Original Article

Phlebology

Phlebology
2020, Vol. 35(10) 771–776
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0268355520940921
journals.sagepub.com/home/phl
SAGE

Investigation of chronic venous insufficiency in patients with sleep disorders due to restless legs syndrome

Atıf Yolgösteren[1], Leyla Köse Leba[2] and Aylin Bican Demir[3]

Abstract

Background: We aimed to investigate of chronic venous insufficiency on patients with sleep disorder due to restless legs syndrome.

Method: Five hundred forty-one cases on whom polysomnography was performed due to sleep disorder were evaluated retrospectively. Forty patients with restless legs syndrome were determined. They were examined by history, physical examination, and duplex ultrasonography in terms of chronic venous insufficiency. The sleep stage rates of both groups were compared (that the rate of total sleep time in polysomnography to sleep stages is expressed as minute and percentage has been defined as sleep stage rate).

Result: Chronic venous insufficiency was identified in 20 out of 40 patients (group 1; female, 90%). In group 2, there were patients with only restless legs syndrome but with no chronic venous insufficiency (female, 80%). The mean ages of both groups were 56.4 ± 11.8 and 54.3 ± 14.7 years. Stage 1 sleep rate in group 1 was $5\% \pm 2.7$ and in group 2 was $8\% \pm 3.8$ ($p = 0.006$). Periodic limb movement index (polysomnography finding evaluating involuntary leg movements during sleep) was 11.4 ± 17.5 in group 1, and it was 29.4 ± 37.9 in group 2 ($p = 0.006$).

Conclusion: We recommend that chronic venous insufficiency should be investigated in patients with primary restless legs syndrome diagnosis.

Keywords

Venous insufficiency, restless legs syndrome, sleep disorder

Introduction

Chronic venous insufficiency is a chronic disease causing symptoms such as pain, heaviness, restlessness, cramps, swelling, itching in the legs as a result of structural or functional impairment of the lower extremity veins, and damaging life quality. It has been reported in many studies that the prevalence in the adult population is 14.5–16% and that it is seen three times more in women than in men.[1,2] It is known that advanced age, pregnancy, and family history other than female gender are risk factors for chronic venous disorder (CVD).[3]

Restless legs syndrome (RLS), also known as Willis Ekbom's disease, is known as a neurological disorder occurring usually at nights and in which there has been an irresistible need to move legs after disturbing feelings and in which a transient relaxing appears after moving legs.[4] RLS is one of the major causes of sleep disorder, and one of its clinical features is that it is associated with periodic limb movements (PLM) in sleep. PLM is the supportive polysomnographic finding of RLS.[5] Although RLS is usually primary (or idiopathic), risk factors such as decreased iron stores in the central nervous system, dopaminergic dysfunction, advanced age, pregnancy, genetic factors, and many chronic diseases are also accused.[6] Although it is seen in 5–15% of the adult population in the general

[1]Faculty of Medicine, Department of Cardiovascular Surgery, Bursa Uludağ University, Bursa, Turkey
[2]Faculty of Medicine, Department of Neurology, Necmettin Erbakan University, Konya, Turkey
[3]Faculty of Medicine, Department of Neurology, Bursa Uludağ University, Bursa, Turkey

Corresponding author:
Atıf Yolgösteren, Faculty of Medicine, Department of Cardiovascular Surgery, Bursa Uludağ University, Bursa, Turkey.
Email: atif@uludag.edu.tr

population, its prevalence varies.[7] Compared to men, its incidence is higher in women.[8]

Although not emphasized until recently, studies investigating the relationship between RLS and cardiovascular diseases have been conducted in recent years.[9] The relationship between RLS and CVD is remarkable especially in terms of similar prevalence and many common risk factors.[10] In most of the previous studies, RLS was considered only as a neurological disorder, and venous insufficiency findings were ignored. Moreover, considering that RLS is both an important cause of sleep disturbance that impairs the comfort of life and a symptom of CVD, we thought it was important for neurologists and phlebologists to investigate the relationship between them.[8,11] In this study, we aimed to investigate the prevalence of chronic venous insufficiency (CVI) in patients with RLS on whom polysomnography (PSG) was performed due to sleep disorder, and to evaluate the relationship between CVI and RLS with polysomnographic data.

