Restless Legs Syndrome in Pediatric Patients With Nephrotic Syndrome

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Abstract

Background. Restless legs syndrome (RLS) is a sleep disorder characterized by an urge to move or the presence of unpleasant sensations in the extremities. The prevalence of RLS is higher in children and adults with chronic kidney disease and in adults with glomerular disease. *Objective*. To determine the prevalence of RLS in children with nephrotic syndrome. *Methods*. We studied 50 children with nephrotic syndrome and 22 controls. The following surveys were administered: Pediatric Emory RLS questionnaire, Pediatric Daytime Sleepiness Scale, and Pediatric Sleep Questionnaire. *Results*. Children with nephrotic syndrome were 9.0 ± 4.4 years old, 27 were male, and 27 were in remission. The prevalence of RLS was similar in the nephrotic syndrome cases and controls, whether or not indeterminate cases were considered positive: 14.0% versus 13.6% including indeterminate cases, and 8.0% versus 9.1% excluding indeterminate cases. *Conclusion*. RLS is not more common in children with glomerular disease compared to healthy controls.

Keywords

restless leg syndrome, nephrotic syndrome, pediatric

Introduction

Restless legs syndrome (RLS) is a relatively common neurological sleep disorder. It manifests as an urge to move or the presence of unpleasant sensations in the extremities, symptoms that are worse with inactivity, relieved by movement, and most severe at night. RLS has been shown to interfere with sleep onset and negatively affect sleep duration and quality, leading to impaired cognition, daytime functioning, and overall quality of life. The specific pathophysiology of RLS is not well understood, but primary factors implicated in pathogenesis are central dopaminergic dysfunction, low iron levels, and genetics.[1]

RLS is not an infrequent problem in children. It occurs in 1.9% of children 8 to 11 years old and in 2.0% of adolescents 12 to 17 years old. This approximate 2.0% prevalence in 8 to 17 year olds exceeds that of both nonfebrile seizure disorders and diabetes type 1 and 2 combined.[2] Furthermore, studies have reported that in adults with RLS, 25% had onset of their symptoms between 10 and 20 years of age, and 18% had onset before 10 years of age.[1]

In adults, the high prevalence of RLS in those with end-stage kidney disease (ESKD) and chronic kidney disease (CKD) has been well established. Up to 62% of adult patients with ESKD have RLS,[3] and 26% of adults with CKD have RLS.[4] It was also demonstrated recently that in adults, there is a significantly higher prevalence of RLS in those with nephrotic syndrome than in healthy controls (22.8% vs 4%).[5]

In children, there have been several studies that evaluate the prevalence of RLS in children with CKD based on the diagnostic criteria established by the National Institutes of Health in 2003.[6] In one single-center study of 26 CKD patients, 35% had RLS,[7] while in a separate multicenter study of 159 CKD patients, 10.1% had RLS.[8] In 2013, it was documented that RLS was more prevalent in 154 CKD patients than in 85 normal healthy children between the ages of 8 and 18 (15.3% vs 5.9%, $P = .04$).[9] However, unlike in adults, there have been no studies to date that evaluate the prevalence of RLS in children with nephrotic syndrome. Therefore, we conducted a cross-sectional

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noninterventional survey study comparing the prevalence of RLS in children with nephrotic syndrome to healthy controls. We simultaneously assessed sleep characteristics and daytime sleepiness to determine associations with RLS.

Methods

Study Design and Patient Population

This single-center, cross-sectional, noninterventional survey study was performed in children with nephrotic syndrome and healthy controls, ages 3 to 18 years. Children were recruited from the Nephrology Outpatient Clinic at either the NYU Fink Ambulatory Care Center or Bellevue Medical Center. Cases of nephrotic syndrome included children having a urine protein/creatinine (Up/c) ratio >2 g/g at the time of diagnosis. Patients with nephrotic syndrome were included regardless of whether their disease was in relapse, remission, or resistant to therapy. Controls were healthy children with normal kidney function being evaluated in the Nephrology Clinic for hematuria, low-grade proteinuria, or urinary tract infection. A convenience sample of 7 patients >18 years of age with nephrotic syndrome who were still being followed by the Pediatric Nephrology service were also included. Patients and controls were excluded if they were non-English speaking.

