

## Observational Study

## Restless legs syndrome is contributing to fatigue and low quality of life levels in hemodialysis patients

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**Author contributions:** Giannaki CD substantial contributions to conception and design of the study, acquisition of data, analysis and interpretation of data; drafting the article, making critical revisions related to important intellectual content of the manuscript; and final approval of the version of the article to be published; Lazarou A, Atmatzidis E, Stefanidis I, Hadjigeorgiou GM and Sakkas GK substantial contributions to conception and design of the study, making critical revisions related to important intellectual content of the manuscript; final approval of the version of the article to be published; Hadjigavriel M, Michael A, Damianou L and Pantzaris M substantial contributions to conception and design of the study, acquisition of data; making critical revisions related to important intellectual content of the manuscript; final approval of the version of the article to be published.

**Institutional review board statement:** This study was approved by the National Bioethics Committee of Cyprus (no. EEBK EII/2012.01.74).

**Informed consent statement:** All study participants provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** None.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Invited manuscript

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**Received:** January 28, 2017

**Peer-review started:** February 12, 2017

**First decision:** April 18, 2017

**Revised:** June 20, 2017

**Accepted:** July 7, 2017

**Article in press:** July 9, 2017

**Published online:** September 6, 2017

### Abstract

#### AIM

To examine whether hemodialysis (HD) patients with restless legs syndrome (RLS) are subjects of greater fatigue and impaired quality of life (QoL) compared to HD patients without RLS.

#### METHODS

Eighty five stable HD patients participated in this study. According to their RLS status, the patients were divided

into the RLS group ( $n = 23$ ) and the non-RLS group ( $n = 62$ ). QoL, fatigue, sleep quality, daily sleepiness and depression symptoms were assessed by using various questionnaires. Finally, biochemical parameters including iron, ferritin, hemoglobin, hematocrit and parathormone were assessed.

## RESULTS

The HD patients with RLS scored worse in all the questionnaires used in the study ( $P < 0.05$ ). The patients with RLS were more likely to receive the HD therapy on the morning shift, whilst 43.5% of the RLS patients reported to experience the RLS symptoms also during HD. The severity of RLS was correlated with fatigue, depression score and sleep quality ( $P < 0.05$ ).

## CONCLUSION

HD patients with RLS are subject to lower QoL related parameters and greater fatigue compared to HD patients without RLS. RLS should be successfully managed in order to improve the QoL of the sufferers.

**Key words:** Sleep quality; Depression; Secondary restless legs syndrome; Fatigue; Quality of life

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**Core tip:** Restless legs syndrome (RLS) is very common in patients receiving hemodialysis therapy. It seems that the hemodialysis patients who suffer also from RLS are subject of greater fatigue levels and they are experience even more impaired quality of life, sleep quality, daily sleepiness and depression symptoms compared to their free RLS counterparts.

Giannaki CD, Hadjigavriel M, Lazarou A, Michael A, Damianou L, Atmatzidis E, Stefanidis I, Hadjigeorgiou GM, Sakkas GK, Pantzaris M. Restless legs syndrome is contributing to fatigue and low quality of life levels in hemodialysis patients. *World J Nephrol* 2017; 6(5): 236-242 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i5/236.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i5.236>

## INTRODUCTION

Restless legs syndrome (RLS) (also called as Willis-Ekbom disease) is a sensory-motor sleep disorder which is very common in hemodialysis (HD) patients. It is called also as uremic RLS and it is affecting almost 30% of the HD population<sup>[1]</sup>.

According to the literature, the symptoms' severity of uremic RLS is worse compared to the idiopathic RLS<sup>[2]</sup>, whilst a number of studies highlight the negative effects of this extremely distressing sleep disorder on many aspects of the patient's quality of life (QoL), overall health and wellbeing<sup>[1]</sup>.

In particular, data derived mainly from cross-sectional studies reveal that the HD patients with RLS

experience significantly poorer sleep quality<sup>[3]</sup>, increased insomnia<sup>[4]</sup> and motor activity during sleep<sup>[5]</sup>, higher depression symptoms<sup>[6]</sup>, increased anxiety levels<sup>[7]</sup> and increased muscle atrophy<sup>[6]</sup> compared to HD patients without RLS. Moreover, RLS motor and sensory symptoms may appear also during HD therapy<sup>[8]</sup> inducing significant disturbance of the patient's rest and patience. Therefore is not surprising that the HD patients with RLS are characterized by even poorer QoL levels compared to HD patients without RLS<sup>[1]</sup>.