Methods

In this study, 541 cases, on whom PSG was performed due to sleep disorder diagnosis at the Neurology Department sleep laboratory in Bursa Uludağ University Medical Faculty between July 2017 and December 2019, were evaluated retrospectively. Among these patients, 42 patients diagnosed with RLS were determined according to diagnosis criteria developed by the International Restless Legs Syndrome Study Group and revised in 2014.[12]

These were patients who did not have any accompanying disease or pregnancy, who had primary RLS diagnosis, and whose hemogram, electrolyte, urea, creatinine, glucose, iron, ferritin, folic acid, and thyroid hormone values were at normal levels. The RLS severity scale results, composed of 10 questions, of these patients with RLS diagnosis were obtained from records and their RLS scores were determined.[4]

The severity of symptoms was divided into four groups: mild (1–10 points), moderate (11–20 points), severe (21–30 points), and extremely severe (31–40 points).

The implementation of PSG in our neurology clinic was routinely performed as follows: two-channel electrooculogram together with six-channel electroencephalography, jaw, right and left tibialis anterior, body posture, oro-nasal thermal sensor ECG with thoracic and abdominal movements, pulse, respiratory sounds, oxygen saturation, and synchronous video recording.[13] The sleep stage rates of both groups were compared (that the rate of total sleep time in PSG to sleep stages is expressed as minute and percentage has been defined as sleep stage rate).

Scoring criteria for PLM index were as follows[14]:

1. Leg movement must last minimum 0.5 s and maximum 10 s.
2. Minimum increase over EMG amplitude in relaxation position must be 8 microvolts.
3. There must be at least four consecutive movements.
4. In order to accept the fact that leg movements are PLM series, the duration between movements must be 5 to 90 s.
5. This leg movement must not occur within a 0.5-s period of any respiration event.

Of 42 patients with RLS invited to hospital to be evaluated, 40 of them came. They were examined by history, physical examination, and duplex ultrasonography in terms of CVI. The clinical classification of patients having CVI findings were carried out according to CEAP criteria.[15] Only patients with CVI on the bilateral lower extremity were included in the study. Duplex ultrasonography was performed by the same doctor while patients were remaining standing. Reflux in the venous system was defined as follows: reverse flow in superficial and deep veins > 0.5 s, in femoropopliteal veins > 1 s, and in perforating veins > 0.35 s.[16] Considering that 9.6% of the asymptomatic population has venous reflux, only patients with reflux findings in duplex ultrasonography that is P r according to the pathological classification of CEAP were accepted as CVI.[17–19]

CVI was determined in 20 out of 40 patients with RLS. Patients were divided into two groups: those with CVI and RLS (group 1, 20 patients) and those with RLS only (group 2, 20 patients).

All patients' sex and age and whether they were having any treatment were recorded. Those whose apnea-hypopnea index was ≥ 5, those having sleep apnea syndrome diagnosis criteria, and those whose PSG and examination data were deficient were excluded.

Statistics

Whether the data show normal distribution was examined by Shapiro-Wilk test. T-test for comparing two groups of RLS-score, age, sleep N2-N3, REM sleep, and total sleep percentage, N2, N3, REM sleep times for normally distributed data, N1, sleep latency, and REM for PLM index for non-normally distributed data Mann-Whitney U test was used in comparison of the two groups between latencies. Pearson chi-square test was used for PLM index in the examination of categorical data, Fisher's exact Chi-square test in gender comparison, and Fisher-Freeman-Halton test in RLS rating. Significance level was determined as

$\alpha = 0.05$. Statistical analysis of the data was performed in IBM SPSS 23.0 (IBM Corp. Released 2015, IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., Armonk, NY) statistical package program.

