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Original Article

Insomnia in maintenance haemodialysis patients

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Abstract

Background. Studies in the last 15 years have shown a high prevalence of sleep disorders in maintenance haemodialysis (HD) patients.

Methods. To investigate whether the new technical and therapeutic advances of the last decade have had a positive impact on sleep disturbances in HD patients: 694 patients (384 males, 310 females) were surveyed using a specific questionnaire; their clinical, lifestyle and dialysis data were also recorded.

Results. Forty-five per cent of patients ($n=311$; 156 males, 155 females) complained of insomnia, defined either by delayed sleep onset and/or night-time waking, and were included in the insomnia group; the remainder were used as controls (control group). There was a significantly higher risk of insomnia in patients with >12 months on dialysis, in patients dialysed in the morning ($P<0.003$), and in patients with higher parathyroid hormone (PTH) levels ($P<0.05$). Body mass index, body weight gain and blood pressure did not differ between the groups, and neither did the dialysis parameters. Creatinine and urea plasma levels were higher in the control group *vs* the insomnia group ($P<0.001$), but there was no difference in haemoglobin concentrations or use of erythropoietin, calcitriol and antihypertensive drugs. Cigarette smoking, caffeine or alcohol intake were comparable in the two groups. The most frequently recorded sleep disorders were night-time waking (92%), trouble falling asleep (67%) and early morning waking (62%). Restless leg symptoms were described in 52% of patients with insomnia.

Conclusions. The prevalence of insomnia in HD patients is still very high; elderly patients, and those with longer time on dialysis and high levels of PTH are at major risk of insomnia, whereas type of dialysis, haemoglobin levels and behavioural factors do not seem to play a critical role in determining this sleep disorder.

Keywords: haemodialysis; insomnia; sleep disorders; uraemia

Introduction

Insomnia is commonly defined as the subjective sensation of short, unsatisfying sleep, despite the ability to sleep [1]. It may be secondary either to trouble falling asleep and/or to night-time waking, which must be persistently present (i.e. three to four times a week for several weeks) [2]. Insomnia is a rather common sleep problem, the prevalence of which ranges between 4 and 29% of general population; such a broad spectrum depends on several variables such as its classification [2,3], the characteristics of the population under study [2,4,5], and the methodological approaches used to survey patients [7]. Its prevalence is commonly reported to be higher in elderly or anxious subjects, and in chronically ill patients [8,9]; among the latter, uraemic patients on dialysis in particular complain about insomnia and other sleep disorders [10–13].

Beyond the obvious negative influence on daytime life, the effects of sleep disorders should not be underestimated for clinical reasons. It has been reported, in fact, that fragmented sleep due to obstructive sleep apnea may result in worsening of cardiovascular risk profiles [14], and that sleep deprivation may negatively affect the immune function [15]; it seems possible, therefore, that sleep disturbances may influence the leading causes of death in maintenance haemodialysis (HD) patients, i.e. cardiovascular events and infections. Moreover, the presence of periodic limb movements in sleep (PLMS), a rather common sleep disturbance, has recently been proposed as a predictor of mortality in end-stage renal disease patients [16].

Several studies carried out in the last 20 years have unequivocally demonstrated a high percentage of HD patients affected by sleep disorders [10–12]. These studies, however, have evaluated sleep disturbances in small patient samples, all coming from single dialysis units. This could have influenced the real prevalence of the phenomenon as a consequence of the particular

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dialysis strategies and/or psychological problems resulting from peculiar relationships between HD patients and unit personnel. To date, no data are available on a large population of dialysis patients from different dialysis units.

The aim of the present study was to evaluate the actual prevalence of insomnia (strictly defined as either trouble falling asleep and/or night-time waking) and other sleep disturbances in a large population of HD patients from several dialysis units in the same geographical area of Naples and its neighbourhood. We wanted to correlate these disturbances with clinical, demographic and dialytic data.

An additional aim of our study was to understand whether the huge improvement over recent years in dialysis techniques, clinical knowledge and pharmacological therapies might have modified the prevalence of insomnia substantially.

