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Review Article

Update of sleep alterations in depression

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ABSTRACT

Sleep disturbances in depression are up to 70%. Patients frequently have difficulty in falling asleep, frequent awakenings during the night and non-restorative sleep. Sleep abnormalities in depression are mainly characterized by increased rapid eye movement (REM) sleep and reduced slow wave sleep. Among the mechanisms of sleep disturbances in depression are hyperactivation of the hypothalamic-pituitary-adrenal axis, CLOCK gene polymorphism and primary sleep disorders. The habenula is a structure regulating the activities of monoaminergic neurons in the brain. The hyperactivation of the habenula has also been implicated, together with sleep disturbances, in depression. The presence of depression in primary sleep disorders is common. Sleep disturbances treatment include pharmacotherapy or Cognitive Behavioral Therapy.

1. History

Sleep is classified into 2 phases: sleep without rapid eye movement (NREM) and sleep with REM [1,2]. REM sleep is initiated when noradrenergic and serotonergic activities are decreased while cholinergic activity increases [3].

Sleep alterations are common among patients with major depression (MD) and form part of the diagnostic criteria for this disease. Patients with MD frequently demonstrate difficulty in initiating sleep, frequent awakenings during the night, earlier than desired awakenings and nonrestorative sleep [4–6]. Other main symptoms are decreased total sleep and disturbing nightmares [7].

Several epidemiological studies demonstrated that patients with MD have increased frequency of sleep abnormalities and these continue even during periods of remission, being more common in divorced patients and with higher scores for the anxiety subscale of the hospital anxiety and depression scale [8]. On the other hand, patients with persistent insomnia but without depression show a higher risk of developing MD than in normal sleepers [9].

2. Biological mechanisms for the sleep alterations in MD

To explain the sleep abnormalities in MD, there are several biological models, among them some for the study of neuroendocrinal factors, irregularities in the circadian genes and functional, neuroanatomical neuroimaging studies. The

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neuroendocrinal factors may have an important role on sleep abnormalities of MD, such as the corticotropin-releasing hormone (CRH), adrenocorticotropin and cortisol [10,11].

In relation to cortisol and adrenocorticotropin hormones are concerned, the elevated levels are observed mainly during the night; they are markers of acute episodes of MD [12]. Some have observed endocrinal alterations that are characteristic of MD (decrease of slow wave sleep and increase of cortisol) in young individuals after the administration of CRH [13]. Therefore, an analysis has revealed that children classified as "poor" sleepers did show an increase in cortisol during the morning, compared with children that were normal sleepers [14].

Elevated cortisol levels, under conditions of stress, have been associated with an increased number of intermittent awakenings and increases time in phases N1 and N2 [14]. Furthermore, some psychological difficulties such as anxiety, impulsiveness and social inhibition, which are common findings in MD, are usually related with a decrease in sleep efficiency [14].These data strengthen themselves since with the use of CRH antagonist, R121919, in depressed patients, there is an increase in the slow wave sleep. This suggests that the antagonism of the corticotrophin-releasing hormone normalizes sleep in patients with depression [15].

The intimate relationship between insomnia and depression could also be determined at a genetic level in the control of biological rhythms. Circadian rhythms are controlled by a synchronizer localized at the suprachiasmatic nucleus (SQN) in the anterior hypothalamus. Among the genes that interact with the SQN are the CLOCK genes which have an important influence upon the sleep pattern. Some studies have indicated that patients with MD have a variant in the polymorphism of the CLOCK genes (they have the C alleles) [16], and therefore suffer from initial insomnia, which becomes acute during the antidepressant treatment, as compared with patients who do not possess this specific variant [17,18]. Other genes implicated with MD as well as insomnia are the polymorphisms of the monoamino-oxidase A gen and the promoter of the serotonin transporter gene, the latter being correlated with an insomnia of higher severity [19], as well as citalopram side effects, an antidepressant [20].

Studies in rats have described other time marker genes, being highlighted as the gen miRNAs-182, which codes the endogenous modulation of the circadian cycle. An association has been found between the delayed insomnia in patients with MD and the presence of an upper expression of the miRNAs-182 gene, due to the increase of its mutated form, expressed by the T allele of the polymorphism rs76481776, the gene pre-miR-182. This mutated form is immature and generates deregulation of the sleep–wake cycle due to the decrease of the blank sites of the mi RNAs-182 mature gene. This mechanism has been proposed as part of the causing effects of the sleep disorders in patients with MD, especially in the presence of late insomnia [21].

