

SCIENTIFIC INVESTIGATIONS

## The High Prevalence of Restless Legs Syndrome Symptoms in Liver Disease in an Academic-Based Hepatology Practice

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**Study Objectives:** Survey-based epidemiologic studies suggest that restless legs syndrome (RLS) affects approximately 10% of the general population and can cause significantly reduced quality of life due to sleep disturbance. This condition is more prevalent in certain disease states, such as iron deficiency anemia, neuropathy, and renal insufficiency. No such prevalence data exists for RLS in liver disease. The aim of the present project was to assess the self-reported prevalence of RLS using an RLS symptom specific questionnaire in patients presenting to a tertiary hepatology clinic with chronic liver disease (CLD). This was a convenience cohort study of established chronic liver disease patients being seen at a tertiary referral center. A one-page survey querying RLS symptoms was administered in hepatology clinic to patients with chronic liver disease. Restless legs syndrome (RLS) symptoms as agreed upon by the International RLS Study Group were incorporated as 5 key questions. Of 141 completed surveys, 88 were positive yielding a questionnaire based prevalence of RLS of 62% in this select population. RLS risk factors were further assessed through chart review and self-report and using a logistical regression analysis. Comparison between those reporting RLS symptoms and those who did not revealed only self-reported neuropathy to be significantly higher in those with RLS. RLS associated with risk factors accounted much of the total prevalence. Of those with RLS symptoms, 23 surveyed were

without known RLS risk factors. This yields a convenience sample prevalence of unexplained RLS symptoms of 16.3% (CI: 10.6-23.5) in this population. There did not appear to be a correlation between the severity of liver dysfunction including the presence of cirrhosis or the etiology and the prevalence of RLS symptoms. Quality of Life (QoL) surveys specific to RLS completed suggest RLS symptoms result in significantly diminished QoL, with an average QoL score of 68 on a 0-100 scale.

**Conclusion:** This study is the first investigation of RLS prevalence in liver dysfunction. This select population of medically complex patients who all have some degree of liver dysfunction appear to have a surprisingly high prevalence of RLS symptoms. While much of this prevalence may be the result of known secondary causes further investigation is warranted to explore the relationship between RLS and liver dysfunction.

**Keywords:** RLS, sleep disturbance, quality-of-life, cirrhosis, liver disease

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**R**estless Legs Syndrome (RLS) is a clinical syndrome that affects approximately 10% of the population based on epidemiologic surveys.<sup>1-7,22</sup> Its impact on sleep quality and quality of life can be significant. It is a syndrome most often identified by the following tetrad of symptoms: focal akathisia (an irresistible desire to move localized to the extremities that is periodic and distressing due to abnormal sensations), motor restlessness,

quiescagenic symptoms (engendered or exacerbated by remaining at rest), and circadian phenomenon (symptoms worsen in the evening/night for a person entraining to a normal circadian rhythm).<sup>1,7</sup> This condition is more prevalent in advanced age groups and in certain disease states such as uremia,<sup>1,8,18-20</sup> iron deficiency anemia,<sup>1,11</sup> and neuropathies.<sup>14,16</sup> Review of the literature suggests the prevalence may double to quadruple from that of the general population in these conditions. There is also ample evidence of inheritance pattern in the idiopathic form, with up to 50% able to identify a first-degree relative also affected.<sup>1,10,12</sup>

Identification of these populations has led to increased awareness of this condition and increased therapies aimed at improving QoL.<sup>17</sup> RLS rarely resolves on its own and typically worsens symptomatically over time in the idiopathic form.<sup>1,17</sup> There is little known about the natural history of secondary RLS in association with specific disease states but in renal patients the severity is not progressive.<sup>20</sup>

While certain disease states have previously been identified as having a much higher prevalence of RLS, no such prevalence

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data exists for RLS in CLD. Identifying a higher prevalence of RLS may lead to early identification and treatment of RLS in this population.

