ORIGINAL ARTICLE

Time evolution of restless legs syndrome in haemodialysis patients

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ABSTRACT

Background. Restless legs syndrome (RLS) is characterized by an urge to move the extremities, accompanied by paraesthesiae, in the evening and at night. Uraemic RLS, a type of secondary RLS, occurs commonly in chronic kidney disease and end-stage renal disease. Progression of uraemic RLS over time is unclear. Therefore we investigated the prevalence, progression over time, risk factors and impact on survival of uraemic RLS in a cohort of dialysis patients.

Methods. We reviewed at the 7-year follow-up a cohort of haemodialysis (HD) patients we had previously investigated for RLS, through interviews, validated questionnaires and analysis of demographic and clinical data.

Results. At the 7-year follow-up, RLS was present in 16% of patients, with a persistence rate of 33%. A correlation was obtained between RLS and older age, diabetes, low albumin and low body mass index. RLS was associated with reduced overall survival (median survival of 3.3 versus 3.7 years), particularly with the continuous form of RLS (1.61 years). There was a higher incidence of myocardial infarction and peripheral vascular disease, although not reaching statistical significance. RLS patients had absolute higher scores in all quality of life domains. A large majority of study patients (96%) reported being symptom-free within a few days or weeks following kidney transplantation.

Conclusions. The development of RLS, especially the continuous form, in patients undergoing HD has important consequences associated with decreased survival. Our results indicated an association between uraemic RLS and ageing, diabetes and malnutrition. Considerable efforts should be focused on the treatment of RLS, since it significantly and persistently impacts the quality of life of HD patients. Kidney transplantation could represent an effective treatment option for that RLS impacts on dialysis patients' quality of life, thus confirming the secondary nature of RLS in most HD patients.

Keywords: chronic kidney disease, dialysis, end-stage renal disease, restless legs syndrome

INTRODUCTION

Restless legs syndrome (RLS) is a neurologic sensorimotor disorder characterized by an urge to move the extremities, accompanied or caused by peculiar, unpleasant sensations (paraesthesiae) in these extremities. Symptoms are likely to appear or worsen at rest, are temporarily relieved by movement of the affected limb and are more severe in the evening and at night, frequently leading to sleep disturbances [1].

RLS is mainly an idiopathic disorder (primary RLS), but it also may accompany various medical conditions (secondary RLS), including pregnancy, iron depletion, peripheral neuropathy, radiculopathy and rheumatoid arthritis. Uraemic RLS, a type of secondary RLS, occurs commonly in chronic kidney disease and end-stage renal disease (ESRD). The diagnosis of RLS is based on the 2003 International RLS Study Group (IRLSSG) consensus, which defines the four essential diagnostic criteria [2]. RLS can be classified into intermittent (I-RLS) and continuous (C-RLS) forms, based on the progression of symptoms as reported by patients [3].

The prevalence of RLS among the general population in Western countries is 5–10%, and it is commonly associated with a positive family history and female sex [4, 5]. RLS has a higher prevalence, ranging from 20% to 30%, among ESRD patients undergoing haemodialysis (HD) [6].

The aetiology of uraemic RLS is still unclear. Evidence supporting a link between renal failure and RLS is scarce and mainly shows an association of RLS with reduced urine output in dialysis patients [7], RLS symptom improvement after kidney transplantation and recurrence of the condition after graft failure [8, 9]. RLS negatively impacts outcomes in patients with ESRD undergoing long-term HD, with prominent effects on sleep quality and quality of life and notably associated with higher mortality at 2.5 years of follow-up [10–13]. Systemic inflammation has been linked to poor sleep quality in HD patients and in the general population, but evidence linking RLS directly to inflammation is still lacking [14]. Recently an association between RLS and cardiovascular disease or cardiovascular risk factors was established in the general population [15], which is in agreement with our own previous report on a cohort of dialysis patients [16].

This study aimed to determine the prevalence and progression of RLS over time, its potential risk factors, its impact on quality of life and survival and also the effects of kidney transplantation on RLS in a cohort of chronic dialysis patients 7 years following their initial assessment [7].