The results of our study are of particular interest because they confirm the high prevalence of sleep disorders in HD patients; the risk of insomnia is higher in elderly patients and in patients with longer time on dialysis, and is not linked to the most important clinical and dialytic data.

Subjects and methods

Seven-hundred-and-thirty-seven HD out-patients, treated in 21 different haemodialysis units in Naples and its neighbourhood, were enrolled in the study. All patients in each unit were surveyed by their nephrologist during routine treatment using a simple yes/no questionnaire as described previously by Holley *et al*. [11]. All patients included in the survey were on a regular dialysis schedule for at least 6 months. Forty-three patients were excluded because of refusal, intercurrent illness or psychiatric disorders. Question 1 of the questionnaire (see Appendix) was aimed at informing the patients about sleep disorders, but was not discriminating. The other questions dealt with symptoms of insomnia. With respect to Holley's questionnaire [11], we made no effort to obtain information about the personality of the patient; questions were to address only the self-perceived symptoms of sleep disorders. Bed partners were not surveyed and polysomnography was not performed.

All patients answering 'yes' at least once were again surveyed using a new questionnaire, inquiring how many days a week the disturbance was present and the subjective causes of the disturbance (anxiety, depression, fear, pruritus, bone pain, tremors, abdominal pain, unintentional leg movements). Only patients with difficulty falling asleep and/or night-time waking, occurring 7 nights a week for at least 1 month, were included in the insomnia group; the remaining patients (even those with occasional sleep disturbances) were included in the control group.

For each patient a special form was filled out by the attendant nephrologist, including some clinical and dialytic data, as well as pre-dialysis plasma values of creatinine, urea, haemoglobin (Hb) and parathormone (PTH). PTH plasma samples were analysed, in different labs, by commercial RIA kits (intact PTH, range: 10–75 pg/ml). Some information about patient lifestyle, limited to cigarette smoking and daily intake of coffee and alcohol, was also included.

Statistical analysis

Odds ratios (OR) and corresponding 95% confidence intervals were computed using unconditional multiple-logistic regression models. All the regression equations included terms for age, sex and HD unit. The possible confounding effects caused by age and sex was controlled through their stratification. Analysis of proportions among groups were evaluated by means of the Wald χ^2 test. The two-tailed Student's *t*-test for unpaired data was used when appropriate. A P value <0.05 was considered statistically significant. The data are expressed as mean $\pm$ 1 standard deviation (SD). The median value is reported in parentheses.

Results

The mean age of our patients ($n=694$; 385 males and 309 females) was 61.0 ± 14.4 years, and the average time on dialysis was 60.1 ± 53.8 months. There was no difference in body mass index (BMI) between males (23.6 ± 3.6) and females (23.6 ± 4.5). All patients underwent a standard bicarbonate dialysis using the following membranes: haemophan (36%), cuprophane (29.6%), polysulfone (16.1%), cellulose acetate (14.3%), PMMA (2%) and others (2%).

Only 95 out of 694 patients (14%) answered 'no' to all the questions of the first questionnaire; this means that 86% of the patients had some sleep disturbance. According to the proposed classification, 311 patients (44.8%) were considered to have insomnia (insomnia group); the remaining 383 were included in the control group.

Causes of uraemia (including diabetes) did not differ between the groups. The characteristics of the two groups are summarized in Table 1. In patients with insomnia there was a relative prevalence of females and a slightly higher mean age. Therefore, to avoid confounding effects, all regression equations were adjusted for age and sex. No difference in the two groups was

Table 1. Clinical and dialytic characteristics of patients in the two groups being studied (insomnia group, $n=311$; control group, $n=383$)

