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SCIENTIFIC INVESTIGATIONS

Restless legs syndrome is associated with long-COVID in women

Leonard B. Weinstock, MD, FACG[1]; Jill B. Brook, MA[2]; Arthur S. Walters, MD[3]; Ashleigh Goris, RN, BSN, MPH, CIC, FAPIC[4]; Lawrence B. Afrin, MD[5]; Gerhard J. Molderings, MD[6]

[1]Departments of Medicine, Missouri Baptist Medical Center and Washington University School of Medicine, St. Louis, Missouri; [2]Biostatistics, Private Practice, Truckee, California; [3]Division of Sleep Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee; [4]Infection Prevention and Control and Clinical Quality, Missouri Baptist Medical Center, St. Louis, Missouri; [5]Department of Mast Cell Studies, Hematology/Oncology, AIM Center for Personalized Medicine, Purchase, New York; [6]Institute of Human Genetics, University Hospital Bonn, Bonn, Germany

Study Objectives: Sleep disturbance is common in long-COVID (LC). Restless legs syndrome (RLS) is characterized by sleep disturbance and has been reported after viral infections. Therefore, we evaluated RLS symptoms cross-sectionally in individuals with LC at both current and pre–coronavirus disease 2019 (pre-COVID-19) time points.

Methods: Adults on LC-focused Facebook pages were recruited for an online assessment of symptoms before COVID-19 infection and during their present LC state in a cross-sectional manner. The LC group documented baseline symptoms retrospectively. Questions were included about the presence/severity of RLS symptoms and assessments of fatigue, quality of life, and sleep apnea. A control group was recruited and included individuals ≥ 18 years of age who never had overt symptoms of COVID-19. Pregnancy was an exclusion criterion for both groups.

Results: There were 136 participants with LC (89.7% females, age 46.9 ± 12.9 years) and 136 controls (65.4% females, age 49.2 ± 15.5). RLS prevalence in females with LC was 5.7% pre-COVID-19 and 14.8% post-COVID-19 ($P < .01$) vs 6.7% in control females. Severity of RLS was moderate in both groups. Logistic regression predicting post-COVID-19 RLS among females with LC failed to find significant effects of hospitalization, sleep apnea, neuropathic pain severity, or use of antihistamines and antidepressants.

Conclusions: The baseline prevalence of RLS in females with LC was similar to the general population group as well as to patients in epidemiological studies. The prevalence significantly increased in the LC state. Postinfectious immunological mechanisms may be at play in the production for RLS symptoms.

Keywords: COVID-19, long-COVID, fatigue, long-haul-COVID, restless legs syndrome

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disturbance and neurological symptoms are common in long-COVID. The prevalence of restless legs syndrome has not been investigated to a significant degree in long-COVID.

Study Impact: The prevalence of restless legs syndrome was increased in female participants with long-COVID. Postinfectious immunological mechanisms are possibly at play in the production for restless legs syndrome symptoms.

INTRODUCTION

A significant number of patients with acute coronavirus disease 2019 (COVID-19) go on to experience long-COVID (LC) also known as long-haul COVID, post-COVID inflammatory syndrome, and postacute sequelae of COVID-19.[1] The largest studies reported LC symptoms in 1) 23.2% overall, and in 50% of those hospitalized, of 1.9 million Americans; 2) 44.2% of 1,142 hospitalized Spaniards; and 3) 47.1% of 2,649 hospitalized Russians.[2–4]

Neurological complications of acute COVID-19 infection are common: 36% of 214 hospitalized patients in a Chinese study and 57% in 854 hospitalized patients in a Spanish study experienced complications, including stroke, altered consciousness, headaches, and dizziness.[5,6] Theories for these problems include brain infection by the virus, effect of cytokines, thrombosis, and neuroinflammation with microglia–T-cell interactions.[5,7,8] In contrast, the most common chronic neurological symptoms in LC in descending order are fatigue, memory loss, cognitive dysfunction ("brain fog"), anosmia, ageusia, headache, neuropathy, nausea, tremor, and vision disturbance.[1] Tinnitus and hearing loss can be significant in LC.[9] Postural orthostatic tachycardia syndrome is reported in LC and has been theorized to be due to development of autoantibodies or mast cell activation syndrome (MCAS).[10,11] MCAS is a common multisystemic disorder with inflammatory and/or allergic manifestations caused by unregulated, aberrant mast cells.[12] We found recently that MCAS symptoms are common in LC.[13]