MATERIALS AND METHODS

We previously investigated uraemic RLS in a cohort of 162 HD patients enrolled between March and December 2008 [7]. In the present study we reassessed this population for RLS at the 7-year follow-up between January and June 2015 by analysing demographic and clinical data, conducting interviews and using validated questionnaires.

Clinical data were systematically retrieved from patients' records, including the presence of comorbidities as given by the Charlson comorbidity index (CCI) [17] and its adapted form for ESRD patients (CCI-ESRD) [18]. We also assessed for new cardiovascular events, including myocardial infarction, peripheral vascular disease and cerebrovascular disease. Kidney-related factors recorded were causes of kidney failure (glomerular, interstitial, diabetic, vascular, polycystic and ESRD), dialysis vintage and frequency, residual diuresis, dialysis technique and

dialysis efficacy. We conducted clinical interviews to evaluate the presence of the following sleep disturbances: RLS and a positive family history in first-degree relatives (according to the IRLSSG criteria [2]), nocturnal leg cramps and insomnia (according to the International Classification of Sleep Disorders, 2nd edition [19]) and subjective sleepiness using the Epworth Sleepiness Scale (ESS) [20, 21]. The temporal relationship between sleep complaints and kidney disease was investigated, as well as RLS severity using the International RLS Rating Scale (IRLSRS) [22]. To determine the relationship between RLS and kidney transplantation, we used specific questions to explore improvement or complete resolution of RLS symptoms, as well as symptom worsening, after transplantation. Quality of life, fatigue and depression were assessed using the 36-item Short Form (SF-36) questionnaire [23] and Fatigue Severity Scale (FSS) [24].

This study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975 (revised in 2000).

Statistical analysis

All collected data were statistically analysed for the entire study population and different subgroups (e.g. patients with and without RLS). Results were expressed as mean ± standard deviation (SD) and frequency for categorical and continuous variables, respectively. Subgroups of patients with RLS and those without RLS were compared using non-parametric analysis, as data were not normally distributed (using Mann–Whitney U test and chi-squared test for categorical and continuous variables, respectively). The Fisher's exact test was used, instead of the chi-squared test, when the frequency of a variable observed in a subgroup was <5%. Survival was analysed using Kaplan–Meier curves and multivariate Cox regression models. P-values <0.05 were considered statistically significant.

RESULTS

Survival, risk factors and new cardiovascular events

Of a total of 162 patients from the original study cohort, two patients were lost to follow-up (median 7.25 years). Of the remaining 160 patients, 110 died (68.8%) and 50 survived (31.2%). The median overall survival was 3.55 years [95% confidence interval (CI) 2.73–4.07] (Figure 1). Of the 50 surviving patients, 32 were still undergoing dialysis treatment and 18 had kidney transplantation. Residual diuresis was present in only three dialysis patients. Comparison between transplant and dialysis patients showed a difference in age only between the two groups, which was statistically significant (52.70 ± 11.43 versus 64.00 ± 12.85 years, respectively; P = 0.005).

Of the 32 patients on dialysis, 4 patients were excluded from re-evaluation for cognitive impairment (2) or refusal (2); another 1 refused questionnaires FSS, SF-36, ESS but accepted re-evaluation for RLS; 1 transplanted patient refused to participate, so 5 patients refused the re-assessment for RLS (the other 1 refused only questionnaires ESS, FSS, SF36. Of the 18 transplanted patients, 1 refused to take part in re-evaluation. Therefore, of the 50 surviving patients, a total of 45 patients were re-evaluated.