	Insomnia group	Control group
Sex (male/female)	156/155	229/154
Age (years)	63.1 ± 12.9 (66)	59.1 ± 15.3 (62)
Time on dialysis (months)	65.1 ± 55.1 (48)	56.0 ± 52.4 (36)
BMI (kg/m^2)	23.8 ± 3.7 (23.5)	23.4 ± 4.1 (23.1)
Body weight gain (kg)	3.3 ± 0.9 (3.0)	3.3 ± 1.0 (3.0)
Mean BP (pre-dialysis; mmHg)	98.1 ± 10.9 (100)	97.9 ± 9.7 (100)
Mean BP (post-dialysis; mmHg)	90.5 ± 11.6 (93.3)	90.1 ± 10.5 (93.3)
Dialysis duration (min/week)	701 ± 86 (720)	702 ± 83 (720)
Blood flow (ml/min)	292 ± 21 (300)	295 ± 24 (300)
Membrane surface (m^2)	1.36 ± 0.2 (1.3)	1.36 ± 0.3 (1.3)

Data are expressed as means $\pm$ 1SD; median values are reported in parentheses (when available). BMI, body mass index (calculated using post-dialysis body weight).

observed in BMI, in average weight gain, or in mean blood pressure, both before and after dialysis. Parameters of dialysis were comparable between the two groups (Table 1).

A significant association was observed between insomnia and each category of variable time on dialysis >1 year (Table 2). Dialysis schedule also influenced the onset of insomnia: patients on dialysis in the morning shift had a significantly higher risk of insomnia than patients in the afternoon (Table 2). Patient distribution on the different dialysis shifts differed neither with respect to time on dialysis nor in any of the parameters considered in the study.

PTH levels were slightly higher in patients with insomnia than in control patients (189 ± 261 *vs* 152 ± 235 pg/ml, $P < 0.05$). When the concentrations of PTH were stratified, a significantly higher risk for insomnia was recognized in patients of the 3rd tertile (Table 2). In patients with time on dialysis >85 months, the risk of insomnia for the highest levels of PTH (3rd tertile) was even greater (OR: 3.1; 95% CI: 1.4–7.1; $P < 0.01$).

Unexpectedly, plasma concentrations of both urea and creatinine were significantly greater in the control group compared with the insomnia group ($P < 0.001$, minimum value). Hb levels were similar in the two groups. Erythropoietin (Epo) and calcitriol were extensively and equally used by the patients of both groups, and there were no differences in the type and dosage of antihypertensive drugs, mostly clonidine. As expected, a significantly higher intake of sleeping pills was observed in patients with insomnia ($P < 0.0006$). These data are summarized in Table 3.

Behavioural factors such as cigarette smoking (number of cigarettes), coffee (number of cups/day) or wine consumption (ml/week) were similar in both groups.

The characteristics of the sleep disorders experienced by HD patients are listed in Table 4. Many patients reported multiple disturbances. Patients with insomnia mostly complained of nocturnal awaking (92%) and, to a lesser extent, difficulty falling asleep (67%). Other symptoms included early waking in the morning, restless legs syndrome (RLS), and daytime sleepiness: most of the latter 'sleepy' patients napped during the day (81%). There was no relationship between occurrence of RLS and blood parameters, dialysis shift or behavioural factors.

Sleep complaints were also recorded by patients in the control group, although with lower incidence and/or sporadic appearance (Table 4). Time spent in the bed was only slightly higher in control patients (7.7 ± 1.5 *vs* 7.1 ± 1.7 h; $P < 0.05$).

The possible subjective causes of insomnia are shown in Table 5. Some patients reported multiple reasons. For comparison, the causes of sleep disorders of patients in the control group are also reported. A

Table 2. Odds ratio (OR) and 95% confidence interval (CI) according to time on dialysis, dialysis shift and PTH plasma levels

	Insomnia group	Control group	OR[a]	95% CI	*P* value
Time on dialysis (months)					
⩽12 months	73	98	1[b]		
13–48 months	84	119	1.7	1.1–2.8	0.03
49–84 months	54	74	1.8	1.2–2.8	0.006
⩾85 months	86	68	1.7	1.1–2.7	0.01
Dialysis shift					
Afternoon	143	223	1[b]		
Morning	168	160	1.6	1.2–2.2	0.003
PTH levels (pg/ml)					
I (49)	90	128	1[b]		
II (149)	99	118	1.2	0.8–1.7	0.4
III (>149)	109	111	1.5	1.0–2.2	0.05

χ^2 trend = 5.64 ($P < 0.05$) for time on dialysis; χ^2 trend = 3.82 ($P = 0.05$) for PTH levels.
[a]OR and 95% CI calculated using logistic regression, adjusted for terms of sex, age and haemodialysis units.
[b]Reference category.

