system (CNS) functions. Such CNS disturbances are intrinsic to the sleeping-waking brain where the common symptom elements in all these illnesses are poor quality of sleep, nonspecific pain, fatigue, and psychological distress in the absence of known disease pathology.

More than 90% of patients with FMS, most of whom are women, describe poor quality of sleep. Irrespective of its duration, the sleep is often perceived to be light and unrefreshing. The patient may be aware of restlessness with kicking and involuntary leg movements, or may have a sleep-related breathing disorder such as loud snoring and interruptions to breathing. On the rare occasion that sleep is restful, there is substantial improvement in daytime symptoms. Indeed, unrefreshing or nonrestorative sleep are correlated to the myalgia and tender points in FMS.[2]

Because all the physiological functions of the body are intimately linked to the sleeping/waking brain it would be expected that the perturbations of certain neurotransmitter and neuroendocrine functions that are linked to the sleep/wake functions would contribute to physiologic and behavioral hypersensitivities that occur in people with FMS and its comorbid clinical conditions. In particular, evidence for deregulation of the pituitary-adrenal neuroendocrine axis and autonomic functions have been identified.[3] Increased overnight sympathetic activity is consistent with the notion of autonomic neurotransmitter dysfunction during the sleep of patients with fibromyalgia.[4]

This article defines nonrestorative sleep and summarizes the epidemiological, clinical, and experimental evidence that show how such perturbations of the sleeping-waking brain are core to the understanding and management of the unrefreshing sleep, variable diffuse myalgia, fatigue, and psychological distress of patients with FMS.

What is Nonrestorative Sleep?

Unrefreshing or nonrestorative sleep differs from insomnia. Whereas insomnia, characterized as difficulties in falling and/or staying asleep, can be assessed using standard quantitative behavioral and sleep electroencephalogram (EEG) measures, nonrestorative sleep is essentially a qualitative phenomenon that has characteristic sleep and waking symptoms. Whether sleep is refreshing or not is not dependent on how long we sleep or when we sleep. For example, a brief daytime "power nap" may be refreshing and energizing. An 8-hour undisturbed overnight sleep may feel exhausting, as though one has not slept all night. These qualitative sleep symptoms of nonrestorative sleep include a feeling that sleep is light or superficial. Upon awakening in the morning there is a lack of feeling refreshed with stiffness and perhaps overall aching. There is variable physical and mental fatigue, hypersensitivity to noxious environmental and bodily stimuli, dysphoria, and symptoms of autonomic disturbances.

Implications of Nonrestorative Sleep to Fibromyalgia syndrome and Comorbid Conditions

The epidemiological studies show that nonrestorative sleep is a key component of FMS and related disorders. As in people with FMS, unrefreshing sleep is the most prevalent of the eight CFS case-defining symptoms, being endorsed by 88% to 95% of cases identified in population-based studies and 70% to 80% of cases in clinic-based studies.[5] In FMS, unrefreshing sleep is accompanied by increased tenderness or no overnight improvement in pain and well-being.[6] Furthermore, patients with FMS, CFS, and temporomandibular joint disorder report cognitive and performance impairments that relate to the chronic sleep disturbance. The pain and fatigue tend to decline from mid-morning to mid-afternoon so that after 3 pm patients commonly complain of feeling profoundly mentally and physically exhausted to the point where they are unable to think properly or carry out any meaningful tasks. They do not perceive that they actually slow down in performing a cognitive task.7 When they go to bed at night they feel no better than when they wake up the following morning. Overall, the disturbances in sleep physiology contribute to poor quality of sleep and a vicious cycle of unrefreshing sleep, morning aching, stiffness, and fatigue.

The Significance of the Sleeping-Waking Brain to Musculoskeletal Pain and Fatigue

Animal Studies

Nociception and Sleep Physiology

Both animal and human studies have demonstrated the specificity of abnormal sleep to the development of pain and fatigue. The animal studies show that sleep deprivation, ie, rapid eye movement (REM) sleep deprivation, promotes increase in pain sensitivities and behavior.[8]

Central Nervous System Neurotransmitters, Pain, and Sleep Physiology

Recent research suggests that specific neurotransmitter functions influence CNS hypersensitivity that alters sleep and promotes pain. In particular, inhibition of CNS serotonin (5-HT) synthesis by p-chlorophenylalanine induces insomnia and a hyperalgesic state in animals and humans.[9] Furthermore, high levels of CSF substance P (SP) are known to occur in FMS. Andersen and colleagues[10] hypothesized that the SP operating through a neurokinin pathway would influence nociception and sleep. Whereas neurokinins have been implicated in modulating pain and mood, little is known about their effect on sleep/wake behavior. Intracerebral ventricular administration of SP in sufficient quantities that did not induce nociceptive response in mice was sufficient to reduce their sleep efficiency, increasing latency to onset to sleep and provoking awakenings from sleep. A neurokinin-1 (NK1) receptor antagonist reversed the interfering effect upon sleep by SP. This study demonstrates that blocking the SP-induced insomnia by prior treatment of the rats with NK1 receptor antagonist provides support for the arousing effect of SP on the sleeping-waking brain. This research provides an animal model for studying sleep disturbances and pain in FMS. Furthermore, this model could be employed to determine the interrelationship of CNS 5-HT and SP with the hypothesis that 5-HT deficiency results in increased levels of SP in the CNS, leading to sensitivity to sensory stimuli and sleep disturbances. If such experiments support this hypothesis then there would be a rationale to reducing nonrestorative sleep and hypersensitivity with specific drugs that augment CNS 5-HT and inhibit aspects of SP metabolism.