Patients were approached either at the time of their routine clinic visit or over the telephone. Informed consent was obtained from a parent/guardian or from the patient if he/she was 18 years or above. Assent was obtained from children between the ages of 7 and 17, using an age-appropriate form. The parent/guardian and the patient were both present during the completion of the survey instruments. The study protocol was approved by the New York University Langone Medical Center and the Bellevue Medical Center Institutional Review Boards.

Instruments

Each study participant completed an RLS diagnostic questionnaire, a sleepiness scale, and a quality of sleep questionnaire. Children's drawings of extremity discomfort were not used in this study.

The Pediatric Emory RLS diagnostic questionnaire was developed by members of the Division of Pediatric Nephrology and Pediatric Neurology at Emory University.[9] It is based on National Institutes of Health Consensus guidelines[6] and adapted from prior adult RLS questionnaires for the pediatric population. The questionnaire was completed by the parent/guardian for those children aged 8 to 12 and independently if subjects were 13 or older.

Participants first answered 5 questions: (*a*) growing pains, (*b*) difficulty sitting or lying still, (*c*) uncomfortable leg sensations with a strong urge to move the legs, (*d*) recurrent need to move legs while sitting/lying down, and (*e*) request for leg massage for these feelings, as an RLS screen. Those who answered no skipped further questions about RLS. Those who answered yes to any of the above completed the full questionnaire. The questionnaire included 4 questions to identify potential RLS mimics: muscle cramps, positional discomfort, swelling of the joints, and skin rash/infection. The questionnaire also included a section to identify sleep disturbances, as it is one of the diagnostic criteria for RLS in children aged 2 to 12 years. This was defined as (*a*) sleep duration <7 hours, (*b*) sleep latency >30 minutes, or (*c*) sleep maintenance problems (≥2 full arousals per night or per week). A positive RLS result was defined as a score of either definite or probable RLS. Cases were labeled indeterminate if they were not definite, probable, or clearly negative. This categorization was applicable if (*a*) patient was positive for criteria in one question but negative for criteria in another question or (*b*) patient answered not sure for one criterion but met all other criteria.

The Pediatric Daytime Sleepiness Scale (PDSS)[10] consists of 8 questions used to evaluate daytime sleepiness. Answers are arranged in a Likert-type scale format from 0 to 4. Total scores ranged from 0 to 32, with higher scores indicating greater daytime sleepiness.

The Pediatric Sleep Questionnaire (PSQ)[11] consists of 22 questions to evaluate quality of sleep and need for polysomnography testing. It screens for sleep-related breathing disorders, daytime sleepiness, and daytime behavioral problems. Each item scored as 1 point, and if the total score is >8, subjects were referred for a formal sleep evaluation with a clinician.

Statistical Analysis

A sample size calculation based on an estimate prevalence rate of RLS amounting to 20% and 5% in patients with nephrotic syndrome and healthy controls, respectively, indicated that 43 children needed to be studied in each group. The categorical results of the Pediatric Emory RLS questionnaire were compared using the χ^2 test. The PDSS is scored continuously and was analyzed using a Student's *t* test. The PSQ was omitted from further analysis because preliminary results did not warrant comparison between the 2 groups. No correction for multiple comparisons was made when assessing the RLS findings because only 2 scales were evaluated. Findings were considered significant if the *P* value was <.05.

Table 1. Characteristics of Cases and Controls.

	Demographics				
	Age	N	Male	Female	Age
NS	≤18	50	27	23	9.2 ± 4.4
Controls	≤18	22	12	10	9.0 ± 4.4

Abbreviation: NS, nephrotic syndrome.

Table 2. Nephrotic Syndrome Patients: Clinical Features.

