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

Christoforos D Giannaki, Michael Hadjigavriel, Akis Lazarou, Aristos Michael, Loukas Damianou, Efthimios Atmatzidis, Ioannis Stefanidis, Georgios M Hadjigeorgiou, Giorgos K Sakkas, Marios Pantzaris

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

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

**INTRODUCTION**

Restless legs syndrome (RLS) (also called as Willis-Ekemb 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$^{[1]}$.

According to the literature, the symptoms’ severity of uremic RLS is worse compared to the idiopathic RLS$^{[2]}$, 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), overal health and wellbeing$^{[3]}$.

In particular, data derived mainly from cross-sectional studies reveal that the HD patients with RLS experience significantly poorer sleep quality$^{[4]}$, increased insomnia$^{[4]}$ and motor activity during sleep$^{[5]}$, higher depression symptoms$^{[6]}$, increased anxiety levels$^{[7]}$ and increased muscle atrophy$^{[8]}$ compared to HD patients without RLS. Moreover, RLS motor and sensory symptoms may appear also during HD therapy$^{[8]}$ 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$^{[1]}$.

On the other hand, it is well known that the majority of the HD patients have significant levels of fatigues$^{[9]}$. Fatigue experienced by the HD patients has both mental and physical aspects and could significantly affect the QoL levels of this specific population$^{[10]}$. In the study by Jhamb et al$^{[11]}$, 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$^{[12]}$, whilst RLS severity was assessed by using the International RLS Severity Scale (IRLS)$^{[13]}$. 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-
Fatigue levels were assessed by using the fatigue severity scale (FSS)\(^{[15]}\). The patients’ depression symptoms were assessed by using the self-rating depression scale developed by Zung\(^{[16]}\). Daily sleepiness status was assessed by using the Epworth Sleepiness Scale (ESS)\(^{[17]}\). Finally, the patients’ subjective sleep quality was assessed by the Pittsburgh sleep quality index (PSQI)\(^{[18]}\).

**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 (\(P = 0.026\)).

**DISCUSSION**

The main finding of the current study is that the
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\textsuperscript{[10]}. Interestingly, in line with our findings, RLS has been reported to associate with greater fatigue levels in patients on HD\textsuperscript{[11]}. RLS is a sleep disorder which is highly prevalent in the HD population\textsuperscript{[1]}. 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\textsuperscript{[1]}. 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\textsuperscript{[7,19]}. Daily sleepiness has been shown to be associated with fatigue in patients receiving HD therapy\textsuperscript{[11]}. Finally, the data of the current study confirm the well known negative effect of uremic RLS on sleep quality\textsuperscript{[1,4]}, whilst the severity of RLS was correlated with poor sleep quality.

| 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                          | 6.5 to 9.6         | 13.1 to 16.2         | 4.2 to 6.8            |           |
| 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                          | 60.2 to 62.2       | 56.1 to 59.9         | 47.9 to 60.9          |           |
| Fatigue severity scale index     | 4.5 ± 4.8          | 5.8 ± 0.7            | 4.1 ± 1.1             | 0.000     |
| 95\% CI                          | 3.7 to 5.6         | 4.0 to 6.0           | 3.2 to 4.6            |           |