At the 7-year follow-up, the entire follow-up cohort was younger, compared with the original study cohort at initial evaluation (mean age 59.76 ± 13.38 versus 66.5 ± 14.3 years, respectively; P = 0.002), and had fewer comorbidities [CCI: 4.09 ± 1.95
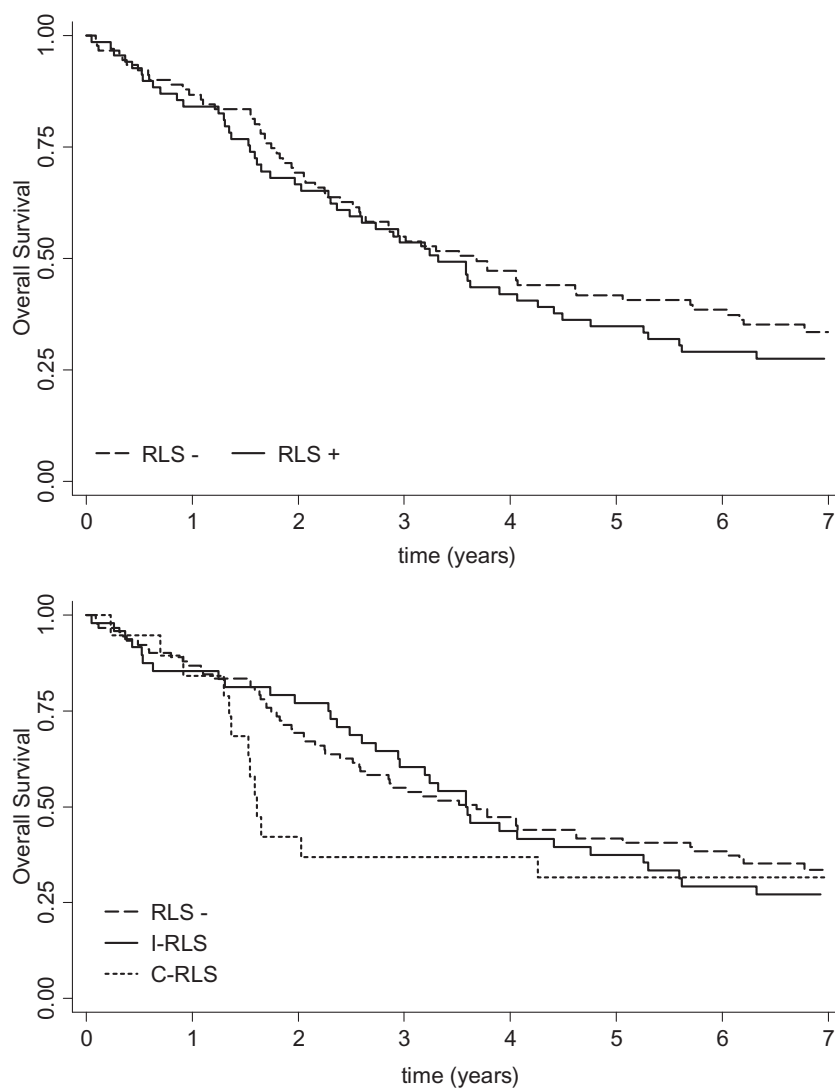
FIGURE 1: Kaplan–Meier curves for patients with and without RLS and those with I-RLS and C-RLS variants.

versus 4.8 ± 2.0, respectively (P = 0.035); CCI-ESRD: 1.89 ± 2.07 versus 2.8 ± 2.3, respectively (P = 0.017)] and a lower prevalence of diabetes [5/45 (11%) versus 42/162 (26%), respectively; P = 0.017]. Convection dialysis was used in 54% (15/28) in the follow-up cohort compared with 21% (32/162) in the original cohort (P = 0.0003). Patient characteristics at initial evaluation and the 7-year follow-up are summarized in Table 1.

Univariate analysis using Kaplan–Meier curves did not show an association between RLS and survival (Figure 1). Mortality was observed in 72% (50/69) of patients with RLS compared with 66% (60/91) of those without RLS. The median overall survival was 3.32 years in patients with RLS versus 3.68 years in those without RLS (P = not significant). Comparison between I-RLS and C-RLS patients showed the median overall survival was inversely correlated with the frequency of symptoms (I-RLS 3.59, C-RLS 1.61), which was not statistically significant (Figure 1).

The first multivariate analysis (Table 2, model a) evaluated 5-year overall survival in initial cohort and demonstrated an increased mortality risk in patients >65 years of age and those with diabetes and low albumin, but not in patients with RLS. The second multivariate model (Table 1, model b) compared 5-year overall survival in I-RLS and C-RLS patients and showed a

nearly 3-fold increased mortality risk in patients with C-RLS compared with those without RLS [hazard ratio 2.942 (95% CI 1.425–6.074); P = 0.0035]. Other factors associated with increased mortality using model b were age >65 years, diabetes, male gender, low body mass index (BMI) and low albumin.