Results

RLS was determined in 42 out of 541 patients whose records were examined. However, our study was carried out on 40 patients since two of them did not come for the CVI examination. CVI was determined in 20 out of 40 patients (group 1; 18 female, 90%). In group 2, there were patients with only RLS but with no CVI (16 female, 80%). No CVI symptoms other than restless legs were present on any patients in both groups (such as pain, itching, swelling, and feeling of burn).

The mean ages of group 1 and group 2 were 56.4 ± 11.8 years and 54.3 ± 14.7 years, respectively ($p = 0.628$) (Table 1).

Eleven patients in group 1 (57.9%) and eight patients in group 2 (42.1%) were having medical treatment. The treatment rates between the two groups were similar ($p = 0.317$). When examining the treatment conducted, in group 1, there were 10 patients receiving pramipexole (91%) and one patient gabapentin (9%), and in group 2, there were four patients receiving pramipexole (50%), one patient diazepam (12.5%), one patient pregabalin (12.5%), one patient ropirinole (12.5%), and one patient pramipexole and gabapentin (12.5%). While RLS score in group 1 was 19.7 ± 8 and in group 2 was 21.3 ± 9.3, and no statistically significant difference was found between the groups (Table 1).

Regarding PSG findings, stage 1 sleep rate in group 1 was $5\% \pm 2.7$, whereas that in group 2 was $8\% \pm 3.8$ and this rate was significantly lower in group 1 ($p = 0.006$). No statistically significant difference was determined between the two groups in terms of stage 2 sleep rate, stage 3 sleep rate, and REM (rapid eye movement) stage sleep rate ($p = 0.892$, $p = 0.222$, and $p = 0.706$), respectively (Table 2). Total sleep duration, sleep efficacy, and sleep latency were of similar characteristics in the two groups ($p = 0.256$, $p = 0.429$, and $p = 0.820$, respectively). While the PLM index was 11.4 ± 17.5 in group 1, it was 29.4 ± 37.9 in group 2, and this rate was significantly lower in group 1 ($p = 0.006$) (Table 2).

No correlation was determined between RLS scores obtained by complaints from which they suffered and PLM indexes obtained during all-night sleep recordings.

According to CEAP classification, in group 1, there was one patient with C0, and there were seven patients with C1, nine patients with C2, and three patients with C3 (5%, 17.5%, 22.5%, and 7.5%, respectively.) There were no patients with C4, C5, and C6. According to CEAP, no statistically significant relationship was seen between the clinical classification of patients in group 1 and the severity scores of RLS.

Table 1. Comparison of patients' characteristic features and RLS scores.

	RLS + CVI (n = 20)	RLS (n = 20)	p
Age	56.4 ± 11.8	54.3 ± 14.7	0.628
Gender	18 female (90%)	16 female (80%)	0.661
RLS scores	19.7 ± 8	21.3 ± 9.3	0.581

CVI: chronic venous insufficiency; RLS: restless leg syndrome.

Discussion

In our study, RLS was present in 7.7% of patients followed in the sleep laboratory owing to sleep disorder. This result is consistent with the results in the literature.[20] However, what is most striking in our study is that CVI was determined in almost half of the patients having RLS diagnosis and examined due to sleep disorder. Although no significant differences occurred between the two groups included in our study in terms of PSG findings, we think that there are some results that need to be taken into consideration.

