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Relation between insomnia mood disorders and clinical and biochemical parameters in patients undergoing chronic hemodialysis

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ABSTRACT

***Background*: Sleep disturbances are usually the outcome of a complex interplay between intrinsicfactors and environmental influences. Aim of this study was to investigate the incidence of insomnia and to assess its relation to clinical and laboratory parameters in hemodialysis patients.**
***Methods*: Using Athens Insomnia Scale (AIS), sleeping profile of 45 subjects (32 male, 13 female, mean age 59±16.2 years) was evaluated. According to AIS, patients were divided into two groups. Group A comprised 32 patients with score 0-9 (absence of sleep disorders), whereas group B included 13 patients scoring higher than 9 (clinically assessed disorder). Subjects were compared in terms of socioeconomic, clinical, laboratory parameters and presence of depression (assessed by Hamilton Depression Scale, HAMD).**
***Results*: No significant difference was observed with respect to age, sex, family status, education, selfesteem, coffee and alcohol consumption, time in hemodialysis and laboratory parameters. Group B demonstrated significantly lower albumin levels (3.65±0.38 and 3.9±0.24g/dL respectively, p<0.01), higher CRP levels (1.88±1.9 and 0.92±0.64mg/dL respectively, p<0.01) and exhibited depression (HAMD score 13.4±6.4 and 7.8±5.9 respectively, p<0.005). Moreover, significant correlation was observed when AIS scores were related to albumin (r=-0.29, p<0.05), CRP (r=0.38, p<0.01) and HAMD scores (r=0.54, p<0.0001).**
***Conclusions*: Sleep disorders are common in hemodialysis patients. They seem to be related to high CRP and low albumin levels and demonstrate strong correlation to mood disorders, which are equally common to such patients.**

Key words: *Insomnia, Depression, Mood disorders, Hemodialysis*

INTRODUCTION

Hemodialysis (HD) has enabled physicians to prolong the life of patients with renal failure by reversing several of the metabolic derangements associated with the uremic state. The quality of life (QoL) perceived by end-stage renal disease (ESRD) patients, however, remains poorer than that of the general population. Focusing on the QoL of these patients is now of increasing importance particularly in light of evidence that QoL may potentially impact mortality in a variety of conditions, including ESRD (1-3). The Dialysis Outcomes and Practice Pattern Study (DOPPS), a large international observational study, demonstrated that QoL indicators from the Medical Outcomes Study Short Form (SF-36) were associated with differential survival and morbidity (4-6).

Generally, patients suffering from chronic diseases frequently experience sleep disturbances. It is recognized that medical illnesses can adversely affect sleep quality, and that pain, infection and inflammation can induce symptoms of excessive daytime sleepiness and fatigue. However, it is less clearhow sleep quality affects disease progression and morbidity. In addition, chronic patients may also have a primary sleep disorder that further contributes to an aggravation of the morbidity. The role of sleep disturbances in the morbidity of various chronic conditions and how these disorders affect responses and compliance to medical therapy has been insufficiently studied (7-9). Patients with renal failure have been shown to have high rates of sleep apnea, periodic limb movements, insomnia, and restless legs syndrome. Symptoms are common and increasingly recognized as problematic for ESRD patients treated with dialysis. Insomnia is a subjective complaint of insufficient or inadequate sleep. Timing determines the three main types of insomnia: delayed

sleep onset, impaired sleep continuity, and early morning awakening. Excessive daytime sleepiness has subjective and objective components.

Sleep disturbances can have a variety of underlying causes and contributing factors and are often the outcome of a complex interplay between intrinsic factors and environmental influences.

A number of studies on ESRD have demonstrated the importance of sleep quality using individual items rather than using a scale score to assess sleep complaints and most reports have not examined the wide variety of potential underlying factors. The aim of this study was to investigate incidence of sleep disorders, especially insomnia and to assess its relation to biological, lifestyle and psychological parameters in uremic patients on chronic hemodialysis treatment.