Regarding long-term complications, we found a higher incidence of myocardial infarction in RLS patients compared with non-RLS patients (30% versus 25%, respectively; P > 0.05) and of peripheral vascular disease in C-RLS patients compared with I-RLS and non-RLS patients (43.8, 32.6 and 35.4%, respectively; P > 0.05), although these were not statistically significant. Moreover, the occurrence of at least one new cardiovascular event was more frequent in RLS patients compared with non-RLS patients (66.1% versus 62.2%, respectively) and in C-RLS patients compared with I-RLS patients (68.8 and 62.8%, respectively); however, these results were not statistically significant.

RLS and other sleep disorder characteristics. At 7-year follow-up, 7/45 patients (16%) met the diagnostic criteria for RLS (71% for I-RLS and 29% for C-RLS), while only 3 patients (7%) reported a family history of RLS among first-degree relatives. Only 6/18 patients who were positive for RLS criteria at initial evaluation

Table 1. Clinical and demographic data and sleep disorders in the entire study population and follow-up cohort and in RLS-positive and RLS-negative subgroups at the initial evaluation and 7-year follow-up

Characteristics	Initial evaluation	RLS+ (51 patients)	RLS− (111 patients)	P-value	Follow-up cohort	RLS+ (7 patients)	RLS− (38 patients)	P-value
Age (years), mean ± SD	66.5 ± 14.3	67.76 ± 13.11	65.93 ± 14.84	NS	59.76 ± 13.38	54.57 ± 11.57	60.71 ± 13.61	NS
Female gender, n/N (%)	57/162 (35)	25/51 (49)	32/111 (29)	0.012	19/45 (42)	4/7 (57)	15/38 (39)	NS
BMI, mean ± SD	24.8 ± 4.4	24.76 ± 4.85	24.82 ± 4.19	NS	25.41 ± 4.45	22.26 ± 2.19	25.99 ± 4.53	0.016
CCI, mean ± SD	4.8 ± 2.0	4.92 ± 2.15	4.77 ± 1.88	NS	4.09 ± 1.95	3.86 ± 1.77	4.13 ± 2.00	NS
CCI-ESRD, mean ± SD	2.8 ± 2.3	3.37 ± 2.61	2.52 ± 2.12	NS	1.89 ± 2.07	1.86 ± 2.27	1.89 ± 2.06	NS
Type 2 diabetes, n/N (%)	42/162 (26)	16/51 (31)	27/111 (24)	NS	5/45 (11)	1/7 (14)	4/38 (11)	NS
Family history of RLS, n/N (%)	18/162 (11)	11/51 (22)	7/111 (6)	0.004	3/45 (7)	2/7 (29)	3/38 (7)	0.059
Nocturnal cramps, n/N (%)	83/162 (51)	31/51 (61)	51/111 (46)	NS	7/45 (16)	0/7 (0)	7/38 (18)	NS
Frequent nocturnal cramps, n/N (%)	41/162 (25)	14/51 (28)	26/111 (23)	NS	4/45 (9)	0/7 (0)	4/38 (11)	NS
Insomnia, n/N (%)	78/162 (48)	34/51 (67)	43/111 (39)	0.001	21/45 (47)	6/7 (86)	15/38 (39)	0.039
Frequent insomnia, n/N (%)	70/162 (43)	30/51 (59)	40/111 (36)	0.007	19/45 (42)	5/7 (71)	14/38 (37)	0.059
ESS score, mean ± SD)	6.34 ± 3.83	6.98 ± 4.21	6.04 ± 3.62	NS	5.73 ± 3.96	10.71 ± 3.09	4.78 ± 3.37	0.001
ESS score ≥11, n/N (%)	26/162 (16)	10/51 (20)	16/111 (14)	NS	5/45 (11)	3/7 (43)	2/38 (5)	0.023