On the other hand, it is well known that the majority of the HD patients have significant levels of fatigue<sup>[9]</sup>. Fatigue experienced by the HD patients has both mental and physical aspects and could significantly affect the QoL levels of this specific population<sup>[10]</sup>. In the study by Jhamb *et al.*<sup>[11]</sup>, fatigue was independently associated, among others, with sleep quality and RLS.

The current study aimed to investigate potential differences in QoL, depression levels, sleep quality, fatigue and daily sleepiness status between HD patients with and without RLS. Taking into account the considerable negative effect of RLS on many physical and mental related parameters and especially on sleep, we hypothesize that the HD patients with RLS will present significantly greater fatigue and lower QoL levels compared to their free-RLS counterparts.

## MATERIALS AND METHODS

Eighty-five out of 102 HD patients volunteer to participate in this study. Patients were recruited from the HD units of the General Hospitals of Larnaca and Limassol, Cyprus. After a brief discussion of the purpose of the study and the procedures to be followed, the patients who voluntarily agreed to participate to the study and gave written informed consent included in the cohort. Inclusion criteria were as follows: Being in HD therapy 3 times per week at least 3 mo and with stable clinical condition. Patients received the HD therapy with the morning shift either with the noon shift, both using hollow-fiber dialysers and bicarbonate buffer. Exclusion criteria included treatment with dopamine agonists prior to the study and cognitive inability to complete the various questionnaires.

RLS was diagnosed using the International RLS study group criteria<sup>[12]</sup>, whilst RLS severity was assessed by using the International RLS Severity Scale (IRLS)<sup>[13]</sup>. Information related to when the first RLS symptoms appeared (before or after the institution of HD therapy), whether other members of the patients suffer also from RLS and whether the symptoms of RLS appear also during HD therapy were obtained also.

All patients provided a written consent for participation to the study, which conformed to the principles enumerated in the Helsinki Declaration of 1975. The study was approved by the National Bioethics Committee of Cyprus.

## Questionnaires

QoL levels were evaluated using the SF-36 question-

**Table 1** Patient's characteristics presented as pool data and divided in two groups according to restless legs syndrome diagnosis

Variables	Patients pool data	RLS	Non-RLS	P value
<i>n</i>	85	23	62	-
Female/male	54/31	10/13	21/41	0.414 <sup>1</sup>
Age (yr)	67.3 ± 11.4	67.8 ± 9.6	67.1 ± 12.1	0.801
95%CI	64.8 to 69.8	63.6 to 73.0	64.1 to 70.2	
Weight (kg)	73.3 ± 15.9	77.3 ± 20.4	72.0 ± 14.1	0.205
95%CI		67.5 to 87.2	68.3 to 75.7	
Dialysis shift morning/noon	54/31	4/19	35/27	0.026 <sup>1</sup>
Years in hemodialysis	4.7 ± 5.1	5.2 ± 4.9	4.5 ± 5.2	0.592
95%CI	3.6 to 5.8	3.1 to 7.3	3.2 to 5.9	
IRLS score	-	21.8 ± 6.1	-	-
95%CI		19.1 to 24.5		
Iron (µg/dL)	44.7 ± 18.2	43.0 ± 16.6	45.4 ± 19.0	0.741
95%CI	38.2 to 51.2	30.2 to 55.7	37.3 to 53.4	
Ferritin (ng/mL)	514.4 ± 411.7	443.7 ± 356.5	547.4 ± 441.5	0.567
95%CI	344.4 to 684.3	145.6 to 741.8	320.4 to 774.6	
Hct	36.4 ± 5.3	33.9 ± 5.6	37.7 ± 4.9	0.111
95%CI	34.2 to 38.7	29.2 to 38.7	35.1 to 40.3	
Hb (g/dL)	11.1 ± 1.5	10.1 ± 1.6	11.4 ± 1.4	0.022
95%CI	10.5 to 11.6	8.9 to 11.3	10.8 to 12.0	
Parathormone (pmol/L)	4.9 ± 1.9	4.8 ± 1.7	4.9 ± 2.0	0.97
95%CI	4.2 to 5.5	3.6 to 6.1	4.0 to 5.8	
Albumin (g/dL)	3.6 ± 0.3	3.6 ± 0.3	3.6 ± 0.3	0.853
95%CI	3.5 to 3.8	3.4 to 3.9	3.5 to 3.8	
Diabetes (%)	30 (35.3)	9 (39.1)	21 (33.9)	0.765 <sup>1</sup>
Hypertension (%)	30 (35.3)	8 (34.8)	22 (35.5)	0.832 <sup>1</sup>