## Experimental Procedure

The primary aim of the present study was to determine the self-reported survey-based prevalence of RLS symptoms in patients with liver disease at a tertiary referral academic hepatology clinic and identify factors associated with the presence of symptoms. The secondary aims of the study were 1) to determine if the degree of liver dysfunction correlated with self-reported RLS and 2) to measure the severity of RLS and its impact on QoL through use of validated tools developed by the International Restless Legs Syndrome Study Group (IRLSSG).<sup>23,24</sup>

## Subjects

Patients with CLD seen in an academic-based tertiary hepatology clinic were invited to participate. This was a convenience sample with enrollment from July 2004 to December 2004. Patients with liver dysfunction (abnormal liver function tests and/or histological liver disease) being seen in consultation and follow-up were invited to participate and only those with clinical hepatic encephalopathy were excluded. All patients considered had established liver dysfunction as defined above and with more than 3 months duration of abnormalities in liver function testing (CLD). This population was heterogeneous in age, gender, cause, and severity of chronic liver disease. Those with comorbid diseases known to be associated with RLS were not excluded from participation. The protocol for this study was approved by the institutional review board of the Medical College of Wisconsin and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Consent to participate was obtained at the time of the scheduled hepatology clinic visit by the treating hepatologist. The subjects were asked if they would be willing to fill out a one-page survey and to be contacted by phone for follow-up questions if necessary. The content of the survey was not revealed before consent to participate was obtained to reduce selection bias. Approximately 155 patients were invited to participate, and 141 patients completed the initial screening questionnaire for RLS.

## METHODS

An initial screening survey was administered during a hepatology clinic visit. This survey was based on the validated Johns Hopkins Telephone Diagnostic Interview for RLS which complements the recommended essential diagnostic criteria of the IRLSSG.<sup>7,8</sup> The survey provided background information including recognized conditions associated with RLS, demographics and 5 RLS qualitative screening questions based on IRLSSG and the National Institutes of Health definition of the syndrome.<sup>8</sup>

Survey results were reviewed by the investigators and phone follow-up with individual participants was utilized to confirm the RLS symptoms reported on the survey. In order to be considered for phone confirmation, 3 questions reported as positive were required. These 3 questions related to core symptoms of

RLS: urge to move, unpleasant sensations associated with the urge to move, improvement with activity, worsening with immobility. Two additional questions focused on limb movements: frequent jerking of limbs with sleep, motor restlessness commented on by others, but were not required to consider the survey positive for RLS symptoms. The phone surveys consisted of confirming with the subject that the recognized symptoms of RLS were present, and then completing the International RLS Severity Scale Questionnaire (IRLS)<sup>22-25</sup> which is a validated rating scale of severity based on the discomfort due to RLS, the need to move the legs, the severity of sleep disturbances, the impact of RLS on daily activity and the overall severity of the symptoms and the relief of discomfort by movement. These participants also completed an RLS specific QoL survey, the Johns Hopkins RLS QoL survey.<sup>21</sup> This survey measures the effect of RLS symptoms in the context of their impact on performing activities such as occupational and social responsibilities, and activities of daily living.

A chart audit was also completed on all participants in this study. Items audited included etiology of liver disease and severity based on liver function tests, radiography reports and/or biopsy results, renal function, hemoglobin, ferritin (when available), and additional diagnoses such as anemia, rheumatoid arthritis, polyneuropathy, and diabetic peripheral neuropathy. Alcohol use and medications known to precipitate RLS were also queried.

## Statistical Analysis

The analysis was performed in SAS version 9.1 (The SAS Institute, Cary, NC) and StatXact version 3.0 (Cytel Software Corporation). Continuous variables such as age, RLS QoL and IRLS scores, and blood test results were recorded and reported as mean with 95% confidence interval (CI). Categorical variables such as type of liver disease, the presence/absence of renal dysfunction, neuropathy, iron deficiency, cirrhosis, dopamine antagonist medication use, alcohol use, and gender were converted to percentages and reported with 95% confidence intervals (CI). Group means were compared by the Fisher's test. Correlation between presence of cirrhosis and severity of RLS symptoms using the IRLS and RLS QoL survey were analyzed using the Two sample *t*-test.

The unexplained RLS group was created by excluding all subjects with neuropathy, anemia, iron deficiency, kidney disease, dopamine antagonist medication use, alcohol use, creatinine greater than 2.5, or hemoglobin less than 11. Fisher's test and stepwise logistic regression were used to test for any associated with RLS within the unexplained RLS group. Binomial confidence intervals are given for the prevalence of unexplained RLS in patients overall, and for those with/without cirrhosis. A significance level of 0.05 was used for all comparisons.