Clinical Pattern of NS					Cause of NS		Current Medications		
Remission	Steroid-Sensitive Infrequent Relapser	Steroid-Sensitive Frequent Relapser	Steroid Dependent	Steroid Resistant	MCD	Other	Steroids	Tacrolimus	MMF
11	15	12	9	3	34	16	22	17	13

Abbreviations: NS, nephrotic syndrome; MCD, minimal change disease; MMF, mycophenolate mofetil.

Table 3. RLS Score: Pediatric Emory RLS Questionnaire.

	NS (≤18 Years Old), N = 50	Controls (≤18 Years Old), N = 22
Total RLS (+) (including indeterminate)	7 (3)	3 (1)
RLS (−)	43	19
% RLS (+)	14.0	13.6
% RLS (+) (excluding indeterminate)	8.0	9.1

Abbreviations: RLS, restless legs syndrome; NS, nephrotic syndrome.

Results

Clinical Characteristics

There were a total of 50 cases and 22 controls. Demographic characteristics are shown in Table 1. Cases and controls were well-matched for age. Both groups—children with nephrotic syndrome cases and controls—included slightly more males than females. The activity of the nephrotic syndrome at the time of the survey ranged from remission (n = 11), to infrequent relapse (n = 15), frequent relapse (n = 12), steroid dependent (n = 9), and steroid resistant (n = 3). The most common cause of nephrotic syndrome was minimal change disease. The patients included in this study were taking a variety of immunosuppressive medications including steroids, tacrolimus, and mycophenolate mofetil (Table 2).

Prevalence of Restless Legs Syndrome

The highest estimate of the prevalence of RLS includes the sum of definite, probable, or indeterminate cases. There were 3 indeterminate subjects in the nephrotic syndrome cases and 1 in the control group. If the indeterminate cases were included with the definite and probable cases, then 7 of the 50 nephrotic syndrome cases and 3 of the 22 controls were RLS positive. The prevalence of RLS was similar between the NS cases and controls, whether or not indeterminate cases were included as RLS positive (14.0% vs 13.6% including indeterminate cases, and 8.0% vs 9.1% excluding indeterminate cases; Table 3).

The RLS questionnaires were administered a second time for one child whose parents were concerned that they may not have answered the questions accurately during the first survey. The test results were consistent and negative for RLS both times. In addition, an 11-year-old girl whose questionnaire results were indeterminate underwent a complete sleep study, which was negative for periodic limb movements and the diagnosis of RLS.

Daytime Sleepiness

Based on the PDSS scale of sleepiness (scored 0-32), controls exhibited more daytime sleepiness than did

Table 4. RLS and Daytime Sleepiness: PDSS.

	NS (≤18 Years), N = 50	Controls (≤18 Years), N = 22	RLS (+) (≤18 Years), N = 10	RLS (−) (≤18 Years), N = 62
PDSS score	9.0 ± 5.5	12.5 ± 6.5	13.4 ± 6.9	9.7 ± 5.7
P value		.02		.07
PDSS ≥16: number of children (%)	6 (12%)	4 (18.2%)	3 (30%)	7 (11.2%)
P value	.48		.14	

Abbreviations: RLS, restless legs syndrome; PDSS, Pediatric Daytime Sleepiness Scale; NS, nephrotic syndrome.