<sup>1</sup>For categorical data a  $\chi^2$  test performed. All data are mean ± SD (95%CI). IRLS: International restless legs syndrome severity scale; Hct: Hematocrit; Hb: Hemoglobin.

naire<sup>[14]</sup>. Fatigue levels were assessed by using the fatigue severity scale (FSS)<sup>[15]</sup>. The patients' depression symptoms were assessed by using the self-rating depression scale developed by Zung<sup>[16]</sup>. Daily sleepiness status was assessed by using the Epworth Sleepiness Scale (ESS)<sup>[17]</sup>. Finally, the patients' subjective sleep quality was assessed by the Pittsburgh sleep quality index (PSQI)<sup>[18]</sup>.

### Biochemical assessment

The patient's routine monthly laboratory results were recorded including iron (photometry), ferritin (spectrophotometry, Beckman Coulter AU 680 Chemistry Analyzer), hematocrit, haemoglobin [sodium lauryl sulfate (SLS) method], albumin (photometry) and parathormone (chemiluminescence, ARCHITECT assay, Abbott Laboratories, Wiesbaden, Germany). The biochemical analysis was performed at the clinical labs of the affiliated hospitals under standard hospital procedures.

### Statistical analysis

The differences between the RLS and the non-RLS group in regards to the various variables were examined using independent samples *t* test.  $\chi^2$  tests were used in order to compare the two groups for categorical variables. The Pearson correlation test was used to assess the relationship between the examined variables. All data are presented as mean ± SD and the level of statistical significance was set at  $P < 0.05$ . All analyses were carried out using the SPSS Statistical Package version 19. The statistical review of the study was performed by

a biomedical statistician.

## RESULTS

Twenty-three out of 84 patients (27%) were diagnosed to experience RLS symptoms, whilst 10 out of those 23 RLS patients reported to experience the RLS symptoms also during HD (43.5%). Only 2 patients reported that a member of their family experience also RLS symptoms (8.7%), whereas 3 patients reported to experience the RLS symptoms before the institution of the HD treatment (13%).

The patients' characteristics are presented in Table 1. The patients with RLS were found to have lower hemoglobin levels ( $P = 0.022$ ) compared to the patients without RLS. In addition, the patients with RLS were more likely to receive the HD therapy on the morning shift ( $P = 0.026$ ).

Depression, fatigue, daytime sleepiness and sleep quality data are presented in Table 2. QoL data are presented in Table 3. All the examined parameters were found to be significantly worse in the RLS patients compared to the free-RLS patients ( $P < 0.05$ ). Finally, the IRLS score positively correlated with PSQI ( $r = 0.477$ ,  $P = 0.025$ ), depression score ( $r = 0.551$ ,  $P = 0.010$ ) and fatigue index ( $r = 0.582$ ,  $P = 0.004$ ).

## DISCUSSION

The main finding of the current study is that the

**Table 2** Depression, fatigue, daytime sleepiness and sleep quality data presented as pool data and divided in two groups according to restless legs syndrome diagnosis

Variables	Patients pool data	RLS	Non-RLS	P value
Pittsburgh sleep quality index	7.8 ± 5.1	13.9 ± 2.9	5.5 ± 3.6	0.000
95%CI	6.6 to 7.9	12.6 to 15.2	4.6 to 6.5	
Epworth sleepiness scale	4.3 ± 3.6	6.8 ± 4.3	3.4 ± 2.8	0.000
95%CI	3.5 to 5.1	4.9 to 8.7	2.6 to 4.1	
Zung depression scale	60.8 ± 7.1	58.0 ± 4.0	48.3 ± 6.1	0.000
95%CI	49.2 to 52.4	56.1 to 59.8	46.7 to 49.9	
Fatigue severity scale index	4.5 ± 1.2	5.8 ± 0.7	4.1 ± 1.1	0.000
95%CI	4.3 to 4.8	5.4 to 6.1	3.8 to 4.3	

All data are mean ± SD (95%CI). RLS: Restless legs syndrome.