Subjects and methods

Forty five patients (32 male and 13 female with mean age 59±16.2 years) on chronic hemodialysis was evaluated. Criteria for study inclusion were: being on HD for at least 6 months, being in a clinically stable condition and being ambulant. Exclusion criteria for the study were: evident cerebrovascular disease, major psychiatric illness and major visual or hearing impairment.

Our patients were screened for insomnia with the use of Athens Insomnia Scale (AIS). The latter, consists of eight items, of which five cover the night-time symptoms of insomnia such as difficulty initiating sleep, difficulty maintaining sleep and early morning awakening. Whereas, the remaining three probe daytime consequences of disturbed sleep such as feeling of well-being, functioning capacity and daytime sleepiness. Thus, AIS has been used to assess individual sleep complaints, to measure overall sleep quality and to identify cases of potentially significant insomnia.

A cut-off score of 9, as suggested by recently published studies, was used for the diagnosis of clinically significant sleep disorders. According to AIS scores, patients were divided into two groups. Group A included patients with score 0-9 and thus absence of sleep disorders. On the other hand, group B included patients with scores higher than 9, that is a clinically assessed sleep disorder.

Selection of covariates was guided by parameters that were found to be associated with sleep quality in the general population and among dialysis patients.

Sleep quality has been associated with demographic factors like age and gender. It is also likely that socioeconomic factors affect sleep, possibly mediated by stress. Therefore, marital status, employment and level of education were tested. Lifestyle factors, current smoking and alcohol and coffee consumption, were demonstrated to potentially affect sleep quality. Psychological well-being also seems to play a role, so family and personal psychiatric history and level of self-esteem were considered. Moreover, hemodialysis–related factors such as the mode of dialysis, time on dialysis treatment, the cause of ESRD, and biochemical parameters (hemoglobin, iron, serum albumin, creatinine, urea, electrolytes, lipid profile) were evaluated. The coexistence of diabetes and ischemic heart disease was examined and the C-reactive protein levels were evaluated, since hemodialysis patients have substantial comorbidity and exhibit elevated levels of inflammatory markers, both of which have been associated with reduced sleep quality. Lastly, the Hamilton Depression Scale (HAMD) score was used, for the assessment of the presence of depression.

TABLE I
DEMOGRAPHIC, DIALYSIS AND LIFESTYLE RELATED FACTORS

	Group A	Group B	p
Patients	32 (71%)	13 (29%)	
Gender (M/F)	24/8	8/5	NS
Age (years)	57.5±17.9	63.3±10.5	NS
Mode of dialysis (HD/HF)	25/7	10/3	NS
Time in HD (years)	5.2±3.9	6.7±4.2	NS
Smoking (Y/N)	12/20	3/10	NS
Alcohol (Y/N)	14/18	5/8	NS
Coffee (Y/N)	27/5	10/3	NS

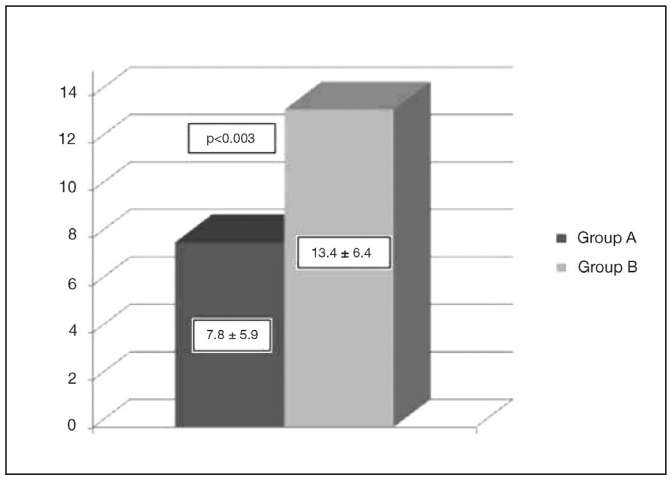

Fig. 1 - Comparison of Hamilton Depression Scale score in the two groups.