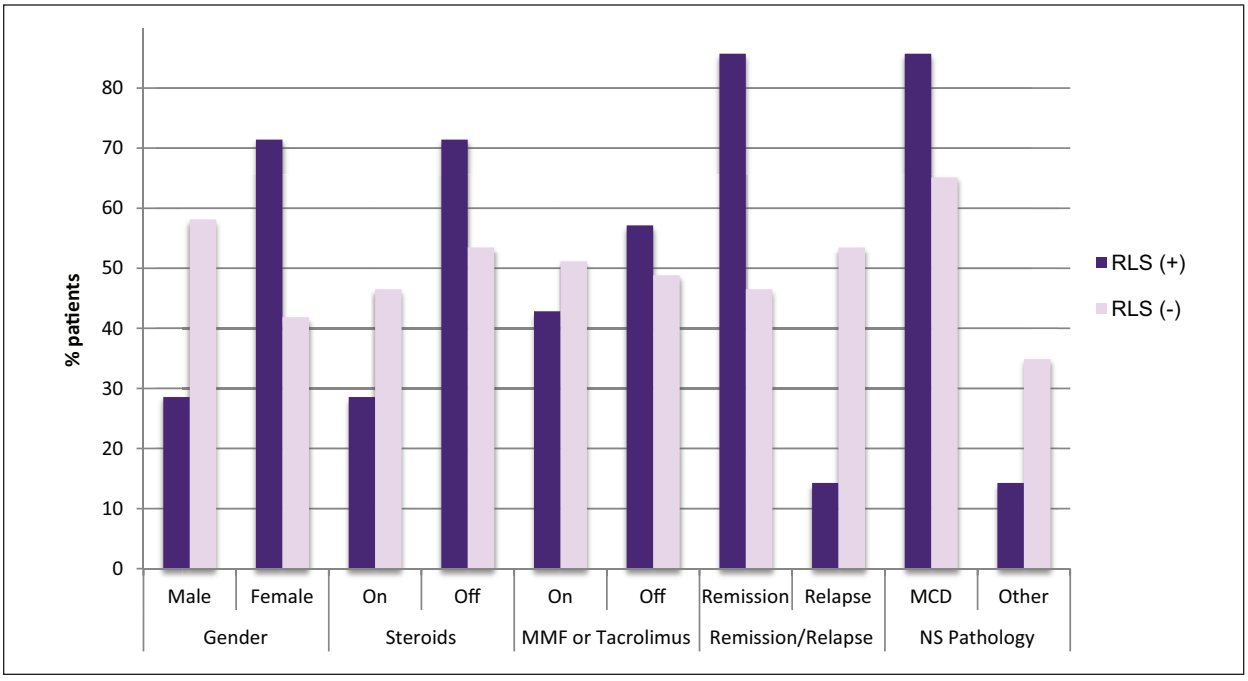

Figure 1. Characteristics of restless legs syndrome (RLS) (+) and RLS (−) nephrotic syndrome patients.

nephrotic syndrome cases (12.5 vs 9.0, $P = .02$). This is contrary to our expectation and remains unexplained. Although not significant, there is also a trend toward RLS-positive subjects experiencing greater daytime sleepiness than RLS-negative subjects (13.4 vs 9.7, $P = .07$). However, the percentage of patients with a PDSS score ≥16, a cutoff that is frequently used to define an abnormal result, was comparable in those with or without nephrotic syndrome and with or without RLS (Table 4).

Characteristics of RLS (+) and RLS (−) Nephrotic Syndrome Patients

In the group of pediatric patients with nephrotic syndrome, the clinical and demographic characteristics of the 7 RLS-positive and 43 RLS-negative cases are displayed in Figure 1. None of the clinical features including gender, current therapy for the nephrotic syndrome, remission/relapse status, or underlying cause of the kidney disease were associated with the presence of RLS. However, these comparisons are limited by the small numbers of patients in the specific subgroups.

Discussion

The key finding of our study is that, in contrast to adult patients with glomerular disease, RLS is not more common in children with glomerular disease compared to healthy controls. This conclusion was not altered by a sensitivity analysis in which indeterminate cases were considered diagnostic of RLS and included in the positive category. The remission/relapse status, gender, or specific medications were not associated with a higher risk of RLS. Interestingly, the higher frequency of RLS in the small subgroup of patients older than 18 years of age (2 out of 7; 28.6%), while not statistically significant from

the younger patients due to the small sample size, is consistent with reports of a higher incidence of RLS in adults with glomerular disease.[5] Confirmation of a higher rate of RLS in these older patients with glomerular disease provides a useful internal positive control and validates the methods used in this study. We recognize that the negative result may reflect the higher than anticipated rate of RLS in the control group. It is worth noting that if the indeterminate cases are excluded, then the incidence of RLS in the patients with glomerular disease and the controls is comparable to previous reports of healthy children. Moreover, the negative findings in this study, namely, that the incidence of RLS is comparable in healthy children and those with glomerular disease, would not be altered even if it is assumed that an equal number of patients were enrolled in each group and all of the additional 28 healthy controls were negative for RLS. This is true if the indeterminate cases are included ($P > .3$) or excluded ($P > .6$) from the RLS-positive group.

