https://doi.org/10.5664/jcsm.9020

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Restless legs syndrome is increased in postural orthostatic tachycardia syndrome

Caroline Dodson, BS[1]; Kanika Bagai, MD, MSC[1]; Leonard B. Weinstock, MD[2]; Emily Thompson, BA[1]; Luis E. Okamoto, MD[3]; Amanda Peltier, MD[1]; Satish R. Raj, MD, MSCI[4]; Arthur S. Walters, MD[1]

[1]Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee; [2]Specialists in Gastroenterology, St. Louis, Missouri; [3]Clinical Pharmacology Division, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; [4]Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Alberta, Canada

Study Objectives: Postural orthostatic tachycardia syndrome (POTS) and restless legs syndrome (RLS) are both characterized by sleep disturbance along with autoimmune/inflammatory features and autonomic dysfunction. However, to our knowledge, there has been no direct study looking at the prevalence of RLS in patients with POTS patients compared with healthy participants (controls).

Methods: Ninety-six physician-diagnosed patients with POTS (89 female and 7 male) and 130 controls (99 female and 31 male) were administered the Cambridge Hopkins questionnaire. Participants who were diagnosed with probable or definite RLS on the Cambridge Hopkins questionnaire were then contacted to determine the severity of RLS with the International Restless Legs Scale.

Results: More patients with POTS (15 of 96; 15.6%) than controls (6 of 130; 4.6%) were diagnosed with probable or definite RLS on the Cambridge Hopkins questionnaire (P = .0048). A sensitivity analysis with only female respondents yielded similar results. RLS severity was in the moderate range (12.23 ± 9.22).

Conclusions: There is a higher prevalence of RLS in patients with POTS patients compared with controls. This association may have to do with shared increased inflammatory/autoimmune load and autonomic dysfunction.

Keywords: postural orthostatic tachycardia syndrome (POTS), restless legs syndrome (RLS), inflammation, autoimmune, autonomic

Citation: Dodson C, Bagai K, Weinstock LB, et al. Restless legs syndrome is increased in postural orthostatic tachycardia syndrome. *J Clin Sleep Med*. 2021; 17(4):791–795.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Postural orthostatic tachycardia syndrome and restless legs syndrome are both characterized by sleep disturbance along with autoimmune/inflammatory features and autonomic dysfunction. However, to our knowledge, there has been no direct study looking at the prevalence of restless legs syndrome in patients with postural orthostatic tachycardia syndrome compared with healthy participants.

Study Impact: This study shows that the prevalence of restless legs syndrome is greater in patients with postural orthostatic tachycardia syndrome than controls. This study has implications for clinical recognition, pathophysiology, and treatment. Clinicians should look carefully for restless legs syndrome in patients with postural orthostatic tachycardia syndrome and vice versa.

INTRODUCTION

It is estimated that 500,000 to 3 million people in the United States are affected by postural orthostatic tachycardia syndrome (POTS), which is characterized by orthostatic symptoms including palpitation, excessive rise in heart rate (≥30 beats/min in adults) with upright posture, mental clouding, dyspnea on standing, chest pain, and concentration difficulties in the absence of orthostatic hypotension.[1–3] Younger individuals, specifically those in the 15- to 45-year range, have a higher chance of being affected by POTS. This is especially true for females, with about 80% of those diagnosed with POTS being female.[4]

Restless legs syndrome (RLS) is characterized by (1) an urge to move the legs often associated with uncomfortable feelings in the legs; (2) symptoms that are worse when at rest, for example, lying or sitting; (3) symptoms that are worse later in the day or at night; and (4) at least temporary relief of the symptoms by activity such as walking, stretching, or bending the legs. About 2.5% of the population is affected by RLS in a serious enough way to want to seek medical attention. There is a slight female predominance of RLS in the general population.[5–8]

Both disorders can be accompanied by significant sleep disruption and autoimmune/inflammatory dysfunction; autonomic dysfunction has also been implicated in both disorders.[1–24] This study was designed to determine whether RLS is more common in patients with POTS than in healthy participants (controls) and, to our knowledge, is the first study of its kind.