The most important thing, which makes researchers suggest the relationship between RLS and CVI, is the fact that patients have a number of common risk factors, such as familial history, female sex, older age, and pregnancy.[3,7] The following step after these common characteristics are determined is to determine whether there are consistencies in the physiopathology of the two diseases. The depletion in dopaminergic activity in RLS was thought to be responsible by a number of researchers, and dopamine agonists were shown to improve symptoms.[7,21] Nevertheless, different mechanisms have been taken into account in venous insufficiency. The increase in pressure and venous volume as a result of venous reflux triggers endothelial activation, adhesion molecules increase, the inflammatory process begins, and inflammatory mediators contribute to deterioration of the venous wall structure. Afterwards, extracellular fluid increases and tissue hypoxia develops. Their exposure to hypoxia causes dysfunction in peripheral nerves.[11,22,23] Although the depletion in dopaminergic activity may be responsible, in the physiopathology of RLS, it shows us that the culprit in restless leg symptoms is the hypoxia of peripheral nerves due to venous insufficiency.

The most important study, which examines the relationship between RLS and CVI and will shed light on

Table 2. Comparison of polysomnographic data between groups.

	RLS + CVI (n = 20)	RLS (n = 20)	p
Sleep latency (min)	39.4 ± 43.7	41.2 ± 56.5	0.820
Sleep efficacy (%)	78 ± 17.4	73.6 ± 79.5	0.429
Total sleep duration (min)	336.4 ± 58.4	310.2 ± 83	0.256
NREM stage 1 (%)	5 ± 2.7	7.8 ± 3.8	0.006
NREM stage 2 (%)	45.6 ± 9.6	46 ± 12.1	0.892
NREM stage 3 (%)	30.4 ± 7.4	30.4 ± 12	0.222
REM stage (%)	15 ± 5.3	15.7 ± 5.3	0.706
PLM index	11.4 ± 17.5	29.4 ± 37.9	0.006

CVI: chronic venous insufficiency; NREM: non-rapid eye movement; PLM: periodic limb movements; REM: rapid eye movement; RLS: restless legs syndrome.

the literature, is the prospective study conducted by McDonagh et al.[10] It was shown in that study that the prevalence of RLS was higher in patients with CVI (98%) and that underlying CVI was present in 91% of patients having no CVI complaint but in whom RLS was determined. In addition, according to CEAP classification, it was observed that RLS scores increased as the clinical classification worsened. In the same study, the rate of females was extremely high both in patients with RLS and in those with CVI. These were strong findings that support the association of RLS with CVI. In our study, CVI was also present in 50% of patients and females over 40 years old constituted the majority of them. RLS scores were similar in both groups and no relationship between them was determined in terms of skin findings. However, no relationship may have been established since the number of patients was low in our study and there were no patients with C4, C5, and C6 stage skin lesions. In different studies carried out by McDonagh et al., it was seen that RLS prevalence was high in patients with CVI and that this rate even rose up to 28% in patients with recurrent venous insufficiency.[24,25] Although we studied the prevalence of RLS in patients with CVI, we obtained similar results in terms of their association.

As RLS has been regarded as a primary neurologic disorder so far, drugs related to the peripheral and central nervous system has naturally been administered in its treatment. Depending upon data about its pathogenesis, dopaminergic agents have commonly been preferred.[21] In addition, the fact that RLS is one of the causes of sleep disorder has increased the variety of medications concerning the nervous system. Though such agents have given rise to a decrease in symptoms in patients with primary RLS, they have common side effects limiting their use.[7,26] When studies suggesting that CVI is present in a significant majority of patients with RLS diagnosis are taken into consideration, in order to relieve RLS symptoms, it may be a choice to administer venotonic drugs, the side effects of which are very low. In a study conducted on 10,263 patients in France, it was reported that symptoms were relieved by venotonic drugs in 80% of these patients, even though the prevalence of RLS was 8.5%.[27] We think that the results of this study complement each other with the pathological mechanism in the restless leg due to venous insufficiency. In our study, despite the fact that patients had RLS treatment, venous insufficiency had just been diagnosed and treatment had not been started yet. Prospective studies to be carried out with a significant number of patients may produce interesting results.