Sleep disturbances occur in 34% of patients with COVID-19 in general.[14] A Spanish multicenter study revealed that 35% of 1,142 patients with COVID-19 who were discharged from the hospital had poor sleep quality after 7 months.[15] An Egyptian study of 182 participants at 6 months post-COVID-19 infection utilized the Pittsburgh Sleep Quality Index.[16] Poor sleep was

found in 65% of the participants, and the risk factors included a history of diabetes, oxygen support, and mechanical ventilation. At 6 months after the infection, fatigue or muscle weakness and sleep difficulties were the main symptoms of patients who had recovered from COVID-19.[17] In this study of 1,655 patients, 26% had sleeping difficulties as noted on a general questionnaire.

Restless legs syndrome (RLS) is a sensorimotor disorder with the compelling urge to move the extremities, often associated with discomfort, occurring at rest, usually in the evening or bedtime, and improving temporarily with movement.[18] The prevalence of RLS is approximately 7%.[19] Patients have a poor quality of life and poor sleep.[18,19]

RLS has been associated with inflammation, immune disorders, iron deficiency, peripheral neuropathy, hypoxia, endorphin deficiency, autonomic dysfunction, postinfectious states, and most recently, MCAS.[20–25] In a review of secondary RLS, it was found that inflammation and/or immune disturbances were present in 95% of the 38 highly associated disorders, diseases, and conditions.[20]

A single case report detailed a man who had short-lived RLS that occurred during acute COVID-19 infection.[26] One paper reviewed possible effects of home confinement on established RLS patients in the setting of the world pandemic of COVID-19.[27] We are unaware of studies of the prevalence of RLS developing in a population with LC.

In light of prior reports of postviral RLS, potential concerns about sleep disturbances in LC, and multiple online posts complaining of RLS-type symptoms in LC support groups, we hypothesized that the prevalence of RLS would be increased in LC. We examined the prevalence, risk factors, and severity of RLS in LC in a cross-sectional manner using a general population control group as a comparator group.

METHODS

Two groups were examined in this cross-sectional survey study: 1) patients with LC and 2) general population controls. Questions about pre-COVID and post-COVID symptoms were administered at a single point in time in a cross-sectional manner in the LC group. The participants with LC filled out a pre-COVID-19 questionnaire by recall at the same time they filled out an identical post-COVID-19 questionnaire. The duration of time between filling out the questionnaire and their COVID-19 infection was determined. Control participants completed an identical questionnaire a single time. Questions included validated assessments of fatigue,[28,29] quality of life,[30] sleep apnea,[31] and RLS. The 5 RLS diagnostic questions of the International RLS Study Group Criteria were queried, and, if these were positive, the Cambridge-Hopkins RLS Diagnostic Questionnaire was filled out, followed by the Self-Assessed International RLS Severity Rating Scale and the RLS Post-Sleep Questionnaire.[32–35] Two of the investigators (L.B.W. and A.S.W.) individually reviewed the Cambridge-Hopkins Diagnostic Questionnaires to confirm who should be diagnosed with RLS. For the Self-Assessed International RLS Severity Rating Scale, score interpretation is: 0–10 = mild, 11–20 = moderate, 21–30 = severe, and 31–40 = very severe.

The study was approved by the Missouri Baptist Medical Center Investigational Review Board in St. Louis, MO. All participants gave informed consent. Data collection started in October 2020 and ended May 2021. LC-focused Facebook group organizers were contacted to allow us to advertise an online study in their groups promoting an investigation of symptoms present before and after COVID-19 infection. No other descriptors were provided that might bias recruitment. This group was then compared to a general population control group. The control group was composed of employees and their spouses from the Missouri Baptist Medical Center and the office of the lead investigator (L.B.W.). The other exclusion criteria for all groups were age < 18 years, current pregnancy (or pregnancy during COVID-19), and a known history of acute COVID-19 in the control group.