NS, not significant.
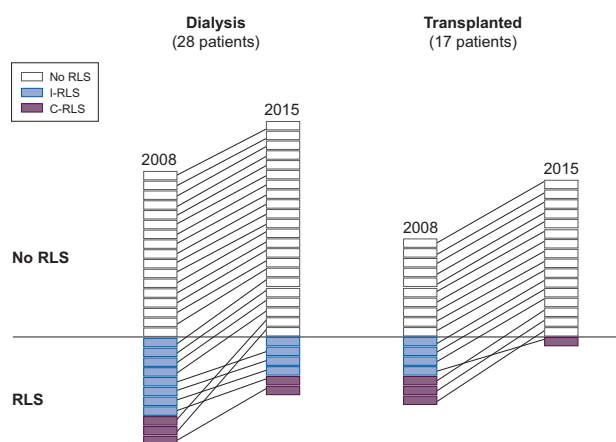
FIGURE 2: Prevalence and trends of RLS in dialysis and transplanted patient groups.

remained positive, with a persistence rate of 33%. Of two patients who reported new onset of RLS symptoms, one was symptom-free following transplantation. A total of 16% (7/45) and 9% (4/45) of patients reported nocturnal leg cramps and frequent nocturnal leg cramps, respectively. Insomnia was present in 47% (21/45) of patients and frequent insomnia in 42% (19/45). Finally, the average ESS score was 5.73 ± 3.96, with 11% (5/44) of patients scoring ≥11, which is the threshold for excessive daytime sleepiness.

Patients with RLS had a mean score of 20.43 ± 8.18 on the IRLSRS (taking into account that the patient with RLS had the lowest score of 8 following transplantation), whereas 7 years earlier, at initial evaluation, the average score was lower (15.30 ± 7.40). About 14% of patients (1/7) related the onset of RLS to the development of chronic kidney failure, while 43% (3/7) associated it with the start of dialysis treatment. Furthermore, 28% (2/7) associated worsening of RLS symptoms with chronic kidney failure and 71% (5/7) with dialysis treatment. A family history of RLS in first-degree relatives was found in 7% of dialysis patients (2/28 patients still suffering from RLS) and 6% of transplant patients (1/17 being RLS-free after graft). A total of 6/28 (21%) dialysis patients had RLS compared with 1/17 (6%) transplant patients.

Table 2. Results from multivariate Cox regression models predicting 5-year overall survival

Variables	HR	95% CI		P-value
Model a				
RLS versus no RLS	1.245	0.790	1.963	NS
Age, >65 versus ≤65 years	2.067	1.232	3.468	0.0060
Diabetes	2.068	1.212	3.529	0.0077
Gender, male versus female	1.560	0.970	2.511	NS
BMI	0.942	0.884	1.004	NS
ESRD aetiology	1.051	0.926	1.193	NS
CCI	1.118	0.986	1.269	NS
Albuminaemia	0.359	0.201	0.641	0.0005
Model b				
I-RLS versus no RLS	0.955	0.577	1.580	NS
C-RLS versus no RLS	2.942	1.425	6.074	0.0035
Age, >65 versus ≤65 years	2.136	1.262	3.614	0.0047
Diabetes	2.241	1.286	3.908	0.0044
Gender, male versus female	1.735	1.056	2.851	0.0297
BMI	0.921	0.862	0.984	0.0145
ESRD aetiology	1.072	0.942	1.221	NS
CCI	1.115	0.983	1.265	NS
Albuminaemia	0.318	0.177	0.573	0.0001

Model a included RLS (yes versus no) and the following clinical variables: age, gender, diabetes, BMI, ESRD aetiology, CCI and albuminaemia. Model b included RLS (intermittent and continuous versus no) and the following clinical variables: age, gender, diabetes, BMI, ESRD aetiology, CCI and albuminaemia.
HR, hazard ratio; NS, not significant.