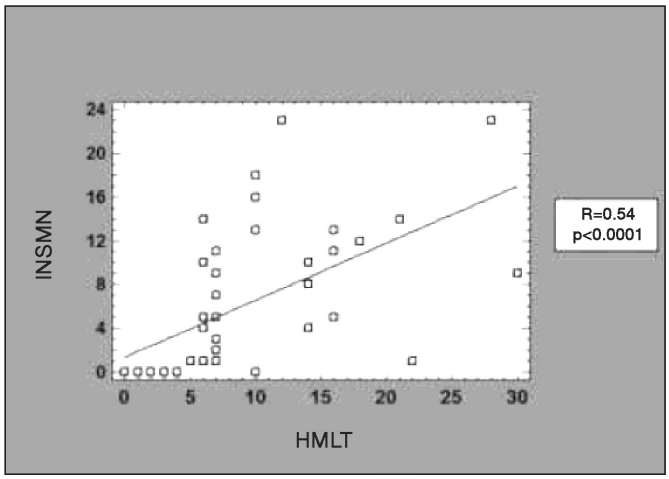

Fig. 2 - Correlation of insomnia with Hamilton Depression Scale.

RESULTS

Thirteen (29%) out of forty-five patients presented with clinically assessed disorder. Non significant difference was observed with respect to age, sex, family status, education, self-esteem, coffee and alcohol consumption, psychiatric history, time in hemodialysis (Tab. I) and laboratory parameters (urea, creatinine, electrolytes, hemoglobin and lipids) (Tab. II). Group B compared to Group A demonstrated significantly lower albumin levels (3.65±0.38 and 3.9±0.24 g/dL respectively, p<0.01), higher CRP levels (1.88±1.9 and 0.92±0.64 mg/dL respectively, p<0.01) and presence of clinically significant depression (HAMD score 13.4±6.4 and 7.8±5.9 respectively) (Fig. 1). Moreover, significant correlation was observed when AIS scores were related to albumin (r=-0.29, p<0.05), CRP (r=0.38, p<0.01) and HAMD scores (r=0.54, p<0.0001) (Fig. 2).

TABLE II
BIOLOGICAL FACTORS

	Group A	Group B	p
Hemoglobin (mg/dL)	11.9±1.5	11.6±1.1	NS
Ferrum (mg/dL)	84.1±41.2	76.9±35.8	NS
Urea (mg/dL)	152.3±31.9	141.4±31.6	NS
Creatinine (mg/dL)	8.5±2.2	7.2±1.7	NS
Potassium (mEq/L)	5.9±1.1	6.1±0.6	NS
Albumin (g/dL)	3.9±0.24	3.65±0.38	0.01
Cholesterol (mg/dL)	171.2±42.3	174.2±43.7	NS
Triglycerides (mg/dL)	178.4±97.1	186.4±92.9	NS
HDL (mg/dL)	35.1±8.1	33.7±7.4	NS
LDL (mg/dL)	99.6±29.3	104.1±30.8	NS
VLDL (mg/dL)	35.7±19.4	37.3±18.6	NS
CRP (mg/dL)	0.92±0.64	1.88±1.9	0.01

Discussion

Data from several studies confirm that sleep problems are frequent in patients with ESRD; with more than half of the patients reporting symptoms of at least one specific sleep disorder. Insomnia is the most common sleep complaint followed by sleep apnea and restless legs syndrome. Patients with sleep disturbances reported higher illness intrusiveness and worse self-perceived health than those without sleep problems. Sleep time is defended by an accumulation of "sleep debt", the need for more sleep that results from sleep restriction. Sleep is known to strongly affect the activity of most brain neurons and sleep restriction seems to have important influences on a vast spectrum of neurobiological and behavioral conditions. On the other hand, sleep is demonstrated to be affected by both the neuroendocrine output and the immune stimulus arm of brain-immune communications. Relevant immune factors include the broad family of immune molecules termed cytokines that include interleukins (IL), chemokines and other immune products that allow immune cells to communicate. Cytokines are pleiotropic, both affecting and originating from many other cells and organs than simply those of the immune system and they are key communicator molecules that affect various aspects of nervous system and neuroendocrine system function. Resultant sleep alterations induced by immune molecules probably affect the course of and the susceptibility to a variety of diseases including infectious, inflammatory, autoimmune and endocrine disturbances. Furthermore, there is some evidence that sleep loss and chronic sleep restriction may be associated with other inflammatory markers in addiction to cytokines and particularly with C-reactive protein that could impact the development and severity of cardiovascular disease as well as daytime sleepiness and fatigue in sleep disorders. A large number of recent studies reported reciprocal interactions between neuroendocrine and immune factors and sleep, and the importance of these interactions seems to be amplified during the course of chronic diseases.