Human Studies

In human subjects the type of experimental pain stimulus during sleep affects the features in the sleep EEG and the stages of sleep.[11] For example, muscle stimuli when applied during sleep cause a decrease in delta (0.5–3.5 Hz) and sigma (12–14 Hz) and increases in α_1 (8–10 Hz) and β (14.5–25 Hz) brain wave frequencies. During joint pain stimulation the delta, theta (3.—8 Hz), and α_1 EEG frequency bands in sleep are decreased. The higher EEG frequencies [α_2 (10–12 Hz), sigma and b bands] are increased. Cutaneous stimuli do not affect the background EEG. Sleepiness does not modulate experimental joint pain. Another experimental study employed to determine whether specific stages in (EEG) sleep are affected by pain showed that all stages of sleep are disrupted by noxious stimulation of muscles and that

quality of sleep was impaired.[12]

As expected, painful stimuli during sleep interfere with sleep physiological functions. However, the converse is also true. The experimental introduction of noise during specific stages of sleep in the early 1970s by Moldofsky and Scarisbrick[13] showed that the disruption of stage 4 non-REM in normal sedentary people by noise stimuli resulted in complaints of unrefreshing sleep, variable aching, and fatigue. Furthermore, they showed increased sensitivity to the application of a pressure gauge to specific anatomical regions that had been identified in FMS patients. Other researchers have confirmed that disruption of slow wave sleep (SWS) produces a generalized hyperalgesic state.[14] In another study looking at a night of either REM or SWS deprivation as well as a night of recovery, both REM and SWS deprivation reduced pressure pain tolerance thresholds. An increase in SWS on the recovery night is associated with an increase in pain tolerance threshold. While sleep deprivation has a specific effect on inducing a hyperalgesic state it does not alter somatosensory functions.[15] Furthermore, as shown in animal studies of REM deprivation, the loss of 4 hours of sleep, which interferes with emergence of REM sleep in humans, induces a hyperalgesic state on the following day.[16] Four hours of sleep versus 8 hours of sleep over 12 consecutive nights causes a 15% reduction in psychosocial behavior and a 3% increase in generalized body pain, back pain, and stomach pain. The fragmentation of SWS appears to interfere with nervous system inhibition of noxious stimuli causing pain as well as increased sensitivity to various nonpainful stimuli, eg, bright light, loud sounds, and strong odors.[17]

Behavioral Measurement of Nonrestorative Sleep in Fibromyalgia syndrome and Related Conditions

The 17-item Sleep Assessment Questionnaire (SAQ©) is a simple easily employed computerized self-rating questionnaire that comprises six factors for determining sleep pathologies. The questionnaire has excellent specificity and sensitivity for assessing FMS and population. The SAQ© showed significantly increased risk of abnormal scores in the nonrestorative sleep (adjusted odds ratio [OR]=28.1; 95% confidence interval [CI], 7.4-107.0), and restlessness factors (OR=16.0; 95% CI, 4.2-61.6) in CFS compared to non-fatigued people. There was no particular increase in prevalence of factor scores for sleep apnea or excessive daytime somnolence.[5]

The Sleep Laboratory Assessment of Nonrestorative Sleep in Fibromyalgia

syndrome

Sleep laboratory assessment typically shows disordered sleep physiology in FMS. Most people with FMS have an arousal disturbance in their sleep EEG, known as the a (7.5–11 Hz) EEG sleep arousal disorder. In 1975, Moldofsky and colleagues6 described an a (7.5–11 Hz) EEG non-REM sleep anomaly in patients with fibrositis (FMS).[6] They proposed that the a EEG sleep anomaly is related to the unrefreshing sleep, diffuse myalgia, and numerous localized areas of tenderness in specific anatomic areas and mood symptoms.[6] Since then, others have reported on the computerized analyses of the a EEG non-REM sleep disorder in patients with FMS.[14] The frequency analyses of the sleep EEG show three varieties of a EEG sleep: phasic (50% of patients versus 7% normals), tonic (20% of patients versus 9% of normals), and low a in 30% of patients versus 84% of normals.[18] Those with the phasic pattern of the a intrusion in SWS are more likely to have increased post-sleep tenderness and subjective pain, poor sleep efficiency, and less SWS than the other groups. Furthermore, morning stiffness, diffuse pain, and discomfort after awakening commonly occur in FMS patients with phasic a sleep. Although a cause-effect relationship between pain and sleep cannot be established, the data suggest that the phasic a sleep pattern is associated with longer duration of pain symptoms, perception of poor sleep, and morning pain. The finding of the a EEG sleep anomaly in children and their mothers suggests the possibility of a familial or genetic influence in the pathogenesis of the disorder.