Table 3. Plasma levels of some biochemical parameters and the use of various drugs in the two study groups

	Insomnia group	Control group
Creatinine (mg/dl)	9.4 ± 2.2 (9.2)	9.9 ± 2.5 (9.5)[a]
Urea (mg/dl)	161 ± 33 (160)	170 ± 35 (1.70)[b]
Haemoglobin (g/dl)	10.5 ± 1.5 (10.5)	10.5 ± 1.2 (10.5)
PTH (pg/ml)	189 ± 261 (95)	152 ± 235 (71)
Epo	242 (78%)	311 (81%)
Calcitriol	231 (74%)	276 (73%)
Sleeping pills	47 (15%)	18 (4.7%)[b]

Data are expressed as means ± 1SD; median values are reported in parentheses.
[a]$P < 0.001$ *vs* the insomnia group; [b]$P < 0.0006$ *vs* the insomnia group.

Table 4. Self-reported sleep behaviours and symptoms of sleep disorders

	Insomnia group	Control group	All patients
Night-time waking	285 (92%)	168 (44%)	453 (65%)
Trouble falling asleep	209 (67%)	75 (20%)	284 (41%)
Early-morning wakefulness	194 (62%)	154 (40%)	348 (50%)
Daytime sleepiness	166 (53%)	122 (32%)	288 (41%)
Restless legs symptoms	142 (46%)	115 (30%)	257 (37%)

Table 5. Main self-perceived causes of sleep disorders in patients in the two study groups

	Insomnia group (%)	Control group (%)
Anxiety	45.0	33.2[a]
Pain	24.1	17.0
Pruritus	19.9	13.1[a]
Depression	13.5	9.4
Dyspepsia	5.2	6.3
Fear	5.8	3.4
Tremors	3.5	3.3
Others	17.7	12.3

[a]$P < 0.04$ *vs* insomnia group.

significant difference was found in the proportions of our patients with in anxiety and pruritus.

Discussion

Nineteen years after the publication of the first paper describing sleep disorders in HD patients [10], the present study clearly shows that insomnia is still a major problem in these subjects, since 44% of our patients complained of this sleep disorder. Our data suggest that time on dialysis, dialysis shift and high levels of PTH are associated with a higher risk of insomnia, whereas the type of dialysis, biochemical parameters and lifestyle behaviours do not seem to play a crucial role in determining it.

Our paper bypasses many shortcomings of previous surveys on sleep disorders in HD patients; the number of patients evaluated in this study is very high. Subjects were dialysed in several different units, but despite this they represent a homogeneous group with respect to race, geographic area, and even type and quality of dialysis, as deduced 'a posteriori'. This allows us to exclude the possibility that the incidence of the phenomenon was negatively influenced by the single-centre effect (due to a particular dialytic strategy and/or particular interpersonnel relationships). Moreover, for the first time the attention has been focused on insomnia alone, assessed by the presence and consistency of well-defined symptoms [2]. This allowed us to divide our population into two distinct groups, an insomnia and a control group, undergoing the same type of dialysis. Previous studies had also included patients with sporadic sleep disturbances or have made statistical comparisons between patients with sleep disorders and normal subjects or patients affected by chronic heart disease [11,17]. In both studies the prevalence of sleep disorders was much greater in HD patients because dialysis represents a unique additional factor, conditioning both the psychological and the physical well-being of the patients. Hence, our efforts were aimed at conventionally dividing dialysis patients into two distinct groups and comparing them.