The primary aims were to determine whether prevalence and severity of RLS and fatigue in LC were 1) similar to controls during their pre-COVID-19, baseline health state and 2) significantly higher after COVID-19. The hypothesis that precovid 19 quality of life was similar to controls and significantly reduced after the development of COVID-19 was also tested. Secondary aim was to determine the predictors of RLS. Mean and prevalence data were compared between participants with LC who developed new-onset RLS after COVID-19 and participants with LC who never had any RLS (before or after COVID-19). A small subanalysis within the larger cross-sectional design was performed. A regression analysis was used to determine what factors might be predictive of RLS in patients with COVID-19. A value of $P < .05$ was considered statistically significant.

To assess the contribution of sleep-disordered breathing to RLS (prior to COVID-19 or newly developed), obstructive sleep apnea risk was assessed as a proxy. Participants were designated as high risk for sleep apnea if their STOP-BANG score was ≥ 3 or if they owned a device for treatment of sleep apnea. All groups were queried about their medicines/supplements, and the LC group was also asked about medicines/supplements used prior to the infection. The medicines/supplements included: 1) those known to worsen RLS (metoclopramide, all nonsedating and sedating antihistamines, melatonin, and all antidepressants and antipsychotics); 2) those reported to improve RLS, COVID-19, and/or LC (benzodiazepines, steroids, and vitamin D); 3) those that could specifically affect acute COVID-19 and/or LC (angiotensin converting enzyme inhibitors, carvedilol, hydroxychloroquine, biological agents, all antihistamines including H1 and H2 receptor blockers, montelukast, aspirin, nonsteroidal anti-inflammatory drugs, melatonin, and vitamins C and D).

RESULTS

Overall, there were 136 participants with LC (89.7% female, age 46.9 ± 12.9 years) and 136 control participants (65.4% female, age 49.2 ± 15.5). None of the 14 male participants with LC had RLS before or after COVID-19. Two male control participants had RLS. There were not enough male participants to

Table 1—Clinical characteristics of female participants.

	Controls	Patients with Long-COVID
Sample size, n	89	122
Age, mean (SD)	47.1 (15.4)	47.5 (12.1)
BMI, mean (SD), kg/m^2	25.1 (5.0)	28.2 (8.3)
Race, %		
White	93.3%	88.5%
Black	3.4%	3.3%
Asian	1.1%	1.6%
Hispanic	0%	0%
American Indian	0%	0%
Other	2.2%	6.6%

BMI = body mass index, SD = standard deviation.

do meaningful tests of RLS prevalence. Accordingly, comparisons were limited to the females of each group (Table 1).

There were no significant differences between the females in age [$F(2,276)=0.08$, $P = .92$] or proportion of Caucasian/White participants (χ^2 [2, n = 279] = 4.6, $P = .10$). One-way analysis of variance with Tukey honestly significant difference post hoc analysis on body mass index showed that female participants with LC had significantly higher mean body mass index (± standard deviation) (28.2 ± 8.3 kg/m^2) than the control participants (25.1 ± 5.0 kg/m^2). Among the female participants with LC, 97 (79.5%) had a positive COVID-19 test and 19 (15.6%) were hospitalized for COVID-19. Antibody testing was not available at the time of the infection for 8 of the 122 women. Medications and dietary supplements are shown in Table 2. The mean (± standard deviation) duration between symptoms of COVID-19 and the day that the participants with LC filled out both questionnaires was 193 (± 161) days.