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

| 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 ± 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 ± 63.4           |           |
| Physical function                | 46.9 ± 29.1        | 38.4 ± 28.2          | 50.1 ± 29.1           | 0.107     |
| 95\% CI                          | 40.5 ± 53.4        | 25.8 ± 50.9          | 42.5 ± 57.9           |           |
| Role physical                    | 45.3 ± 42.4        | 28.4 ± 38.8          | 51.6 ± 42.2           | 0.027     |
| 95\% CI                          | 35.9 ± 54.7        | 11.2 ± 45.6          | 40.6 ± 42.7           |           |
| Body pain                        | 72.3 ± 23.1        | 63.9 ± 24.3          | 75.4 ± 22.0           | 0.045     |
| 95\% CI                          | 67.1 ± 77.4        | 53.1 ± 74.7          | 69.6 ± 81.1           |           |
| General health                   | 47.0 ± 16.4        | 37.1 ± 14.4          | 50.7 ± 15.6           | 0.001     |
| 95\% CI                          | 43.4 ± 50.6        | 30.6 to 45.5         | 46.6 ± 54.8           |           |
| Vitality                         | 48.3 ± 16.1        | 36.1 ± 14.5          | 52.8 ± 14.2           | 0.000     |
| 95\% CI                          | 44.7 ± 51.8        | 29.6 ± 42.5          | 49.1 ± 56.6           |           |
| Social functioning               | 71.8 ± 20.8        | 65.5 ± 21.7          | 74.1 ± 20.2           | 0.098     |
| 95\% CI                          | 67.2 ± 76.4        | 55.9 ± 79.1          | 68.9 ± 79.4           |           |
| Mental health                    | 52.2 ± 45.3        | 43.9 ± 47.5          | 55.3 ± 44.4           | 0.316     |
| 95\% CI                          | 42.2 ± 62.3        | 22.8 ± 65.0          | 43.7 ± 66.9           |           |
| Reported health                  | 57.1 ± 12.1        | 50.7 ± 10.7          | 59.5 ± 11.8           | 0.003     |
| 95\% CI                          | 54.4 ± 59.8        | 45.9 ± 55.4          | 56.4 ± 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.
tiredness feelings. It is known that exercise training alone\cite{22,23} or in combination with dopamine agonists\cite{24} 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\cite{20}. 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 be associated with RLS, in contrast with previous studies\cite{25,26}, 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\cite{27}. Notably, low haemoglobin levels may contribute to greater levels of fatigue in the HD population\cite{28}. However, we should note that many cross-sectional studies did not confirm an association between lower hemoglobin levels and RLS presence in HD patients\cite{29}.

According to the literature, familial component appear to be high in idiopathic RLS\cite{30}. In contrast, familial component reported to be significantly lower in patients with uremic RLS compared to idiopathic RLS\cite{30}. 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\cite{30}. 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\cite{31}. Moreover, no gender differences were found in regards to the RLS presence in our study, confirming previous studies\cite{32}, and in contrast to others\cite{27}.

Diabetes prevalence did not differ between groups. It is known that RLS has been linked to various diseases, including diabetes and hypertension\cite{33}. 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\cite{16,34}. 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\cite{20,35} 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.

REFERENCES

1 Giannaki CD, Hadjigeorgiou GM, Karatzaferi C, Pantzaris MC, Stefanidis I, Sakkas GK. Epidemiology, impact, and treatment options of restless legs syndrome in end-stage renal disease patients: an evidence-based review. *Kidney Int* 2014; 85: 1275-1282 [PMID: 24107848 DOI: 10.1038/ki.2013.394]

2 Gkizis V, Giannaki CD, Karatzaferi C, Hadjigeorgiou GM, Mitas C, Kouedakis Y, Stefanidis I, Sakkas GK. Uremic versus idiopathic restless legs syndrome: impact on aspects related to quality of life. *ASAI O J* 2012; 58: 607-611 [PMID: 23069899 DOI: 10.1097/MAT.0b013e31826e0900]

3 Gade K, Blaschke S, Rodenbeck A, Becker A, Anderson-Schmidt H, Cohrs S. Uremic restless legs syndrome (RLS) and sleep quality in patients with end-stage renal disease on hemodialysis: potential role of homocysteine and parathyroid hormone. *Kidney Blood Press Res* 2013; 37: 458-463 [PMID: 24247595 DOI: 10.1159/000355727]

4 Muesi I, Molnar MZ, Ambrus C, Szefert I, Kovacs AZ, Zoller R, Barottf S, Remport A, Novak M. Restless legs syndrome, insomnia
and quality of life in patients on maintenance dialysis. *Nephrol Dial Transplant* 2005; 20: 571-577 [PMID: 15671074 DOI: 10.1093/ndt/ggh564]

5 Enomoto M, Inoue Y, Nambu K, Munowaza T, Matsuura M. Clinical characteristics of restless legs syndrome in end-stage renal failure and idiopathic RLS patients. *Mov Disord* 2008; 23: 811-816; quiz 926 [PMID: 18074382 DOI: 10.1002/mds.21882]