METHODS

We administered a validated questionnaire for the diagnosis of RLS, the Cambridge-Hopkins questionnaire (CH-RLSq).[25]

The CH-RLSq is a self-administered questionnaire that probes the 4 major symptoms of RLS and excludes mimics such as leg cramps and positional discomfort. It is validated as a stand-alone instrument for the diagnosis of RLS. It was validated against the Hening-Hopkins Telephone Diagnostic Interview for RLS, which served as the gold standard for the validation study.[25,26] It has excellent clinimetric properties, with a sensitivity of 87.2%, specificity of 94.4%, positive predictive value of 87.2%, and negative predictive value of 94.53%.[25,27] One weakness of the validation study as pointed out by the authors of the validation study themselves is that the study was done in blood donors where the prevalence of RLS might be expected to be higher than in the general population. However, the authors provide an estimate of what the positive predictive value would be in a general population with an estimate of 63.4%.[25] In our study, the CH-RLSq, was self-administered. If participants were diagnosed with definite or probable RLS, they were then contacted for a phone interview to determine RLS severity with the International Restless Legs Scale.[28]

The study was approved by the Vanderbilt University Institutional Review Board, and all participants provided their informed consent and signed a written consent form before distribution of any materials. The CH-RLSq was administered as part of a more generalized questionnaire that queried demographics of the patients, such as age, sex, previous medical problems, and medications. To eliminate bias, the CH-RLSq questionnaire was administered without the participants knowing that the goal of the study was to determine whether RLS was present. All questionnaires were self-administered. Each questionnaire was then reviewed for final determination of RLS by the senior author (AW).

We recruited 81 patients with POTS from a national POTS patient meeting. We also recruited 15 patients with POTS from a Vanderbilt employee email distribution list. We recruited 65 control participants from the aforementioned patient meeting and 65 control participants from the Vanderbilt employee email distribution list. Altogether, there were 96 patients with POTS (89 female and 7 male; age, 32.8 ± 11.6 years; range, 18–62 years) and 130 controls (99 female and 31 male; age, 40.7 ± 12.5 years; range, 20–64 years). For conference attendees, the CH-RLSq was administered in person in paper format, but for participants who were recruited through the Vanderbilt email distribution list, the CH-RLSq was administered via REDCap, which is an internet-based database.

Patients with POTS had to answer affirmatively that POTS had been diagnosed by a physician. If this question was not answered positively, the patient was excluded from further analysis.

RLS was diagnosed by the 4 standard criteria developed by the International RLS Study Group as incorporated into the CH-RLSq. The CH-RLSq also excludes common mimics of RLS such as leg cramps and positional discomfort.[25]

The CH-RLSq was scored using the specific algorithm developed with the questionnaire. A definite diagnosis of RLS required questions 1–10 to all be answered affirmatively. A probable diagnosis of RLS can be obtained if either question 1 or 10 is answered negatively, with the remaining 9 questions answered affirmatively. Question 1 asks "Do you have or have you had recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down?" Question 10 asks "Do these feelings occur only when sitting or only when lying down?" and is considered negative if the respondent answers "only when sitting." A diagnosis of indeterminate RLS is made when questions 1 and 2 are both answered affirmatively but the criteria for definite or probable RLS or no RLS are not met. A diagnosis of not RLS is made when both questions 1 and 2 are answered negatively. Question 2 asks "Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down?" The last 3 questions, 11–13, are used as a severity index and to determine age of onset and are not used to make the diagnosis.[25]

The International Restless Legs Scale is a validated instrument for determining RLS severity over the week before scale administration and consists of 10 questions, each rated with 0–4, with a maximum severity score of 40.[28]

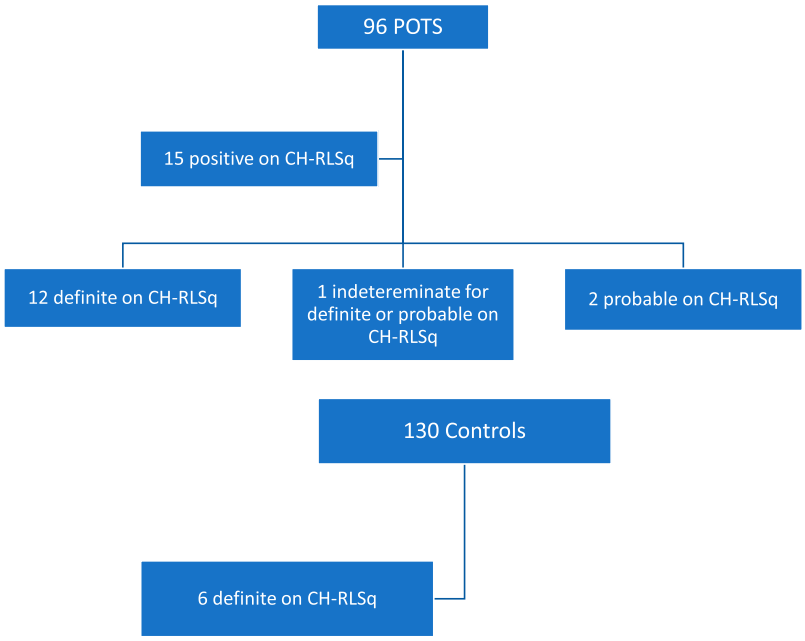
Statistical analysis

Age and scale data are reported as mean ± standard deviation, with categorical data presented as percentages with statistical significance calculated by χ^2.