In healthy individuals, during No REM sleep, the metabolic activity decreases on the frontal, temporal and parietal cortices, in contrast with waking levels; individuals with MD do show a non-significant decrease in activity in the same areas of waking during the beginning of sleep. It is possible that this reduction may reflect a deficit in the processes related to sleep–wake cycle, present in MD as a decreased synaptic potentiation. Other brain areas involved in emotional regulation (anterior cingulate cortex, amygdala, thalamus) also had a smaller decline in metabolic level from waking to No REM sleep. Compared with normal individuals, these structures have an increase in metabolism during sleep. Depressed subjects can also present an increase in metabolic activity within these cortical and subcortical structures during REM sleep, due to the fact that these alterations reflect imbalance of the monoaminergic-cholinergic systems in MD [10,22].

The habenula consists of a pair of small adjacent nuclei to the medium dorsal thalamus. It is divided between medial and lateral portions [23].The lateral habenula (LHb) receives stimuli from several structures such as the internal segment of the globus pallidus. On the other hand, LHb stimulation inhibits the activity of serotonergic and dopaminergic neurons of the brain stem and this, in turn, stimulates the selective inhibitors of serotonin reuptake, which act upon the axon pre-synaptic terminals to suppress LHb hyperactivation. Dopamine has also an excitatory effect on the activity of LHb, upon which the chronic activation of the dopaminergic inputs of LHb contributes to the hyperactivation of the LHb in MD. Although during sleep, some studies demonstrated that the lesion in LHb reduces the REM sleep, due to the fact that the activity of the LHb neurons is indispensible for the maintenance of the REM sleep, this maintenance being obtained by means of the modulation of the serotonergic activity [24]. Considering the regulation of LHb in serotonergic system, it is reasonable to think that LHb is involved in the regulation of sleep and mood, since, in accordance with the obtained evidences, the hyperactivity of LHb causes heterogeneous symptoms such as reduced motor activity and alteration in REM sleep, which are typical of MD. [24].

3. Comorbidity of the primary sleep disorders and MD

Certain primary sleep disorders, such as obstructive sleep apnea (OSA) and restless legs syndrome (RLS), are more common in patients with MD than in the general population. OSA is defined by frequent episodes of partial (hypopnea) or complete (apnea) obstruction of the superior airway during sleep [25]. It is associated with MD in an odds ratio of 2.4 in men and 5.2 in women [26]. The high comorbidity of OSA with depression indicates that both disorders share a common neurobiological risk factor [27]. The former is demonstrated by studies of cerebral images which suggest that the hypoxemia from OSA has an impact on mood [28]. In addition, MD and OSA have been associated with metabolic syndrome.

It has been postulated that the reduction of serotonin levels in MD worsens the function of the superior airway dilating muscles, a factor that could contribute to OSA; however, this is not demonstrated properly since antidepressants do not improve OSA; besides, the first treatment option for this pathology is the continuous positive airway pressure (CPAP) [29].

As far as RLS is concerned, this is a neurological disorder characterized by an irresistible urgency in moving the legs,

especially during rest. This symptom worsens during the night and improves when walking [30].

In an additional study, it has been demonstrated that 26% of patients with MD presented symptoms of RLS, concluding that MD is a risk factor for RLS (with an odds ratio of 1.64). Ohayon, in a telephonic survey, found out that psychiatric disorders have a 50% risk factor to develop RLS [31,32].

The elevated comorbidity of RLS and MD is explained in part by dopamine hypofunction in patients with RLS who also suffer from chronic insomnia, because they have also a risk factor to develop MD [31,33]. Narcolepsy is a neurological disease characterized by irresistible sleep episodes, besides alterations on the REM sleep, caused by hypocretin deficiency. Neuroanatomical studies indicated that hypocretin projections are widespread, including limbic structures, the locus ceruleus and the raphe nucleus. Due to the latter, it regulates mood and several neuroendocrinal functions [34]. According to Ohayon's investigation, 19.2% of all narcoleptic patients demonstrated MD, in comparison with only 6.4% of the general population [35]. Some of the additional mechanisms which could also explain the comorbidity of MD in narcolepsy are obesity or overweight, physical inactivity, excessive daytime sleepiness, involvement of quality of life of the patient as well as subjacent medical and sleep disorders.