Table 3 demonstrates RLS prevalence, severity and sleep impact, fatigue, quality of life, and potential clinical risk factors among females in each group. The RLS prevalence pre-COVID-19 (5.7%) was similar to that among control participants (6.7%; $\chi 2$ [1, n = 211] = 0.09, $P = .8$). Female LC participants had significantly higher prevalence of RLS after COVID-19 compared to before COVID-19 (14.8% vs 5.7%, $P < .01$). Among those with RLS, severity scores and sleep impact scores did not significantly differ at present day between the LC group and controls. For the Self-Assessed International RLS Rating Scale, scores for all women with RLS were 10–20 or moderate severity. Pre-COVID fatigue scores were slightly but significantly lower than those of controls ($t[160.1] = 2.4$, $P = .02$), but escalated significantly and doubled after COVID-19 [$t(121) = -18.6$, $P < .0001$]. Pre-COVID quality of life scores resembled those of controls [$t(160.1) = -0.6$, $P = .5$], but then dropped steeply and significantly post-COVID [$t(121) = 15.6$, $P < .0001$].

As shown in Table 4, the 13 females with new onset RLS post-COVID-19 were compared to the 102 females post-COVID-19 without a history of RLS either pre-LC or post-LC. The remaining 7 females with pre-LC RLS—2 of whom no longer reported RLS post-COVID-19—were removed from the comparison. There were 2 participants who had RLS prior to developing COVID-19 and then, for unknown reasons, no longer experienced RLS. This explains the changes from 13 new cases vs 18 total in the post-COVID group. There were no statistically significant differences between these 2 groups when comparing means (or prevalence) of the following variables: age, hospitalization for COVID-19, COVID-19 confirmed by testing, ownership of sleep apnea device, high-risk STOP-BANG score, designation of "high sleep apnea risk", neuropathic pain severity, fatigue, quality of life score, or use of various medicines/supplements. Table 4 includes a small subanalysis within the larger cross-sectional design.

Among women with LC, univariate logistic regression did not identify any of the following tested variables as predictors of new-onset RLS after COVID-19: hospitalization for COVID-19

Table 2—Number and percentage of female participants taking various medications and dietary supplements.

	Controls	Pre-COVID-19 Participants with Long-COVID	Post-COVID-19 Participants with Long-COVID
Antihistamines	24 (26.9%)	45 (36.9%)	70 (57.4%)[c]
Antidepressants	20 (22.5%)	24 (19.7%)	22 (18.0%)
NSAIDS	32 (36.0%)	54 (44.3%)	75 (61.5%)[c]
Immunosuppressants[a]	4 (4.5%)	9 (7.4%)	34 (27.9%)[c]
Montelukast	3 (3.4%)	11 (9.0%)	13 (10.7%)
Steroids	2 (2.2%)	6 (4.9%)	32 (26.2%)[c]
Benzodiazepines	10 (11.2%)	17 (13.9%)	22 (18.0%)
Vitamin C	27 (30.3%)	45 (36.9%)	79 (64.8%)[c]
Vitamin D	43 (48.3%)	64 (52.4%)	87 (71.3%)[c]
Melatonin	8 (9.0%)	18 (14.8%)	46 (37.7%)[b,c]

[a]Immunosuppressants included hydroxychloroquine, 5 different immune modulators, and 10 different biological agents. [b]Significantly different from controls. [c]Significantly different from pre-COVID-19 participants with long-COVID. COVID-19 = coronavirus disease 2019, NSAID = nonsteroidal anti-inflammatory drug.

Table 3—Mean and prevalence data describing clinical characteristics potentially related to RLS and long-COVID in female participants.

	Controls	Pre-COVID-19 Participants with Long-COVID	Post-COVID-19 Participants with Long-COVID
RLS prevalence, n (%)	6 (6.7%)	7 (5.7%)	18 (14.8%)[c]
RLS Severity Score, mean (SD)[a]	14.0 (4.5)	[d]	18.1 (7.8)
RLS Sleep Impact Score, mean (SD)[a]	5.0 (1.4)	[d]	9.6 (3.8)
Fatigue severity, mean (SD)	19.5 (8.6)	16.8 (6.6)	34.7 (10.7)[c]
Quality of life, mean (SD)	73.3 (21.6)	75.0 (16.8)	40.4 (21.6)[c]
Ownership of sleep apnea device, n (%)	2 (2.2%)	6 (4.9%)	8 (6.5%)
High-risk STOP-BANG score, n (%)	6 (6.7%)	24 (19.7%)[a]	42 (34.4%)[c]
High sleep apnea risk, n (%)[b]	8 (9.0%)	26 (21.3%)[a]	44 (36.1%)[c]
Neuropathic pain severity, mean (SD)	4.5 (3.0)	2.7 (2.3)[a]	5.6 (2.7)[c]

