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Review Article

Sleep and Menopause: Review

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Abbreviations: MHT: Hormone Replacement Therapy; ICSD: International Classification of Sleep Disorders; RF: Risk Factors; AIS: Athens Insomnia Scale; PSQI: Pittsburgh Sleep Quality Index; MRS: Menopause Rating Scale; SL: Sleep Latency; SWS: Slow Wave Sleep; PSG: Polysomnography

Introduction

Objectives

a. To recognize sleep characteristics and their classification

b. To assess the prevalence and type of sleep disturbances most frequent in this stage of life

c. To evaluate the relationship between sleep disturbances and vasomotor symptoms and the role of hormone replacement therapy of menopause (MHT) plays in preventing them.

Sleep Characteristics and Classification of Sleep Disturbances

Sleep consists of REM and non-REM (rapid eye movement) periods that happen cyclically. Each one lasts between 90 to 120 minutes, and in one night there are approximately 4 to 6 cycles. During the first half of the night, non-REM cycles predominate, which are related to physical and mental restitution. On the contrary, in the second half of the night, REM cycles predominate, which participate in mental and emotional functions, including memory [1].

According to ICSD-3 (International Classification of Sleep Disorders), sleep disturbances are classified as it shows on Figure 1 [2]. Insomnia is, by far, the most frequent condition, and this disorder includes any disorder in the conciliation or maintenance of sleep that produces diurnal disorders. Within respiratory disorders, there is the sleep apnea, which is defined as repeated episodes of collapse of the upper airway during sleep. This results in sleep quality deterioration due to intermittent hypoxemia, decreased REM sleep and slow wave sleep, which is important for memory. Affected patients complain of daytime sleepiness, insomnia and numerous of other symptoms (snoring, gasping, choking, memory impairment) leading to an impaired quality of life. The risk factors (RF) for its development are age, male sex and the presence of android obesity. Postmenopausal women present 2.6 to 3.5 times more risk than premenopausal women to present it. Physiological factors explaining this increased prevalence include weight gain, fat distribution changes due to increased testosterone production and a decreased level of circulating female gonadal hormones. Without treatment, it constitutes an independent RF for the development of hypertension, cardiovascular disease, arrhythmia, stroke and therefore an increase in mortality [3]. And finally, less frequent disorders such as narcolepsy (within the group of hypersomnia), parasomnias (REM / non-REM) or restless legs syndrome (within movement disorders).

- Insomnia
- Respiratory disorders related to sleep
- Disorders related to hypersomnia of central origin
- Circadian rhythm disorders
- Parasomnias
- Movement disorders related to sleep
- Other sleep disorders

Figure 1: Classification of sleep disorders according to ICSD-3 (International Classification of Sleep Disorders) [2].

Prevalence of Sleep Disorders in the Peri and Post menopause

Regarding the prevalence of sleep disorders during the transition to menopause and post menopause, the large studies

showed an increase in it, specifically in this period of life. The WHI study showed a prevalence of 54% in the group of women aged 45-59 years [4], while the SWAN study, which included women between 40-55 years, 38% [5]. Another large Japanese study, which included more than 1400 women, demonstrated a prevalence like the WHI: 50.8% insomnia in peri and postmenopausal women [6]. Regarding the scientific evidence in Latin American women, a study that included 6079 women between 40 and 59 years old from 11 countries of Latin America was carried out [7], whose objective was to determine the prevalence of sleep disturbances in middle-aged women using validated scales. The questionnaires included were the Athens Insomnia Scale (AIS), a self-filling questionnaire to assess sleep disorders, the Pittsburgh Sleep Quality Index (PSQI), another self-filling questionnaire that evaluates the quality of sleep in the last 4 weeks, the Menopause Rating Scale (MRS), a questionnaire that identifies the frequency and intensity of climacteric symptoms divided into 3 domains, Goldberg Anxiety and Depression Scale and Brief Scale of Abnormal Drinking, to rule out anxiety or depression and inadequate alcohol consumption, respectively. In that study, they found that 56.6% of women had some type of sleep disturbance (insomnia, poor sleep quality or both). The prevalence of Insomnia increased 39.7% in the group of younger women (40-44 years) to 45.2% in the group of postmenopausal women (55-59 years) with a significant difference between both groups (p=0.009). Regarding sleep quality, the prevalence of poor sleep quality increased from 40.3% in the first group to 49.3% in the second, with an also significant difference (p=0.0001).

Regarding the scales, the AIS presented an increase in the total postmenopausal score from 4.90 to 5.81 (p=0.0001) and of all the individual items, with nighttime awakening being the highest score and difficulty in induction of sleep the greatest increase (32.8%) in postmenopausal women. Regarding the PSQI, an increase in the total postmenopausal score from 4.28 to 5.30 was also observed (p=0.0001), with the drowsiness item having a peak in peri and early post menopause. In postmenopausal women, the item "medication requirement" (increased by 55.9%) and "sleep latency" (increased by 25.3%) increased significantly.