4. Alterations in sleep architecture in patients with MD

A significant proportion of patients with MD exhibit alterations in sleep architecture, in comparison with good sleepers. These alterations include a decrease of the slow wave sleep, reduction of latency after the first episode of REM sleep, as well as an increase in the percentage and density of REM (in other words, increase in eye movements per minute during REM sleep) [36], the latter being associated with nightmares and vivid dreams. They also present a decrease in sleep efficiency, which is related with an increase in sleep latency and with awakenings after the beginning of sleep (WASO) [37]. Some studies with patients with history of MD demonstrated that the alterations in sleep architecture will persist during the remission even with the posterior withdrawal of the antidepressant [38]. In general, relapses and the improvement of depressive symptoms are frequently preceded by alterations in sleep architecture [39].

5. Antidepressant effect and electroencephalogram

Electroencephalogram (EEG) shows major alpha wave activity with the eyes closed in patients with MD, which is interpreted as a decrease in cortical activity. Besides, EEG has also been utilized to point out that patients with MD who respond to fluoxetine, imipramine and amytriptilin, have major alpha power, especially at the occipital level [40]. In another study, depressed patients who responded to fluoxetine differed from nonresponders in the asymmetry of the alpha rhythm, which indicated a major activation of the right brain hemisphere in comparison with the left [15].

Tarn et al. found a significant decrease in beta activity at 4 weeks of treatment with amytriptilin [41].

Considering the effects of antidepressants upon sleep, the potency of these drugs in suppressing the REM sleep differ, for example, clomipramine and fenelzine do completely suppress REM sleep. It has been considered that since the majority of antidepressants suppress REM sleep, this suppression could be due to the antidepressants; however, trimipramine, mirtazapine and bupropione increase REM sleep [15]. The polysomnographic abnormalities that are characteristic of MD improve with antidepressant therapy, although fluoxetine does not restore the normal sleep pattern in patients with remitted depression [42].

6. Treatment of MD and sleep alterations

The treatment of sleep alterations (specifically insomnia) is divided into pharmacological and non-pharmacological.

Considering the pharmacological one, Franzen et al. studied depressed patients with persistent insomnia treated with selective inhibitors of serotonin reuptake, which were assigned to a placebo or Zolpidem (agonist of the benzodiazepine receptors). Compared with the placebo group, patients treated with Zolpidem improved their diurnal function and their quality of sleep [43].

Sedative antidepressants such as mirtazapine, trimipramine and Amytriptilin are frequently prescribed in clinical practice for MD and insomnia, concomitantly, although little evidence supports its long-term usage [44].

On the other hand, Trazodone is an antidepressant with a mechanism of action that involves the inhibition of the serotonin transporter and antagonism to the 5HT2A and 5HT2C receptors, besides having antihistaminergic properties and, in a small proportion, some anticholinergic property. It is effective upon the reduction of sleep alterations in depressed patients due to its sedative effects [45].

A novel antidepressant is Agomelatine, which is an agonist of the MT1 and MT2 receptors and an antagonist of the 5HT2C receptors. From its effects upon sleep, we can point out the increase in sleep efficiency, improvement in terms of quality and quantity of sleep, increase in slow wave sleep and normalization of REM sleep in MD [46,47].

From the non-pharmacological treatment, we include behavioral interventions such as the instructions for the control of stimuli and sleep restrictions. The Behavioral Cognitive Therapy for insomnia encompasses cognitive components to correct dysfunctional beliefs towards sleep. These interventions have been demonstrated as effective in improving sleep [43].

Manber et al. evaluated the Behavioral Cognitive Therapy in patients with MD and insomnia, where they found improvement in insomnia symptoms as well as in productivity, energy, severity of the depressive symptoms, suicidal thoughts and self-esteem [48].

7. Conclusions

There is a close association between sleep alterations and depression, leading to the development of several neurobiological models of study which try to explain such relationship. However, the presence of abnormalities during sleep is a predictive sign for the beginning or a relapse of MD. There are effective treatments for insomnia in MD, highlighting Zolpidem and Agomelatine. From the nonpharmacological point of view, the Behavioral Cognitive Therapy seems to be effective upon insomnia as well as for the symptoms of MD.

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