There have been few studies evaluating RLS on patients with CVI, depending on patient's anamnestic data and clinic characteristics. In the literature, we did not come across any study investigating this subject with PSG findings in patients examined due to sleep disorder. In order to investigate the prevalence of CVI or patients with sleep disorder owing to RLS and to obtain more reliable data, we investigated the association between CVI and RLS in patients on whom PSG was performed. Compared with the other group, we determined a lower stage 1 sleep duration and percentage in those diagnosed with CVI in group 1. This means that the patients with CVI in group 1 fell asleep easily. Besides, the PLM index, a significant finding for RLS, was determined to be lower in group 1. This result may appear to contradict with information that night cramps frequently occur in patients with CVI.[28] We are of the opinion that more detailed studies should be carried out in order to eliminate this contradiction due to the fact that night cramps are subjective findings and that the number of patients was low in our study. No significant differences were found between groups in view of PSG findings. The fact that stage 1 sleep duration and PLM index were lower in the group with CVI may suggest that RLS symptoms associated with CVI were milder. This opinion needs to be supported by more comprehensive studies.

Limitations

It is a significant limitation that our study was retrospective. Although many phlebologists defined C3 and above as CVI according to CEAP, in our study, we accepted patients with reflux in Doppler USG as CVI, regardless of their clinical appearance. Moreover, although the data belonging to 541 patients were researched, few patients with RLS were determined. Only clinical classification according to CEAP was carried out on patients with CVI. All patients

included in the study had CVI in the bilateral lower extremity. Some of them had reflux in different anatomical regions on different legs. Some of them had reflux on one leg in one anatomical region (for example, saphenofemoral junction) and on the other leg in two to three anatomical region (for example, saphenofemoral junction + deep veins + perforating veins). We thought that evaluating refluxes according to the anatomical regions with the number of patients present would lead to statistical confusion and would not a healthy result. Therefore, we did not evaluate reflux sites in our study. Similar studies in which other factors are classified according to CEAP may present interesting results. Treatment side effects were not evaluated in patients receiving treatment due to RLS. CVI treatment was started but follow-up was not done.

Conclusion

In our study, CVI was determined in almost half of patients with sleep disorder due to RLS. This result suggests that CVI may be the underlying cause in a significant number of patients who are thought to have primary RLS. Therefore, we recommend that CVI should be investigated in patients with primary RLS diagnosis. Moreover, more comprehensive studies to be conducted may suggest that CVI may be an etiologic factor for RLS. One of the important parts of our study is that it was carried out on patients on whom PSG was performed owing to sleep disorder. In our study, PSG findings revealed no significant differences between the two groups. We think the fact that there were few patients in our study affected this. However, we think that the fact that CVI was determined in a lot of patients experiencing sleep disorder problems due to RLS is a significant finding. It is important that our results and opinions be supported by prospective studies to be conducted on a greater number of patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was received from Bursa Uludağ University Clinical Trials Ethics Committee, in accordance with the Declaration of Helsinki (approval number: 15.04.2020-6/15).

Guarantor

AY

Contributorship

Study idea: AY; Data management: LKL, ABD; Manuscript writing and editing: AY, LKL.

Acknowledgements

The authors thank all the healthcare professionals who have contributed to this work.