## RESULTS

Ninety subjects were found to have a positive initial RLS survey. When the symptoms were reviewed via phone follow up, two surveyed were felt to be false positives. Twelve subjects with positive initial RLS surveys could not complete the follow-up phone surveys for QoL and severity scores.

Eighty-eight subjects reported the core 3 symptoms of RLS present and of this group 32% reported additional symptoms of limb jerking and motor restlessness witnessed by others. The self-reported prevalence of RLS in our convenience population based on this survey was 88/141 or 62% (95% CI:± 8.25), which is significantly greater than the general population prevalence rate of 10% ( $p < 0.00001$ ). Of those enrolled for the study there was a nearly equal ratio of male to females in both those reporting RLS symptoms (m:f=1.09) and those without symptoms (m:f=0.83). The mean age was not significantly different ( $52.7 \pm 9.1$  vs.  $56.4 \pm 14.2$ ) between these groups.

Stepwise logistic regression analysis for RLS associated risk factors was done for both those reporting RLS and those who did not report RLS symptoms. These risk factors included: kidney disease, iron deficiency, neuropathy, known medication triggers such as dopamine antagonists, and/or alcohol use. The statistical analysis findings are summarized in table 1. There was no significant difference between the groups with the exception of self-reported neuropathy which was more commonly reported in the RLS group at 85.1% ( $\pm 19.8$ ) vs. 57.0% ( $\pm 9.5$ ) by Fisher's test ( $p = 0.0075$ ).

Exclusion of all subjects with risk factors for the development of RLS left a pool of 41 patients, of which 23 reported RLS symptoms. RLS symptoms without risk factors were present in 56.4% (CI:± 15.9) which is statistically significantly higher than the general population prevalence of 10% ( $p < 0.001$  by Fisher's test). Analysis of the markers of liver dysfunction (albumin, INR, total bilirubin, creatinine) in this subgroup without risk factors for RLS comparing those with unexplained RLS and those without symptoms did not reveal any significant differences by *t*-test.

**RLS Quality of Life and Severity Assessment**

We were able to contact 76 subjects with a RLS positive survey for the RLSQoL questionnaire and 74 RLS patients responded (2 refused). The mean RLSQoL score for this group was 68 ( $\pm 5.0$ ). This score reflects moderate diminished QoL based on previous validation.<sup>21</sup> Fifty-six subjects completed the IRLS. This consists of 10 questions to assess the severity of RLS symptoms with a possible high score of 40. The mean sum score for the group was 15 (+1.6). The presence of cirrhosis in CLD did not correlate by Two Sample *t*-test for either IRLS ( $p = 0.8$ ) or for RLSQoL score ( $p = 0.7$ ).

**DISCUSSION**

This convenience population survey of chronic liver disease patients uncovered a surprisingly high self reported proportion of RLS in a tertiary referral hepatology clinic population. This is the first such study of RLS in patients with chronic liver disease. While a significant proportion of the prevalence may be explained by coexisting risk factors for RLS such as neuropathy, there is still a substantial excess prevalence of 16% for which there is no obvious explanation. The presence of cirrhosis and severity of liver dysfunction did not translate into worsened QoL or severity of RLS symptoms.

The limitations of our study include the use of a convenience population which may lead to selection bias with factors in-

**Table 1—RLS Associated Comorbidities in CLD**

RLS Risk Factor	N	Percent with RLS ( $\pm 95\%$ CI)
Kidney Disease		
Present	17	64.7% ( $\pm 23.8$ )
Absent	124	62.1% ( $\pm 8.9$ )
Anemia		
Present	47	68.1% ( $\pm 14$ )
Absent	94	59.6% ( $\pm 10.3$ )
Iron Deficiency		
Present	31	64.5% ( $\pm 17.5$ )
Absent	110	61.2% ( $\pm 9.4$ )
Neuropathy**		
Present	27	85.2% ( $\pm 14.8$ )
Absent	114	57.0% ( $\pm 9.5$ )
Medications or other (Dopamine antagonist, alcohol use, antihistamines etc.)		
Present	51	68.6% ( $\pm 13.4$ )
Absent	85	60.0% ( $\pm 10.9$ )