Mechanisms associated with Climacteric Sleep Changes

During menopause, there are changes in 4 different neurotransmitter systems, such as the GABAergic, serotonergic (5HT), noradrenergic (NA) and dopaminergic (DA) systems. Both NA and DA are involved in sleep regulation. Estrogen-dependent changes in serotonin during the transition to menopause may be responsible for changes in sleep, mood and memory. In fact, experimental models confirm that the depletion of 5HT levels in the brain causes insomnia [8]. The impact of hormonal depletion in sleep is demonstrated in clinical studies. In a study conducted in Pennsylvania [9], 1324 healthy volunteers without sleep complaints who spent a night in the sleep laboratory were included. Among other parameters, the total sleep time (as a percentage of bed time, % ST) was evaluated. They observed that in men there was a linear reduction of % ST with age; On the contrary, in women there was a non-significant decrease of % ST with age in women under 50 followed by a significant decrease in those over 50 years.

What is the Relationship between sleep disturbances and vasomotor symptoms?

For a long time was discussed whether if hot flashes disturb sleep, or if there is a sleep disturbance during post menopause, with more frequent awakenings, after which the hot flashes occur. The order of this sequence is related to the type of sleep cycle. REM sleep suppresses thermoregulatory responses; therefore, during the first part of the night, the sequence is hot flash and the awakening afterwards (due to the predominance of non-REM cycles). On the other hand, during the second part, the sequence is in the reverse order (awakening and then suffocation). On the Latin American study previously mentioned, a directly relationship was observed between intensity of hot flushes (item 1 of MRS), AIS and PSQI score. Regarding the rest of climacteric symptoms, a directly relationship was found between total MRS score, insomnia prevalence and poor sleep quality [7].

Sleep and Menopause: Our Experience

MHT: What role does it play?

Although the climacteric symptoms are not the unique cause of sleep disorders in the peri and post menopause period, the MHT in symptomatic women could contribute to improve the sleep quality. In the Pennsylvania study previously mentioned [9], differences were observed in some sleep parameters such as sleep latency (SL) and slow wave sleep (SWS), which constitutes a non-REM sleep phase and is related to memory. The lower SL and the greater SWS, the better is the sleep quality. In this study we found a higher SL and decreased SWS in the group of postmenopausal women without MHT compared to postmenopausal women with MHT and men. SL in postmenopausal women without MHT was 42.1±2.5 min compared with men (P=0.017) and postmenopausal women with MHT (P=0.002). With respect to SWS, postmenopausal women with MHT presented SWS significantly more than men (5.3±0.5% versus 1.1±0.3%, P<0.001), as did postmenopausal women without MHT (3.9±0.4%, P<0.001), although women without MHT had fewer SWS than those with MHT (P=0.049). NAMS (North American Menopause Society) position regarding MHT and sleep disturbances, a review of the literature in 2015 reported that low doses of estrogen or progesterone could improve chronic insomnia in postmenopausal women. At the same time, orally administered progesterone has mild sedative effects, reducing nocturnal awakenings without affecting daily cognitive functions, possibly through a GABA agonist effect.

Progesterone micronized at a dose of 300 mg per night significantly decreases vasomotor symptoms (including daytime and nighttime hot flashes) and thus, adding its sedative effect, improves sleep quality [10]. Therefore, we conclude that MHT

improves the subjective and objective quality of sleep, reducing the frequency of night awakenings and sleep latency time and an increasing the proportion of slow wave sleep, especially in women with vasomotor symptoms.

What about Non-Hormonal Therapy?

Any therapy that improves hot flashes could have a positive impact on the sleep quality. A Cochrane meta-analysis, which included 43 controlled and randomized clinical trials (RCTs), and 4363 participants in total, demonstrated that isoflavones would have benefit in postmenopausal women with sleep disturbances [11]. Another RCT evaluated the sleep complaint in postmenopausal women with insomnia (subjective component) and polysomnography (PSG) (objective component). One group was assigned 80 mg daily of isoflavones and another group placebo for 4 months. Regarding the sleep complaint, it decreased from 90% to 37% in the treatment arm vs 95% to 63% in the placebo arm; on the other hand, regarding PSG parameters, an improvement in sleep efficiency of 78-84% was observed in the treatment arm vs 78-81% in the placebo arm [12].

Conclusion

Although MHT would seem to have a beneficial effect on subjective and objective sleep parameters in peri and post menopause women, its overall impact should be more extensively studied. The precise role of isoflavones and other non-hormonal treatments in sleep disturbances in this period should be established. Based on the available evidence, MHT and non-hormonal therapy are not recommended as a treatment for sleep disturbances in peri and post menopause period as an isolated symptom.

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