RESULTS

Figure 1 is a flow diagram of the study. Altogether, there were 96 patients with POTS (89 female and 7 male; average age, 32.8 years; range, 18–62 years) and 130 controls (99 female and 31 male; average age, 40.7 ± 12 years; range, 20–64 years). There were no significant differences in the usual types of medical problems that are known to precipitate RLS between our patients with POTS and controls with RLS. None of our participants with RLS had peripheral neuropathy or renal failure. One control participant had diabetes and 1 control participant had anemia. More patients with POTS (15 of 96; 15.6%) than controls (6 of 130; 4.6%) were diagnosed with definite or probable or indeterminate RLS on the CH-RLSq ($P = .0048$). Definite RLS was diagnosed based on the CH-RLSq in 12 of 14 patients with POTS and all 6 controls, whereas 2 patients with POTS had probable RLS and 1 patient with POTS had indeterminate RLS. Because our 130 control patients were slightly older than our 96 patients with POTS, we performed a sensitivity analysis comparing the 96 patients with POTS with the 96 of 130 controls who most closely resembled the 96 patients with POTS in age and sex (89 female and 7 male), and results were similar ($P = .037$). Because there was a disproportionate number of females compared with males in our sample, in addition, we performed a sensitivity analysis restricted only to females. This analysis also showed similar results (14 of 89 female patients with POTS had RLS and 6 of 99 female controls had RLS ($P = .032$). We were able to contact 13 of 20 of the participants who were diagnosed with definite or probable RLS on the CH-RLSq for a follow-up telephone call to administer the International Restless Legs Scale to determine RLS severity. The other 7 could not be contacted and were lost to follow-up. The overall average

Figure 1—Flow diagram for the study.



CH-RLSq = Cambridge Hopkins RLS questionnaire, POTS = postural orthostatic tachycardia syndrome.

for the International Restless Legs Scale was 12.23, with a standard deviation of 9.2 for all participants combined (10 patients with POTS and 3 controls), which is in the moderate range (10–20).

DISCUSSION

The principal finding of this study is that RLS is more common in patients with POTS. We found that 15.6% of patients with POTS and 4.6% of controls were diagnosed with RLS on the CH-RLSq ($P = .0048$). A sensitivity analysis restricted to a subgroup of more closely age and sex matched controls and a sensitivity analysis restricted to only female respondents yielded similar results. This is the first report to our knowledge that has assessed the rate of RLS in patients with POTS.

The personal patient interview is considered the gold standard for the diagnosis of RLS.[27] As previously mentioned, the CH-RLSq, which is a self-administered questionnaire, was used to diagnose RLS in this study. The CH-RLSq uses the 4 basic criteria for the diagnosis of RLS, excludes RLS mimics such as leg cramps and positional discomfort, has strong clinimetric properties, and is validated as a stand-alone instrument for the diagnosis of RLS.[25,27] Based on the original validation study, the Ch-RLSq has a calculated false-negative rate of 12.96% and a false-positive rate of 5.46% against the Hening-Hopkins Telephone Diagnostic Interview,[27] with a false-negative rate to false-positive rate differential of 7.5%. This suggests that, if we had used an instrument with a personal patient interview such as the Hening-Hopkins Telephone Diagnostic Interview as part of our procedure, there would be a very slightly higher, although inconsequential, increase in the prevalence of RLS in both our POTS and control populations above what we found in the current study. This calculation might be different, of course, if the original validation of the Ch-RLS had been performed in the general population as opposed to blood donors.

Both RLS and POTS are characterized by sleep disruption, auto immune/inflammatory dysfunction, and autonomic dysfunction.[1–24] These commonalities may be the link that tie the 2 disorders together. Furthermore, RLS is associated with anemia and POTS may be as well. It has been reported that adolescents with POTS have a higher prevalence of iron deficiency, low iron storage, and anemia compared with controls.[29] This could be an additional link between the 2 disorders.