Figure 2 shows the persistence rates of RLS in dialysed and transplant patients. In dialysed patients, the persistence rate was 45% (5/11). Furthermore, the persistence rate for I-RLS was 66% (4/6) and 33% (2/6) for C-RLS. Specifically, C-RLS persisted in one patient, while the other two patients with C-RLS no longer met the criteria for RLS; one case of I-RLS progressed to C-RLS, while four patients with I-RLS no longer met the RLS criteria; and finally, one patient newly developed I-RLS. Of patients who no longer had RLS at the 7-year follow-up, one patient reported an association between their symptom-free state and revascularization of the lower limbs, while another patient described RLS being present only in the first few years of dialysis. In

Table 3. Laboratory parameters in RLS-positive and RLS-negative patients (7-year follow-up cohort)

Laboratory variable	RLS positive ($n = 7$)	RLS negative ($n = 38$)	P-value
Haematocrit (%)	33.28 ± 2.19	36.10 ± 5.90	NS
Haemoglobin (g/dL)	10.28 ± 0.77	11.43 ± 2.03	NS
Iron (μg/dL)	41.30 ± 18.80	56.28 ± 26.53	NS
Transferrin saturation (%)	21.38 ± 9.93	22.89 ± 9.54	NS
Ferritin (ng/mL)	561.16 ± 820.88	267.79 ± 331.40	NS
TIBC (μg/dL)	189.72 ± 35.16	232.41 ± 84.90	NS
UIBC (μg/dL)	145.48 ± 35.75	184.01 ± 84.62	NS
WBC (1000/mm^3)	6.36 ± 1.31	6.23 ± 2.32	NS
Platelets (1000/mmc)	234.76 ± 59.52	202.55 ± 65.08	NS
Creatinine (mg/dL)	7.51 ± 3.72	5.28 ± 4.10	NS
Uric acid (mg/dL)	7.24 ± 1.68	6.62 ± 1.37	NS
PTH (pg/mL)	411.40 ± 220.24	355.80 ± 334.25	NS
Total cholesterol (mg/dL)	172.67 ± 36.80	176.96 ± 57.15	NS
Glucose (mg/dL)	101.72 ± 22.58	98.98 ± 30.47	NS
Albumin (g/dL)	3.88 ± 0.42	4.00 ± 0.37	NS
CRP (mg/dL)	2.19 ± 2.87	0.68 ± 0.47	NS

Values presented as mean ± SD. NS, not significant; PTH, parathyroid hormone.

addition, one patient reported that leg symptoms were not relieved by movement, while three patients with limited walking ability complained of constant pain in the lower limbs.

In the group of transplant patients, the persistence rate of RLS was 14%, with only 1/7 patients still presenting with the condition (specifically with I-RLS, as well as reduced symptoms). All patients who no longer had RLS reported being symptom-free within days or a few weeks following transplantation.

Nocturnal leg cramps were found in 18% (5/28) of dialysed patients, and 11% (3/28) reported frequent nocturnal leg cramps. In the transplant group, nocturnal leg cramps were present in 12% (2/17) of patients, while 6% (1/17) reported frequent nocturnal leg cramps.

Insomnia and frequent insomnia were found in 61% (17/28) and 54% (15/28) of dialysis patients, respectively. In contrast, 24% (4/17) of transplant patients reported insomnia, as well as frequent insomnia, which was statistically significant when compared with their dialysis counterparts (P = 0.034).

Finally, the mean ESS score in dialysis patients was 6.30 ± 4.05 (with 15% of patients scoring ≥11), whereas in transplant patients the mean ESS score was 4.82 ± 3.75 (with 6% of patients scoring ≥ 11).

Association between RLS, clinical data and sleep disorder. Table 2 presents clinical parameters and results of sleep disorder assessments in patients with and without RLS compared with the same groups from the original cohort. At initial evaluation, RLS was more common in females (49% of patients with RLS versus 29% of those without RLS; P = 0.012). At the 7-year follow-up, the association between RLS and female sex persisted, but without reaching statistical significance (57% of patients with RLS versus 39% of those without RLS). Furthermore, a positive family history for RLS (29% with RLS versus 7% without RLS; P = 0.059) and lower BMI (22.26 ± 2.19 in the RLS group versus 25.99 ± 4.53 in the non-RLS group; P = 0.016), as well as insomnia (86% in the RLS group versus 39% in the non-RLS group; P = 0.039), still remained associated with RLS at the 7-year follow-up. At the end of the study, RLS was associated with a higher ESS score (10.71 ± 9.3 in the RLS group versus 4.78 ± 3.37 in the non-RLS group; P = 0.001) and excessive daytime sleepiness (43% of patients with RLS versus 5% of those without RLS; P = 0.023). Moreover, in patients with RLS, we noted a trend (without reaching statistical significance) towards a possible state of chronic inflammation, as shown by increased C-reactive protein (CRP) and ferritin levels; high white blood cell (WBC) counts; decreased levels of albumin, haemoglobin and iron and reduced haematocrit, transferrin saturation, total iron-binding capacity (TIBC) and unsaturated iron-binding capacity (UIBC). Results of laboratory parameters are summarized in Table 3.