6 Giannaki CD, Sakkas GK, Karatzafieri C, Hadjigeorgiou GM, Lavdas E, Liakopoulos V, Tsianas N, Koukoulis GN, Koutedakis Y, Stefanidis I. Evidence of increased muscle atrophy and impaired quality of life parameters in patients with uremic restless legs syndrome. *PLoS One* 2011; 6: e25180 [PMID: 21949401 DOI: 10.1371/journal.\_ \_ \_\_ 0052180]

7 Dikici S, Bahadir A, Baltaci D, AnkaraH, Eroglu M, Ercan N, Sav T. Association of anxiety, sleepiness, and sexual dysfunction with restless legs syndrome in hemodialysis patients. *Hemodial Int* 2014; 18: 809-818 [PMID: 24685647]

8 Giannaki CD, Sakkas GK, Hadjigeorgiou GM, Karatzafieri C, Patramani G, Lavdas E, Liakopoulos V, Koutedakis Y, Stefanidis I. Non-pharmacological management of periodic limb movements during hemodialysis session in patients with uremic restless legs syndrome. *ASAJO* J 2010; 56: 538-542 [PMID: 21245801 DOI: 10.1097/MAT.0b013e31811ce044]

9 Weisbord SD, Fried LF, Arnold RM, Fine MJ, Levenson DJ, Peterson RA, Switzer GE. Prevalence, severity, and importance of physical and emotional symptoms in chronic hemodialysis patients. *J Am Soc Nephrol* 2005; 16: 2487-2494 [PMID: 15975996 DOI: 10.1661/\_ \_ \_ 00520157]

10 Sakkas GK, Karatzafieri C. Hemodialysis fatigue: just “simple” fatigue or a syndrome on its own right? *Front Physiol* 2012; 3: 306 [PMID: 22934057 DOI: 10.3389/fphys.2012.00306]

11 Jhamb M, Liang K, Yabes J, Steel JL, Dew MA, Shah N, Unurh M. Prevalence and correlates of fatigue in chronic kidney disease and end-stage renal disease: are sleep disorders a key to understanding fatigue? *Am J Nephrol* 2013; 38: 489-495 [PMID: 24335300 DOI: 10.1159/000356939]

12 Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelmann JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (ILRSSG) consensus criteria—history, rationale, description, and significance. *Sleep Med* 2014; 15: 860-873 [PMID: 25023924 DOI: 10.1016/j.spmi.2013.03.025]

13 Walters AS, LeBrock C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* 2003; 4: 121-132 [PMID: 14592342]

14 Ware JE. SF-36 health survey update. *Spine* (Phila Pa 1976) 2000; 25: 3130-3139 [PMID: 11124729 DOI: 10.1097/00007632-20001215-0-00008]

15 Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; 46: 1121-1123 [PMID: 2803071 DOI: 10.1001/archneur.1989.00520460115022]

16 Zung WW. A self-rating depression scale. *Arch Gen Psychiatry* 1965; 12: 63-70 [PMID: 14221962 DOI: 10.1001/archpsyc.1965.0020100060008]

17 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540-545 [PMID: 1798888 DOI: 10.1093/sleep/14.6.540]

18 Buyse DJ, Reynolds CF, Monk TH, Berman SR, Kupper DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193-213 [PMID: 2730877 DOI: 10.1016/0165-1791(89)90047-4]

19 Al-Jahdali HH, Al-Qadhi WA, Khogeer HA, Al-Hejaili FF, Al-Ghamdi SM, Al Sayyari AA. Restless legs syndrome in patients on dialysis. *Saudi J Kidney Dis Transpl* 2009; 20: 378-385 [PMID: 19414938]

20 Bossona M, Vulpio C, Tazza L. Fatigue in chronic dialysis patients. *Semin Dial* 2011; 24: 550-555 [PMID: 21917000 DOI: 10.1111/j.1525-139X.2011.00956.x]
Bossola M, Luciani G, Tazza L. Fatigue and its correlates in chronic hemodialysis patients. *Blood Purif* 2009; 28: 245-252 [PMID: 19684391 DOI: 10.1159/000231985]

**P- Reviewer:** Taheri S, Watanabe T  **S- Editor:** Ji FF  **L- Editor:** A  **E- Editor:** Lu YJ