More precisely, it emerges that immune molecules alter the sleep architecture and the sleep deprivation, in its turn, alter neuroendocrine and immune responses. Also, both immune system activation and neuroendocrine responses alter sleep. Lastly, sleep quality probably affects the course and the susceptibility to infectious disease. In our study we examined the association between several factors and sleep disorders; furthermore, we analyzed the correlation between sleep problems and mood disorders. We are aware of some limitations of our study. Although a number of studies in renal patients have been conducted in even smaller samples than ours, a significant limitation of our work is the relatively small number of patients involved. Therefore, the negative findings need to be interpreted with caution: where we did not find an expected association, it may simply be a consequence of low statistical power.

We found no association between sleep disorders and the gender of the patients. This was somewhat surprising. Earlier epidemiological studies showed that insomnia symptoms occur more frequently (1.5 to 2-fold) in women compared with men. Althought sleep complaints are twice as prevalent in women, 75% of sleep research has been conduced in men. More sleep studies in the past five years have included women, but small sample sizes prohibit meaningful sex comparisons. Thus, sex differences in sleep and sleep disorder characteristics, in responses to sleep deprivation, and in sleep-related physiology remains unappreciated. Furthermore, findings from studies based primarily on men are often considered representative of 'normal' even when it is recognized that there are important sleep-related physiological differences in women, including timing of nocturnal growth hormone secretion and differential time course of delta activity across the night. Also, aging is associated with changes in sleep amount, sleep quality, and specific sleep pathologies and disorders. For instance, increased age is associated with increased prevalence of sleep complaints, but we did not observe this tendency either.

Our study does not provide a firm explanation for the lack of these associations. There may be a specific modifying effect of the renal disease on the pathophysiology of sleep disorders, as suggested by others. The pathophysiology of certain sleep disorders (insomnia, RLS, PLMS, and central and obstructive sleep apnoea) may differ in the general population and in the medically ill. This 'renal disease-specific' factor(s) may be reflected partly in the high prevalence of sleep disorders, and partly in the lack of the 'age effect' and 'gender effect' observed in the general population. The finding that cigarette smoking, coffee and alcohol consumption was associated with lower sleep quality has been noted in the general population and in limited studies in the HD patients but not in our study. This may relay to the fact that these studies did not examine change in sleep quality and only partially accounted for potential confounding factors.

Many patients with chronic kidney disease (CKD) do develop some form of sleep disturbance some weeks before

they are begin on dialysis and these problems are viewed as symptoms of uremic toxicity, because they tend to get better with adequate dialysis treatment. Although, uremic toxicity may also be a cause of insomnia in patients on dialysis when the delivered dialysis dose is insufficient we did not find any difference in renal biochemical indices between the two groups of patients. Chronic hypoxia due to anemia has been implicated as a possible explanation for sleep complaints but in our study the mean hemoglobin levels were similar in the patients with and without insomnia. Although anemia is a condition frequently associated with ESRD, Benz et al using recombinant erythropoietin to normalize hematocrit showed only a trend in improvement of overall sleep disordered breathing.