Some patients with FMS have fragmented sleep as a result of sleep-related periodic, involuntary, and arousal disturbances that occur over the course of the night. These periodic sleep-related disturbances include restless legs and involuntary periodic limb movements, sleep apnea, and an underlying periodic arousal disturbance in the sleep EEG known as sleep-related periodic K-alpha or frequent cyclic alternating EEG sleep pattern (CAP).[14] In this high frequency CAP sleep disorder that occurs in frequent sequences of 20–30 seconds, the typical EEG K-complexes of stage 2 non-REM sleep are not followed by sleep spindles as occurs normally, hence the finding of a lower frequency of sleep spindles.[14] This periodic CNS arousal disturbance in the sleep EEG is accompanied by less efficient sleep, unrefreshing sleep, and is correlated to the severity of clinical symptoms in FMS patients.[19]

Topographical EEG localization known as low-resolution electromagnetic tomography (LORETA) shows maximum increase in electrical current densities of the delta and theta sleep EEG frequencies of CAP in the medial frontal and middle temporal gyri in FMS patients.[14] Such localized functional sleep-related EEG changes are consistent with the findings of a variety of brain-imaging techniques for localizing pain perception in FMS.

The specificity of these periodic EEG phenomena for FMS and related disorders remain to be properly studied. Although the tonic a EEG sleep and attenuated CAP may be found in non-complaining people, we do not know whether magnification of these EEG sleep disturbances may predispose to the emergence of FMS/CFS symptoms. One hypothesis that requires consideration is whether a specific noxious event or agent may alter CNS functions where these EEG sleep arousal phenomena emerge to become a feature of the final common neurophysiologic pathway of CNS hypersensitivity and the hyperalgesic state. Various noxious

events have been considered. For example, the a EEG sleep disorder is found in FMS patients who report the onset of symptoms following a psychologically traumatic event such as a non-physically injurious motor vehicle or industrial accident. Some FMS/CFS patients with similar sleep disturbances claim to have the onset of symptoms following a febrile event, but no specific infectious agent has been identified.[14] Yet many FMS and CFS patients do not report any specific event that heralds the onset of symptoms. This lack of clear evidence for a specific triggering etiological agent has lead to the hypothesis that there may be a combined genetic and environmental predisposition to these syndromes where specific genes may be activated, thus affecting sleep disturbances that are involved in the evolution of these syndromes.[20]

Drugs, Sleep, and Fibromyalgia Syndrome

While improvement in the quality of sleep is associated with improvement in the symptoms of fibromyalgia, as yet no specific treatment has been shown to have long-lasting remedial benefits. Most studies are short term. They may be reported to be beneficial for the self-ratings of sleep and pain symptoms in a small proportion of the patients who complete the studies or who can tolerate the treatments. The treatments include behavioral measures, eg, cognitive-behavioral therapy, hypnotherapy, electromyographic biofeedback methods, exercise, acupuncture, and various analgesic-anti-inflammatory medications. Tricyclic drugs, eg, cyclobenzaprine and amitriptyline, have not been shown to alter a non-REM sleep. 5-hydroxytryptophan, a direct precursor of brain serotonin, tends to improve pain and sleep quality, although its effect on the sleep physiology of patients with FMS is unknown. Gabapentin, pregabalin, and carbamazepine, which were originally classified as anticonvulsants, also have sedative properties and antinociceptive effects. Pregabalin, which is an α_2-delta ligand that causes increased cellular expression of calcium channels, reduces the expression of SP and noradrenaline. Recent large-scale controlled studies show that this drug improves the pain, quality of sleep, and fatigue in FMS.[21] Serotonin noradrenaline reuptake inhibitors such as duloxetine and milnacipran, which are known to be helpful for pain in animal studies and possibly sleep, benefit many of the symptoms of FMS[22] but have not been studied to determine their effects on EEG sleep in FMS. The dopamine agonist pramipexole is claimed to be helpful for pain, fatigue, and overall function in a subset of FMS patients.[23] γ-hydroxybutyrate or sodium oxybate reduces a EEG sleep, increases SWS, improves the quality of sleep, and reduces pain and fatigue in FMS patients.[24] If confirmed in large-scale studies, such findings are consistent with the importance of the sleeping /waking brain in the pathogenesis and management of the syndrome.

Conclusion

Clinical, animal, and human experimental evidence indicate that there is an interrelationship of widespread musculoskeletal pain, chronic fatigue, and sleep disturbances in FMS and allied pain syndromes. Diagnostic instruments that assess EEG sleep and ratings of abnormalities in waking behavior enable the assessment and management of patients with such illnesses.

Novel medications that affect CNS neurotransmitter functions, which influence sleep, pain, and mood symptoms, are beneficial in the management of the symptoms of FMS.

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