**Table 3** Quality of life data presented as pool data and divided in two groups according to restless legs syndrome diagnosis

Variables	Patients pool data	RLS	Non-RLS	P value
SF-36 MCS	55.3 ± 16.7	46.6 ± 15.4	58.5 ± 16.1	0.004
95%CI	51.6 to 59.0	39.8 to 53.5	54.3 to 62.7	
SF-36 PCS	51.8 ± 19.4	40.6 ± 18.1	56.1 ± 18.2	0.001
95%CI	47.5 to 56.1	32.5 to 48.6	51.2 to 60.8	
SF-36 total score	55.1 ± 18.8	45.5 ± 17.7	58.7 ± 18.1	0.004
95%CI	51.0 to 59.3	37.6 to 53.3	54.0 to 63.4	
Physical function	46.9 ± 29.1	38.4 ± 28.2	50.1 ± 29.1	0.107
95%CI	40.5 to 53.4	25.8 to 50.9	42.5 to 57.7	
Role physical	45.3 ± 42.4	28.4 ± 38.8	51.6 ± 42.2	0.027
95%CI	35.9 to 54.7	11.2 to 45.6	40.6 to 42.7	
Body pain	72.3 ± 23.1	63.9 ± 24.3	75.4 ± 22.0	0.045
95%CI	67.1 to 77.4	53.1 to 74.7	69.6 to 81.1	
General health	47.0 ± 16.4	37.1 ± 14.5	50.7 ± 15.6	0.001
95%CI	43.4 to 50.6	30.6 to 43.5	46.6 to 54.8	
Vitality	48.3 ± 16.1	36.1 ± 14.5	52.8 ± 14.2	0.000
95%CI	44.7 to 51.8	29.6 to 42.5	49.1 to 56.6	
Social functioning	71.8 ± 20.8	65.5 ± 21.7	74.1 ± 20.2	0.098
95%CI	67.2 to 76.4	55.9 to 75.1	68.9 to 79.4	
Mental health	52.2 ± 45.3	43.9 ± 47.5	55.3 ± 44.4	0.316
95%CI	42.2 to 62.3	22.8 to 65.0	43.7 to 66.9	
Reported health	57.1 ± 12.1	50.7 ± 10.7	59.5 ± 11.8	0.003
95%CI	54.4 to 59.8	45.9 to 55.4	56.4 to 62.6	

All data are mean ± SD (95%CI). SF-36: 36-Item Short Form Health Survey; MCS: Mental component score; PCS: Physical component score; RLS: Restless legs syndrome.

HD patients who suffer also from RLS are subject of greater fatigue levels and they are experience even more impaired QoL, sleep quality, daily sleepiness and depression symptoms compared to HD patients without RLS.

Many factors could contribute to the increased fatigue levels of the HD patients. Recent studies indicate sleep disorders as one of the major factors which may be responsible for the elevated fatigue levels of the HD patients<sup>[10]</sup>. Interestingly, in line with our findings, RLS has been reported to associate with greater fatigue levels in patients on HD<sup>[11]</sup>.

RLS is a sleep disorder which is highly prevalent in the HD population<sup>[11]</sup>. Approximately 27% of the studied patients were diagnosed to experience RLS symptoms; a prevalence which is in line with the published literature in the field<sup>[11]</sup>. We should note that those are the first data regarding RLS from Cyprus.

In addition, approximately 43.5% of the RLS patients reported to experience the RLS symptoms during HD therapy, factor that may contribute to increase fatigability of the patients during their treatment. On the other hand, the findings of the current study reveal that the patients with RLS have significantly worse daily sleepiness status, in line with previous findings<sup>[7,19]</sup>. Daily sleepiness has been shown to be associated with fatigue in patients receiving HD therapy<sup>[11]</sup>. Finally, the data of the current study confirm the well known negative effect of uremic RLS on sleep quality<sup>[1,4]</sup>, whilst the severity of RLS was correlated with poor sleep quality.

Taking into consideration the fact that many HD patients experience elevated fatigue symptoms<sup>[9,20]</sup> and the fact that RLS may contribute to even greater fatigue symptoms, successful management of RLS may help those patients to reduce among others also fatigue and

tiredness feelings. It is known that exercise training alone<sup>[21-23]</sup> or in combination with dopamine agonists<sup>[24]</sup> could ameliorate the severity of uremic RLS symptoms. On the other hand, evidence exists regarding the favorable effect of exercise training on fatigue levels of HD patients, however, RLS presence was not taken into consideration in these studies<sup>[20]</sup>. It would be interesting in future studies to investigate the effects of chronic exercise training on fatigue levels in patients with uremic RLS.