ORCID iD

Atıf Yolgösteren https://orcid.org/0000-0002-4467-3915

References

1. Eberhardt RT and Raffetto JD. Chronic venous insufficiency. *Circulation* 2014; 130: 333–346.
2. Rabe E, Pannier F, Ko A, et al. Incidence of varicose veins, chronic venous insufficiency, and progression of the disease in the Bonn Vein Study II. *J Vasc Surg* 2010; 51: 791.
3. Beebe-Dimmer JL, Pfeifer JR, Engle JS, et al. The epidemiology of chronic venous insufficiency and varicose veins. *Ann Epidemiol* 2005; 15: 175–184.
4. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003; 4: 101–119.
5. Hornyak M, Feige B, Voderholzer U, et al. Polysomnography findings in patients with restless legs syndrome and in healthy controls: a comparative observational study. *Sleep* 2007; 30: 861–865.
6. Winkelman JW. Considering the causes of RLS. *Eur J Neurol* 2006; 13: 8–14.
7. Yeh P, Walters AS and Tsuang JW. Restless legs syndrome: a comprehensive overview on its epidemiology, risk factors, and treatment. *Sleep Breath* 2012; 16: 987–1007.
8. Berger K, Luedemann J, Trenkwalder C, et al. Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med* 2004; 164: 196–202.
9. Winkelman JW, Shahar E, Sharief I, et al. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology* 2008; 70: 35–42.
10. McDonagh B, King T and Guptan RC. Restless legs syndrome in patients with chronic venous disorders: an untold story. *Phlebology* 2007; 22: 156–163.
11. Nicolaides AN. Clinical investigation and reports investigation of chronic venous insufficiency a consensus statement. *Circulation* 2000; 102: 126–163.
12. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria – history, rationale, description, and significance. *Sleep Med* 2014; 15: 860–873.

13. Grigg-Damberger MM. The AASM scoring manual four years later. *J Clin Sleep Med* 2012; 8: 323–332.
14. Zucconi M, Ferri R, Allen R, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Grou. *Sleep Med* 2006; 7: 175–183.
15. Eklöf B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 2004; 40: 1248–1252.
16. Labropoulos N, Tiongson J, Pryor L, et al. Definition of venous reflux in lower-extremity veins. *J Vasc Surg* 2003; 38: 793–798.
17. Rabe E and Pannier F. Clinical, aetiological, anatomical and pathological classification (CEAP): gold standard and limits. *Phlebology* 2012; 27: 114–118.
18. Maurins U, Hoffmann BH, Lösch C, et al. Distribution and prevalence of reflux in the superficial and deep venous system in the general population - results from the Bonn Vein Study, Germany. *J Vasc Surg* 2008; 48: 680–687.
19. Wittens C, Davies AH, Bækgaard N, et al. Editor's choice – management of chronic venous disease: clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2015; 49: 678–737.
20. Pigeon WR and Yurcheshen M. Behavioral sleep medicine interventions for restless legs syndrome and periodic limb movement disorder. *Sleep Med Clin* 2009; 4: 487–494.
21. Bayard M, Avonda T and Wadzinski J. Restless legs syndrome. *Am Fam Physician* 2008; 78: 235–240.
22. Arnould T, Michiels C and Remacle J. Increased PMN adherence on endothelial cells after hypoxia: involvement of PAF, CD18/CD11b, and ICAM-1. *Am J Physiol* 1993; 264: 33–35.
23. Michiels C, Arnould T and Remacle J. Endothelial cell responses to hypoxia: initiation of a cascade of cellular interactions. *Biochim Biophys Acta* 2000; 1497: 1–10.
24. McDonagh B, Sorenson S, Gray C, et al. Clinical spectrum of recurrent postoperative varicose veins and efficacy of sclerotherapy management using the compass technique. *Phlebology* 2003; 18: 173–186.
25. McDonagh B, Huntley DE, Rosenfeld R, et al. Efficacy of the comprehensive objective mapping, precise image guided injection, anti-reflux positioning and sequential sclerotherapy (COMPASS) technique in the management of greater saphenous varicosities with saphenofemoral incompetence. *Phlebology* 2002; 17: 19–28.
26. Sharon D. Restless legs syndrome and sleep related movement disorders. *Sleep Med Clin* 2015; 10: xvii–xviii.
27. Tison F, Crochard A, Léger D, et al. Epidemiology of restless legs syndrome in French adults – a nationwide survey: the INSTANT Study. *Neurology* 2005; 65: 239–246.
28. Hirai M. Prevalence and characteristics of muscle cramps in patients with varicose veins. *Vasa* 2000; 29: 269–273.