Our study demonstrates a significantly higher risk of insomnia in patients with more time spent on dialysis. This is probably due to the progressive appearance of symptoms and concurrent diseases commonly associated with chronic dialytic treatment; one example is the increased risk of insomnia in patients with higher levels of PTH, an hallmark of renal osteodystrophy, often associated with bone pain and/or pruritus. Indeed, the latter two symptoms are reported to be the possible cause of insomnia by about 24 and 20% of our patients, respectively. The same may result from other complications (not investigated in our survey), like cardiovascular or neurological diseases, that usually occur in long-term dialysis patients.

No difference was detected in Hb concentrations, and neither were these levels correlated to any of the parameters considered in the study. The extensive use of Epo and calcitriol in our patients (79 and 74%, respectively) maintained Hb and PTH at acceptable levels; we cannot exclude, however, that pre-existing anaemia (or sub-optimal levels of Hb) and/or osteodystrophy may have induced negative effects in patients with high 'dialytic age', i.e. in patients already on dialysis treatment before these drugs were introduced in their therapy. Delano *et al.* [18] have reported an improvement in insomnia in HD patients with the use of Epo and this finding has recently been confirmed by Benz *et al.* [15]: the rise in Hct from 32.3 to 42.3 induced a significant reduction in the incidence of periodic limb movements in sleep and in the number of its related arousals (−54%).

Plasma concentrations of urea and creatinine ended up being significantly higher in control patients. Such a difference, of no clinical value, is probably explained by the greater number of male patients in the control group and a higher intake of protein, which was possible proof of their general well-being. Although these biochemical indices do not mirror the adequacy of dialysis, when combined with other parameters (time, blood flow, dialyser surface) they may account for a good general management of our uraemic patients; hence, the retention of middle molecules, suggested as a pathogenetic cause of sleep disorders [10], may be reasonably excluded.

The incidence of RLS is greatly reduced in our insomnia patients (45%) compared with the much higher percentage observed by Holley *et al.* (83%) [11], or, more recently, by Walker *et al.* (57%) [13]. Since in the latter study this symptom was related to plasma values of urea and creatinine and, indirectly, to the efficacy of dialysis, it is possible that the greater dialytic efficacy in recent years has contributed positively to the reduction of RLS.

Our study does not offer a clear explanation of why there is an increased risk of insomnia in patients dialysed in the morning shift: the statistical analysis does not show any particular difference among these patients with regard to any of the parameters considered. It is possible that psychological problems, such as the well known early waking, may condition the sleep in patients on the morning shift. It is also possible that the lower prevalence of insomnia in patients on the afternoon shift is due to tiredness and sleepiness in the hours following dialysis, which could enhance their sleep.

Finally, it is also important to note that particular lifestyles do not influence the onset of insomnia: in contrast to previous studies [12,13], in our survey we did not find any relationship between coffee intake and onset of insomnia.

The reported causes of sleep disorders clearly suggest that the psychological status of patients greatly influences the onset of insomnia [19]. The higher frequency of anxiety, even many years after beginning dialysis, appears to be in contrast to the reduced use of sleeping pills reported by the patients in our study compared with others [11,12]; whether this underlies a trend toward genuine reduction in sleep disturbances

or represents the low compliance of patients with the prescription of their nephrologist (high cost of therapy, presence of side effects) cannot be determined using our data. What is certain, however, is that very little attention is devoted by physicians to the problem of sleep disorders [20], since many of the reported causes of insomnia, such as pruritus, anxiety and bone pain, might be conveniently treated, thus improving the well-being of the patients.

In conclusion, our study demonstrates that the prevalence of insomnia in HD patients is still high and sleep disorders represent a major problem. It is possible that in the near future these disturbances may be effectively reduced by further new technical and pharmacological improvements. At the moment, however, a different approach to the problem of insomnia is certainly necessary. Its solution could contribute toward improving the quality of life of HD patients and to decreasing some complications linked to a poor sleep efficacy.

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Appendix 1

Patient questionnaire

Do you think you have any sleep problems?
Do you have any trouble falling asleep?
Do you wake up during the night?
Do you wake up early in the morning?
Do you complain of daytime sleepiness?
Do you have restless legs with nocturnal waking and walking?