Morning-shift HD was found to associated with RLS, in contrast with previous studies<sup>[25,26]</sup>, however, we should note that the association between the time of HD delivery and RLS is still controversial. In addition, hemoglobin levels observed to be significantly lower in the RLS group, confirming previous data<sup>[27]</sup>. Notably, low haemoglobin levels may contribute to greater levels of fatigue in the HD population<sup>[28]</sup>. However, we should note that many cross-sectional studies did not confirm an association between lower hemoglobin levels and RLS presence in HD patients<sup>[6]</sup>.

According to the literature, familiar component appear to be high in idiopathic RLS<sup>[29]</sup>. In contrast, familial component reported to be significantly lower in patients with uremic RLS compared to idiopathic RLS<sup>[30]</sup>. In the current study, approximately 9% of the RLS patients reported that a member of their family experience also RLS symptoms, in line with previous data which reported similar prevalence<sup>[30]</sup>. In addition, 13% of the RLS patients reported that they were experience the RLS symptoms before the start of the HD treatment, showing the association of renal disease and RLS. Interestingly, the RLS symptoms have been reported to ameliorated or disappeared after kidney transplantation<sup>[31]</sup>. Moreover, no gender differences were found in regards to the RLS presence in our study, confirming previous studies<sup>[32]</sup>, and in contrast to others<sup>[27]</sup>.

Diabetes prevalence did not differ between groups. It is known that RLS has been linked to various diseases, including diabetes and hypertension<sup>[33]</sup>. In the current study no such an association was found between RLS presence and diabetes and hypertension presence.

Depression score was found to be significantly worse in the patients with RLS compared to the patients without RLS, confirming previous studies the RLS group<sup>[6,34]</sup>. Moreover, depression score was correlated with the severity of RLS. The depressing effect of RLS on various parameters which are known to affect fatigue levels in HD patients such as sleep, QoL and depression<sup>[20,35]</sup> and the distressful nature of the syndrome itself may explain the higher depression score of the patients of the RLS group.

In conclusion, the findings of the current study confirm the negative effect of RLS on many aspects of QoL, including greater fatigue levels. Measures should be taken in order to manage the RLS symptoms and improve the QoL and general health of the patients with uremic RLS.

## ACKNOWLEDGMENTS

We would like to thank all hemodialysis patients who volunteered for the purposes of this study, as well as the staff at the hemodialysis unit of Limassol General Hospital and Larnaca General Hospital, Cyprus, for their expert advice and valuable help.

## COMMENTS

### Background

Restless legs syndrome (RLS) (also called as Willis-Ekbom disease) is a sensory-motor sleep disorder which is very common in hemodialysis patients. Evidence reveals that RLS negatively affects various aspects of health and quality of life (QoL) in patients receiving hemodialysis (HD) therapy.

### Research frontiers

It is well known that fatigue is one of the most common symptoms experienced by hemodialysis patients. However, it is not clear whether the hemodialysis patients who suffer also from RLS are subjects of greater fatigue levels compared to their free-RLS counterparts.

### Innovations and breakthroughs

The main finding of the current study is that the hemodialysis patients who suffer also from RLS are subject of greater fatigue levels and they are experience even more impaired QoL, sleep quality, daily sleepiness and depression symptoms compared to hemodialysis patients without RLS. Those are the first published data regarding uremic RLS from Cyprus.

### Applications

RLS could induce further impairments on various QoL and overall health parameters in patients receiving hemodialysis therapy. Given that almost 30% of the hemodialysis patients suffer from RLS, measures should be taken (pharmacological or non-pharmacological) in order to ameliorate the RLS symptoms and improve QoL and overall health of the hemodialysis patients.

### Terminology

RLS characterized by an irresistible need to move the legs, usually accompanied by unpleasant sensations. The symptoms of RLS begin or worsen during periods of rest and inactivity (usually at night) resulting in a significant sleep disturbance. The urge to move or unpleasant sensations are partially or totally relieved by movement at least as long as the activity continues.

### Peer-review

The paper is well-written.

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