There are 3 major pathophysiologic mechanisms known to underlie POTS, which include partial autonomic neuropathy, hypovolemia, and the hyperadrenergic state. Two of these are characterized by autonomic dysfunction. Autoimmune mechanisms may also be pertinent to autonomic dysfunction. For example, activating autoantibodies to the α1-adrenergic and β1- and β2-adrenergic receptors have been observed in POTS. Angiotensin II type 1 receptor autoantibodies have been noted in POTS, and sympathetic activation in POTS is associated with increased interleukin-6.[12–17]

Autonomic dysfunction has also been documented in RLS. Patients with RLS have increased autonomic complaints relative to controls including constipation, early abdominal fullness, lightheadedness when standing, heat intolerance, oversensitivity to light, and increased saliva production.[30] On autonomic testing, patients with RLS have changes in cardiovagal control related to the arterial baroreflex and greater peripheral vascular resistance.[31] Patients with RLS also exhibit a tendency to daytime increases in blood pressure and

reduction of sympathetic and parasympathetic amplitude responses during head-up tilt table testing. They are also reported to have a blunted parasympathetic drive to changes in blood pressure.[32] The involuntary movements that occur in 80% of adult RLS, the so-called periodic limb movements in sleep, are accompanied by marked rises in pulse and blood pressures, with rises of blood pressure sometimes more than 20 mm Hg, presumably triggered by the autonomic nervous system. We have postulated that these rises in blood pressure may be the possible reason why RLS is more highly associated with hypertension, heart disease, and stroke. Patients with RLS display a non-dipping pattern of blood pressure at night, a well-known risk factor for the development of cardiovascular disease.[9,11,19,20] It is noteworthy, however, that in our previous polysomnographic study of patients with POTS, we did not find an increased prevalence of periodic limb movements in sleep.[2]

Many other medical disorders that are frequently associated with RLS, such as multiple sclerosis and rheumatoid arthritis, have an autoimmune or inflammatory diathesis.[24] RLS has also been noted to have an association with autoimmune diseases such as inflammatory bowel disease (eg, Crohn's disease) and celiac disease, and we recently noted an increased prevalence of RLS in mast cell activation syndrome, which is characterized by both autoimmune and inflammatory components.[18,22–24] Irritable bowel syndrome and small intestinal bacterial overgrowth suggestive of inflammation occur more in patients with RLS than controls.[21]

This study has implications for clinical recognition, pathophysiology, and treatment. First, because RLS is more common in POTS than in the general population, clinicians should look carefully for RLS in patients with POTS. The reverse is perhaps true as well. Given that both disorders are characterized by autonomic and autoimmune dysfunction, further studies are needed to explore the potential nexus of POTS and RLS through common autonomic and autoimmune/inflammatory mechanisms. The similarities in anemia and low iron stores would also be beneficial for follow-up. These explorations could potentially lead to treatments common to both disorders.

ABBREVIATIONS

CH-RLSq, Cambridge Hopkins Questionnaire
IRLS, International Restless Legs Scale
POTS, postural orthostatic tachycardia syndrome
RLS, restless legs syndrome