In the management of anaemia to achieve a target haemoglobin level of 10.5–11.5 g/dL, 29/45 patients (64.5%) were treated with erythropoietin (all patients in the dialysis group and one patient in the transplant group) and 22/45 (48.9%) were treated with iron supplementation (all from the dialysis group).

No patients received dopamine agonists, opioids or neuroleptics. Furthermore, 6/45 (13.3%) patients were on treatment with benzodiazepines, 3/45 (6.7%) with antiepileptics, 5/45 (11.1%) with gabapentin and 4/45 (8.9%) with antidepressants.

Correlation between RLS and dialysis. In the assessment of the relationship between RLS and dialysis treatment, 67% (4/6) of patients reported no change in RLS symptoms on dialysis days compared with non-dialysis days, while 17% (1/6) of patients reported symptoms worsening the night before dialysis and another 17% (1/6) in the evening following a dialysis session. All patients reported that RLS caused disruption to their dialysis sessions (visual analogue scale of 5.6 ± 1.69), although without resulting in premature dialysis discontinuation, with 17% (1/6) reporting that the disruption occurred rarely (1/6), 50% (3/6) sometimes and 33% (2/6) almost always. We found no correlation between RLS and dialysis technique, vintage, frequency and efficiency as expressed by urea reduction rate and Kt/V.

As shown in Table 4, significantly increased use of convection dialysis was noted among dialysis patients over time compared with the original cohort (P = 0.0002).

RLS impact on fatigue and quality of life. Patients with RLS had absolute higher FSS scores compared with those without RLS (41.57 ± 15.59 versus 36.57 ± 15.32, respectively). Regarding SF-36 assessment, both partial and total scores were worse in patients with RLS (except in terms of change in physical state of health) compared with those without RLS, with results in the category of social activities reaching statistical significance.

Table 4. Comparison of changes in dialysis parameters in HD patients at the initial evaluation and in surviving HD patients with RLS and those without RLS at the 7-year follow-up

Dialysis parameters	Initial evaluation (n = 162)	7-year follow-up cohort (n = 28)	P-value	RLS positive in follow-up cohort (n = 6)	RLS negative in follow-up cohort (n = 22)	P-value
Dialysis technique (HD/HDF), n/N (%)	128/34 (79/21)	13/15 (46/54)	0.0002	2/4 (33/67)	6/16 (27/73)	NS
Dialysis vintage (months), mean ± SD	39.8 ± 44.6	116.82 ± 46.66	0.0001	121.67 ± 34.60	115.50 ± 50.06	NS
Dialysis frequency (sessions per week, mean ± SD	2.8 ± 0.5	3.0 ± 0.0	0.036	3 ± 0.0	3 ± 0.0	NS
URR, mean ± SD	66.7 ± 10.0	64.39 ± 9.51	Ns	68.48 ± 8.12	63.30 ± 9.81	NS
Kt/V, mean ± SD	1.4 ± 0.4	1.29 ± 0.32	Ns	1.44 ± 0.28	1.24 ± 0.32	NS

HDF, haemodiafiltration; NS, not significant; URR, urea reduction rate.