[a]Among those with RLS. [b]"Likely sleep apnea" denotes those who own a sleep apnea device and/or have a STOP-BANG score ≥ 3. [c]Significantly different from pre-COVID participants with long-COVID. [d]Pre-COVID-19 long-COVID data for RLS severity were not possible since these are determined by symptoms during the prior week of the assessment and thus are not accurate as retrospective data. COVID-19 = coronavirus disease 2019, RLS = restless legs syndrome, SD = standard deviation.

(P = .50), high risk for sleep apnea post-COVID-19 (P = .70), post-COVID-19 neuropathic pain severity (P = .14), post-COVID-19 use of antihistamines (P = .85), antidepressants (P = .63), vitamin D (P = .68), benzodiazepines (P = .29), or steroids (P = .79). Melatonin use was significantly higher in the LC state.

DISCUSSION

To our knowledge, the prevalence of RLS in patients with LC has not been studied previously in depth. Prior to COVID-19, the prevalence of RLS in our population of study was similar to

Table 4—Characteristics of newly diagnosed female participants with long-COVID with RLS compared with those without RLS.

	Participants with Long-COVID with New RLS	Participants with Long-COVID without RLS	Test Statistic	*P*	Effect Size
n (%)	13 (11.3%)	102 (88.7%)			
Age, mean (SD), y	46.1 (9.7)	47.1 (12.5)	t(17.5) = −0.36	.73	Cohen's *d* = 0.09
Hospitalized, n (%)	3 (23.1%)	16 (15.7%)	χ^2 (1, n = 115) = 0.08	.78	OR = 1.6 (95% CI 0.4–6.5)
Laboratory-confirmed COVID-19 positive, n (%)	11 (84.6%)	81 (79.4%)	χ^2 (1, n = 115) = 0.00	.94	OR = 1.4 (95% CI 0.3–6.9)
Sleep apnea device ownership, n (%)	2 (15.4%)	6 (5.9%)	χ^2 (1, n = 115) = 0.48	.49	OR = 2.9 (95% CI 0.5–16.2)
High STOP-BANG score, n (%)	3 (23.1%)	36 (35.3%)	χ^2 (1, n = 115) = 0.32	.57	OR = 0.5 (95% CI 0.1– 2.1)
High sleep apnea risk, n (%)[a]	4 (30.8%)	37 (36.3%)	χ^2 (1, n = 115) = 0.01	.93	OR = 0.8 (95% CI 0.2– 2.7)
Neuropathic pain severity, mean (SD)	5.9 (3.0)	4.4 (3.3)	t(16.0) = 1.6	.12	Cohen's *d* = 0.47
Fatigue, mean (SD)	45.5 (9.6)	34.2 (10.9)	t(16.2) = 0.45	.66	Cohen's *d* = 1.1
Quality of life, mean (SD)	35.4 (20.2)	40.6 (21.8)	t(15.8) = −0.87	.40	Cohen's *d* = 0.25
Antihistamine use, n (%)	8 (61.5%)	60 (58.8%)	χ^2 (1, n = 115) = 0.00	1.0	OR = 1.1 (95% CI 0.3–3.7)
Antidepressant use, n (%)	3 (23.1%)	18 (17.6%)	χ^2 (1, n = 115) = 0.01	.92	OR = 1.4 (95% CI 0.3–5.6)
Vitamin D, n (%)	9 (69.2%)	76 (74.5%)	χ^2 (1, n = 115) = 0.00	.94	OR = 0.8 (95% CI 0.2–2.7)
Benzodiazepine use, n (%)	1 (7.7%)	21 (20.6%)	χ^2 (1, n = 115) = 0.55	.46	OR = 0.3 (95% CI 0.03–2.6)
Steroid use, n (%)	3 (23.1%)	27 (26.5%)	χ^2 (1, n = 115) = 0.00	1.0	OR = 0.83 (95% CI 0.2–3.2)