REFERENCES

1. Bagai K, Song Y, Ling JF, et al. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. *J Clin Sleep Med.* 2011;7(2):204–210.
2. Bagai K, Peltier AC, Malow BA, et al. objective sleep assessments in patients with postural tachycardia syndrome using overnight polysomnograms. *J Clin Sleep Med.* 2016;12(5):727–733.
3. Bagai K, Wakwe CI, Malow B, et al. Estimation of sleep disturbances using wrist actigraphy in patients with postural tachycardia syndrome. *Auton Neurosci.* 2013;177(2):260–265.
4. Fedorowski A. Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. *J Intern Med.* 2019;285:352–366.
5. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med.* 2005;165(11):1286–1292.
6. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. *Mov Disord.* 2011;26(1):114–120.
7. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med.* 2004;5(3):237–246.
8. Allen RP, Picchietti DL, Garcia-Borreguero D, et al.; International Restless Legs Syndrome Study Group. 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(8):860–873.
9. Erden EC, Erden İ, Türker Y, Sivri N, Dikici S, Ozşahin M. Incremental effects of restless legs syndrome on nocturnal blood pressure in hypertensive patients and normotensive individuals. *Blood Press Monit.* 2012;17(6):231–234.
10. Manchanda S, Davies CR, Picchietti D. Celiac disease as a possible cause for low serum ferritin in patients with restless legs syndrome. *Sleep Med.* 2009;10(7):763–765.
11. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. *Neurology.* 2007;68(15):1213–1218.
12. Okamoto LE, Raj SR, Gamboa A, et al. Sympathetic activation is associated with increased IL-6, but not CRP in the absence of obesity: lessons from postural tachycardia syndrome and obesity. *Am J Physiol Heart Circ Physiol.* 2015;309(12):H2098–H2107.
13. Yu X, Li H, Murphy TA, et al. Angiotensin II type 1 receptor autoantibodies in postural tachycardia syndrome. *J Am Heart Assoc.* 2018;7(8):e008351.
14. Jacob G, Diedrich L, Sato K, et al. Vagal and sympathetic function in neuropathic postural tachycardia syndrome. *Hypertension.* 2019;73(5):1087–1096.
15. Mar PL, Raj SR. Postural orthostatic tachycardia syndrome: mechanisms and new therapies. *Annu Rev Med.* 2020;71(1):235–248.
16. Peltier AC, Garland E, Raj SR, et al. Distal sudomotor findings in postural tachycardia syndrome. *Clin Auton Res.* 2010;20(2):93–99.
17. Li H, Yu X, Liles C, et al. Autoimmune basis for postural tachycardia syndrome. *J Am Heart Assoc.* 2014;3(1):e000755.
18. Weinstock LB, Walters AS, Brook JB, Kaleem Z, Afrin LB, Molderings GJ. Restless legs syndrome is associated with mast cell activation syndrome. *J Clin Sleep Med.* 2020;16(3):401–408.
19. Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, Walters AS. Rise of blood pressure with periodic limb movements in sleep and wakefulness. *Clin Neurophysiol.* 2007;118(9):1923–1930.
20. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep.* 2009;32(5):589–597.
21. Weinstock LB, Walters AS. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. *Sleep Med.* 2011;12(6):610–613.
22. Weinstock LB, Bosworth BP, Scherl EJ, et al. Crohn's disease is associated with restless legs syndrome [published correction appears in *Inflamm Bowel Dis.* 2014;20(8):1471]. *Inflamm Bowel Dis.* 2010;16(2):275–279.
23. Weinstock LB, Walters AS, Mullin GE, Duntley SP. Celiac disease is associated with restless legs syndrome. *Dig Dis Sci.* 2010;55(6):1667–1673.
24. Weinstock LB, Walters AS, Paueksakon P. Restless legs syndrome—theoretical roles of inflammatory and immune mechanisms. *Sleep Med. Rev.* 2012;16(4):341–354.
25. Allen RP, Burchell BJ, MacDonald B, Hening WA, Earley CJ. Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. *Sleep Med.* 2009;10(10):1097–1100.

26. Hening WA, Allen RP, Washburn M, Lesage S, Earley CJ. Validation of the Hopkins telephone diagnostic interview for restless legs syndrome. *Sleep Med.* 2008;9(3):283–289.
27. Walters AS, Frauscher B, Allen R, et al.; MDS Committee on Rating Scales. Review of diagnostic instruments for the restless legs syndrome/Willis-Ekbom Disease (RLS/WED): critique and recommendations. *J Clin Sleep Med.* 2014; 10(12):1343–1349.
28. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med.* 2003;4(2):121–132.
29. Jarjour IT, Jarjour LK. Low iron storage and mild anemia in postural tachycardia syndrome in adolescents. *Clin Auton Res.* 2013;23(4): 175–179.
30. Shneyder N, Adler CH, Hentz JG, et al. Autonomic complaints in patients with restless legs syndrome. *Sleep Med.* 2013;14(12):1413–1416.
31. Bertisch SM, Muresan C, Schoerning L, Winkelman JW, Taylor JA. Impact of restless legs syndrome on cardiovascular autonomic control. *Sleep*. 2016;39(3): 565–571.
32. Izzi F, Placidi F, Romigi A, et al. Is autonomic nervous system involved in restless legs syndrome during wakefulness? *Sleep Med.* 2014;15(11): 1392–1397.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July 31, 2020
Submitted in final revised form November 18, 2020
Accepted for publication November 18, 2020
Address all correspondence to: Caroline Dodson, BS, Division of Sleep Medicine, Vanderbilt University School of Medicine, Medical Center North A-0118, 1161 21st Ave South, Nashville, TN 37232-2551; Tel: (901) 483-7721; Email: caroline.dodson@vumc.org or carolineddodson@gmail.com

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. This study was supported by internal Vanderbilt University Medical Center funding to Dr. Walters through "Sleep Research in Neurology." Dr. Walters has received funding from the National Institutes of Health and Arbor Pharm for research on restless legs syndrome. Dr. Peltier has been a consultant for Alnylam, Akcea CSL Behring, and Catalyst. Dr. Raj has received research funding from the Canadian Institutes of Health Research (Ottawa, ON, Canada) related to postural orthostatic tachycardia syndrome and is a network investigator of the Cardiac Arrhythmia Network of Canada (London, ON, Canada). All other authors report no conflicts of interest.