As mentioned earlier a number of studies have found reciprocal interaction between sleep disorders and some inflammatory markers. The most relevant finding of our study is the strong correlation between sleep disturbances and the inflammatory markers as assessed by the significantly higher CRP levels in the group of patients with insomnia. Moreover we have found a strong correlation between low albumin levels and sleep disturbances. Serum album concentration is determined by its rate of synthesis, by the catabolic rate constant, by external losses and by redistribution from the vascular to the extravascular space. The cause of decreased albumin synthesis is primarly a response to inflammation (the acute phase response), although it is possible that inadequate nutrition may also contribute. The cause of the inflammatory response is not immediately evident (10). Many patients on a regime of hemodialysis are in a state of chronic inflammation. Also, occult infections of old nonfunctioning arteriovenous grafts (AVG) are a common cause of chronic inflammatory states. Several studies presented data that link occult infection of old nonfunctioning AVG to the occurrence of hypoalbuminemia and elevated C-reactive protein levels (11). We could affirm that hypoalbuminemia and CRP levels are important markers of an existent infectious or inflammatory condition and considering the fact that the stimulation of the immune system can induce sleep alterations, it seems probable that patients with low levels of serum albumin and high CRP levels could report sleep disturbances.

The ‘risk’ of psychological problems in ‘poor’ sleepers could suggest that emotional factors are involved in determining the quality of sleep. Administering a specific questionnaire in the two groups of patients to assess the exact prevalence of depression commonly involved in sleep disorders, we found significantly higher incidence of mood disorders in the patients with sleep disturbances. Sleep disturbances are often reported as an integral part of depressive disorders. As such, they are a part of all contemporary sets of diagnostic criteria for major depression and of all major symptom-based rating scales for depression. Insomnia is a particularly frequent complaint, and it is reported by more than 90% of depressed patients. Although the “kindling” or “illness transduction” model of depression remains hypothetical, there is evidence that people with recurrent depression have more pronounced abnormalities of sleep neurophysiology than those experiencing a single or initial episode.

A number of long-term demographic studies have indicated that there is a longitudinal relationship between insomnia and depression (12-16). For example, one study showed that current insomniacs carry a high likelihood of developing depression in the future (12). Another study carried out by the National Institute of Mental Health (NIMH) Epidemiological Catchment Area Study results, noted that, over a 1-year period, individuals who had no evidence of psychiatric conditions other than insomnia at study outset were much more likely to develop new major depression, a link in the direction of the former to the latter. Such theories have been supported by the high comorbidity of the 2 conditions and shared neurophysiological findings, such as cerebral cortical hyperarousal. Furthermore it is proposed (17) that increased activity of corticotropin – releasing factor (CRF) neurons innervating the noradrenergic neurons of the locus coeruleus is responsible for primary insomnia. CRF regulation has been extensively implicated in the pathogenesis of depression as well (18). Insomnia, especially the persistent variety is possibly enchanced by an underlying vulnerability to depression. The existence of a casual link between insomnia and depression raises the intriguing question of whether effective management of insomnia could offer an opportunity to prevent the future emergence of depressive disorders. However, no empirical evidence exists to support this hypothesis. Indeed, the available data suggest that alternative explanations can also be made regarding the link between insomnia and depression. Specifically, one of the longitudinal studies cited above also shows that current insomnia enchances the risk not only for future depression, but also for substance abuse and anxiety disorders (12). Another study indicates that hypersomnia is even a stronger predictor of future depression than insomnia (13). These findings suggest that, even if a causal link were to exist, it is not confined to insomnia and depression, but may involve many other conditions as well.

Finally, we can affirm that insomnia represents a symptom of an emerging depression or other psychiatric disorder, which has yet to reach syndromal levels. Consequently, insomnia does not represent an autonomous condition, but a symptom of an underlying psychiatric disorder. Such an explanation does not diminish the importance that insomnia may play in psychiatric disorders. Indeed, it emphasizes the importance of properly identifying insomnia in medical populations, because its existence and persistence suggest that the patient should be monitored more carefully for the emergence of a psychiatric disorder in the future.

We conclude that the presence of sleep disturbances, reported by many studies as an aggravating factor for a number of illnesses, seems to comport serious consequences to the general clinical condition of uremic patients influencing directly or indirectly the outcome of the principal illness and any coexistent pathologies. Whereas, sleep disturbances are associated with patient's perceptions of QoL, assessed by diverse measures, as well as depressive affect and may be related to progression of cardiovascular disease, identifying and treating dialysis patients who sleep poorly may significantly improve their lives.

Conflict of interest statement: None declared.

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