\*\*Fisher's test  $p$ -value = 0.0075

cluding surveying a tertiary care population with more concomitant illnesses and patient participation bias. This was not a homogeneous population in that there were a variety of liver diseases ranging from alcoholic liver disease to viral hepatitis to autoimmune disease which may introduces bias. In addition, the subjects were asked to self-report known comorbidities for RLS and this may result in recall bias with under recognition of known secondary causes of RLS such as neuropathy. The role of subclinical or minimal hepatic encephalopathy in liver cirrhosis was not assessed and CNS dysfunction is not directly correlated with liver dysfunction severity. The retrospective nature of chart audit/review may also have limited the assessment of the severity of liver dysfunction at the time of the survey. This is especially important given the lack of effect of the degree of liver dysfunction as measured in the cirrhotic patients by the MELD score on the presence of RLS and the severity of RLS symptoms.

Understanding these limitations, is there a mechanism that could lead to excess risk for RLS in CLD? One possible mechanism involves serotonin dysregulation and dysfunction of the corticospinal tracts. RLS is thought to result from the interaction of cortical dysregulation of subcortical motor and sensory tracts. In liver disease, there is evidence of CNS dysfunction.

Serotonin is a key sleep/wake regulator and serotonin reuptake inhibitors will exacerbate or bring on RLS symptoms in some susceptible individuals.

Lozeva-Thomas demonstrated that there is an excess of 5-HIAA (5-hydroxyindoleacetic acid) and blockade of serotonin release leading to a decreased serotonergic transmission even in compensated cirrhosis.<sup>26</sup> Serotonin precursors such as quinolinic acid and tryptamine, tryptophan metabolites, are increased in the brain and CSF of patients with liver disease.<sup>27,28</sup>

Dysfunction of the corticospinal tracts in CLD has been reported and specialized imaging techniques using magnetic resonance imaging of the brain in chronic liver disease are also abnormal. Proton magnetic resonance spectroscopy studies suggest metabolic abnormalities associated with a disturbance in brain cell volume homeostasis. This appears to be especially true of the structure of the brain stem. Fast Flair techniques in

magnetic resonance imaging (MRI) have revealed reversible abnormalities (with transplantation) in the corticospinal tracts.<sup>27</sup> RLS developing in diseases affecting these tracts is well described.<sup>16</sup>

RLS symptoms may be a reflection of peripheral or central nervous system dysfunction. Complete neurological evaluation may reveal that a significant number of CLD patients have undiagnosed neuropathy. Many of the diseases associated with liver dysfunction such as alcoholism, viral hepatitis, and hemochromatosis can contribute or cause peripheral nerve disease/dysfunction.<sup>29</sup> Electromyography and nerve conduction studies may also reveal an excess of peripheral nerve disease not easily appreciated by these patients.

### SUMMARY

Self-reported RLS symptoms were prevalent in our cohort of patient with CLD. Self-reported comorbid conditions associated with RLS in this population explain much of the prevalence. However there is some evidence from this limited population sampling suggesting CLD may carry additional risk of RLS. The reason for this may be multifactorial. Clearly, there is evidence of both central dysfunction as well as opportunity for the development of peripheral nervous system dysfunction in liver disease. The CLD patient has a large health burden which may only be worsened by RLS. Quality of life measures related to RLS in our study are not significantly different from other RLS QoL population studies using the same instrument suggesting the condition when present in the setting of CLD does not result in a more severe form or excess QoL impairment. Further studies are warranted to better determine if liver dysfunction can directly be correlated with the presence of RLS symptoms. This will require larger multicenter trials carefully controlled for confounding factors. Despite its limitations, this study is to our knowledge the first study of RLS symptoms in liver disease and this work has uncovered that RLS symptoms can be common in those treated for liver disease and can contribute to decreased quality of life.

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### ABBREVIATIONS

RLS = restless legs syndrome  
 CLD = chronic liver disease  
 QOL = quality of life  
 IRLSSG = International Restless Legs Syndrome Study Group  
 IRLS = International RLS Severity Scale Questionnaire  
 MELD = model for end-stage liver disease  
 SD = standard deviation  
 CI = confidence intervals

5-HIAA = 5-Hydroxyindole Acetic Acid

CSF = cerebral spinal fluid

MRI = magnetic resonance imaging

CNS = central nervous system

EMG = electromyography

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