DISCUSSION

In this 7-year follow-up study, our dialysis population [110/160 (68.8%)] had higher mortality, with a median overall survival of 3.55 years (range 2.73–4.07). Although RLS was not associated with survival, mortality seems to be correlated with the severity of RLS symptoms. Multivariate analysis of 5-year overall survival showed a nearly 3-fold increased risk of mortality in patients with C-RLS compared with those without RLS, even when taking into account other factors associated with increased mortality, such as age >65 years, diabetes, male gender, low BMI and low albumin. In our population, the presence of C-RLS represented an even stronger risk factor for mortality than age, nutritional status and diabetes, which are factors known to be associated with high mortality in dialysis patients [25, 26].

Furthermore, we investigated the correlation between RLS and the occurrence of new cardiovascular events and found a higher incidence of myocardial infarction in RLS patients (30% versus 25%) and a higher incidence of peripheral vascular disease in C-RLS patients compared with I-RLS and non-RLS patients (43.8, 32.6 and 35.4%, respectively), but without reaching statistical significance. In addition, our study showed a trend towards an increased risk for developing a new cardiovascular event in RLS patients (66.1 versus 62.2%) and in C-RLS patients compared with I-RLS and non-RLS patients (68.8, 62.8 and 62.2%, respectively). Non-statistical significance of these results could be due to the restricted duration of 7 years of patient follow-up. Interestingly, in a subgroup of 100 patients from the original dialysis population, we found an association between the severity of RLS and the risk for new cardiovascular events, as well as higher short-term mortality [16].

Possible explanations for the lower prevalence of RLS at the 7-year follow-up (32% versus 16%) include increased mortality rate in patients affected by RLS during the course of the follow-up period, especially those with C-RLS (also with a reduction in prevalence from 35% to 29%), the nature of the syndrome that displays RLS has fluctuating nature of symptoms and the beneficial outcomes of kidney transplantation. Furthermore, surviving patients with RLS experienced more detrimental RLS symptoms over time (IRLSRS score 20.43 ± 8.18 versus 15.30 ± 7.40). RLS was confirmed to be more common in women (57% versus 39%) and in patients with a positive family history of RLS (29% versus 7%; P = 0.059). Of note is the association between RLS and poor nutritional status as expressed by lower BMI (22.26 ± 2.19 versus 25.99 ± 4.53; P = 0.016). Interestingly, an increased risk for muscle atrophy in uraemic RLS patients was previously reported [27].

Patients with and without RLS did not differ in terms of dialysis parameters and efficacy, with a lower prevalence of the syndrome in transplant patients [1/17 (6%)] and 6/7 patients reporting full symptom relief within a few days after surgery. To our knowledge, there have been only a few studies on the effects of kidney transplantation on uraemic RLS [8, 9]. Our results suggest that 'uraemic factors' contributing to the high prevalence of RLS among dialysis patients are effectively eliminated only following transplantation and that a correlation exists between RLS symptoms and residual renal function. In contrast, an association between RLS and dialysis efficacy remains unproven and does not support the hypothesis that inadequate removal of medium-sized molecules could play a role in the pathogenesis of uraemic RLS. A recent study [28] suggested that an inflammatory state could be relevant to the pathogenesis of uraemic RLS. It is well known that in dialysis patients, a chronic inflammatory condition, commonly in the context of the so-called malnutrition, inflammation and atherosclerosis syndrome, is often concurrently present [29]. In support of this hypothesis, our patients with RLS showed reduced albumin levels and lower BMI and, without reaching statistical significance, absolute higher levels of inflammatory markers, including CRP, WBC and ferritin, with decreased haemoglobin, iron, transferrin saturation, TIBC and UIBC, suggesting a state of malnutrition and subclinical chronic inflammation.

Finally, we assessed the detrimental role of RLS on quality of life in our study population and found absolute poor SF-36 and FSS scores and a significant association with insomnia (86% versus 39%; P = 0.039) and excessive daytime sleepiness (43% versus 5%; P = 0.023). Literature is equivocal about the impact of RLS on diurnal functioning with contrasting data. We believe that daytime sleepiness is a common and complex disorder in ESRD patients and that other factors, in addition to RLS, may also play a role. Nevertheless, in the presence of RLS, the syndrome can further contribute to worsening of daytime functioning [30].

CONFLICT OF INTEREST STATEMENT

None declared.

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