[a]"High sleep apnea risk" denotes those who own a sleep apnea device and/or have a STOP-BANG score ≥ 3. CI = confidence interval, COVID-19 = coronavirus disease 2019, OR = odds ratio, RLS = restless legs syndrome. SD = standard deviation.

the average prevalence cited in the literature.[18] In this cross-sectional survey study, we found that the prevalence of RLS was increased in the female LC group (5.7% pre-LC baseline compared to 14.8% in the LC state). In comparison to the female control group, there was a statistically significant increase in the prevalence of RLS in the participants with LC. The mean RLS severity and sleep impact was moderate in the LC group at present day and in controls. Logistic regression analysis was used to determine whether the following factors predicted RLS among the female participants with LC: hospitalization for COVID-19, high sleep apnea risk, neuropathic pain severity, and use of antihistamines and antidepressant medications. None were found to be significant predictors of RLS.

The LC participants filled out their pre-COVID-19 questionnaire by recall, which is a major study limitation. Recall bias is present in retrospective studies. In the present study, this bias may have been minimized by a mean recall duration of only 6.4 months.

Recall bias could have affected RLS diagnostic criteria, although the Cambridge-Hopkins Questionnaire is a reliable tool. Accordingly, we felt that the diagnosis of RLS could be made with a reasonable degree of accuracy. Sex imbalance with females with LC outnumbering males with LC is a potential limitation. This is likely due to the makeup of the LC Facebook group and/or sex preference for recruitment. Sex imbalance was found in a concurrent study that recruited participants with LC from the same online groups (78.9% of 3,762 online survey respondents were women).[36] In the largest study to date, LC was more common in women.[2] To overcome this limitation, we confined our analysis to females. In addition, participants with LC from a medical support group might be more ill than other people. We cannot be sure that general control group members did not have unrecognized COVID-19 infection. A blood bank study demonstrated presence of positive antibodies in asymptomatic COVID-19 cases.[37] Among the female participants with LC, 19 (15.6%) were hospitalized for COVID-19. In the total group, a COVID-19 test was positive in 97 (79.5%). Testing was either negative or not available at the time of the infection for the remainder of the participants. The questionnaire did not include details about type of testing or whether the participants had availability to testing, which was an issue in 2020. In addition, false-negative rate of polymerase chain reaction testing is approximately 10%.[38] Finally, in the evaluation of medicines/supplements, we did not look at the effect of usual RLS treatments, which include dopaminergic agents, alpha(2)delta calcium channel anticonvulsants, opioids, or iron that might suppress/affect the recognition of RLS. However, if this had an impact, we would have expected a decreased incidence and/or severity of RLS in the LC group in comparison to the control group, but this was not the case. Other potential treatments for RLS (benzodiazepines, vitamin D, and steroids) did not have an impact on the statistical analysis. Furthermore, considering the recruitment method, we were unable to measure serum ferritin levels on the participants as iron deficiency is common in RLS. Finally, post-COVID-19 participants were taking statistically more melatonin compared to their pre-LC state. Melatonin has been reported to worsen motor symptoms of RLS.[39]

CONCLUSIONS

In this cross-sectional survey, the baseline prevalence of RLS in females with LC was similar to the general population control female group and women in previous epidemiological studies. The prevalence of RLS is increased in the LC state. We theorize that postinfectious immunological mechanisms may be one potential way that RLS could be produced by COVID-19.[20]

ABBREVIATIONS

CI, confidence interval
COVID-19, coronavirus disease 2019
LC, long-COVID
MCAS, mast cell activation syndrome
OR, odds ratio
RLS, restless legs syndrome

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Address correspondence to: Leonard Weinstock, MD, 11525 Olde Cabin Road, St. Louis, MO 63141; Tel: (314) 997-0554; Fax: (314) 997-5086; Email: lw@gidoctor.net

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