RLS is an under recognized clinically entity. However, it is a diagnosis worth considering because it has a substantial effect on patient quality of life and it is an easily treatable condition. The clinical relevance of a diagnosis of RLS in childhood nephrotic syndrome is supported by the observation that RLS-positive patients experience more daytime sleepiness than RLS-negative patients. This finding implies that RLS can contribute to adverse health effects in children with nephrotic syndrome. In addition, RLS may be associated with serious long-term consequences. In a study of 1093 adults with ESKD, those with RLS had a 2.4-fold higher adjusted risk of cardiac and cerebrovascular events and 1.5-fold higher adjusted risk of mortality over a follow-up period of 3.7 ± 0.8 years.[12]

The pathogenesis of RLS remains unclear. It has been linked to alterations in iron metabolism and dopamine signaling within the brain. How renal disease, either chronic reduction in glomerular filtration rate or glomerular barrier dysfunction, impacts on these pathways has not been addressed. The documentation of a higher risk of RLS in both children and adults with CKD suggests that the accumulation of uremic solutes may disrupt cerebral function leading to RLS. One might speculate that glomerular disease with proteinuria might result in disturbances in iron homeostasis and dopaminergic neural transmission leading to RLS. Children with steroid responsive nephrotic syndrome have transient declines in serum iron and transferrin levels during relapses.[13] However, we did not observe any difference between the occurrence of RLS based on remission and relapse status, and therefore, our findings suggest that iron handling is not a pivotal factor in the development of RLS in children with nephrotic syndrome. Brain imaging studies may be needed to ascertain whether kidney disease in general or glomerular dysfunction in particular results in disturbances that lead to RLS.

There are several important limitations of this study, including the following: (*a*) lack of standardized survey tools for RLS to screen children; (*b*) uncertainty about self- or parent-reporting of symptoms in children; (*c*) inability to characterize the condition fully in the indeterminate cases; (*d*) lack of sleep studies to confirm diagnosis in patients for the presence of associated periodic limb movements of sleep seen in 80% of patients with RLS; (*e*) lack of measurements of serum iron or ferritin in the patients with nephrotic syndrome; and (*f*) the failure to perform sleep studies to confirm the diagnosis of RLS in patients whose survey results suggested the presence of the disorder. The questionnaires that were utilized in this project are not fully validated in the pediatric population or in the full age range studied. Therefore, our observations about the incidence of RLS in children with nephrotic syndrome may need to be reassessed if improved instruments with greater sensitivity and specificity are developed and validated to diagnose this condition in children and adolescents.

While caution is warranted in interpreting a negative study, our findings suggest that RLS is not an important feature in children with glomerular disease. It is possible that the neurological abnormalities that trigger RLS in patients with nephrotic syndrome require a longer period of disease or the presence of comorbid conditions to clinically manifest, features that may only occur in adults. Unlike in CKD, screening for RLS, for example, routine use of questionnaires, measurement of serum iron level, and performance of sleep studies is not warranted in pediatric patients with glomerular disease. However, because of the significant morbidity associated with RLS and the potential for successful treatment and improvement in quality of life and clinical outcomes, we encourage pediatric nephrologists to be aware of this complication and evaluate with suggestive symptoms or clinical findings.

Author Contributions

VC, SV, SK, and HT conceived and designed the study. VC, SW, SS, SV, SK and HT recruited patients and collected data. VC, SV, SK, HT analyzed the data. VC, SK, HT prepared the manuscript. VC, SW, SS, SV, SK, HT reviewed and approved the manuscript.

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.

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