ARTICLE

Sleep Disturbances in Children and Adolescents With Non–Dialysis-Dependent Chronic Kidney Disease

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Background: While studies have shown sleep disorders to be common in adults with chronic kidney disease (CKD), pediatric data are scarce.

Objective: To characterize the prevalence of sleep disorders among children and adolescents with non–dialysis-dependent CKD.

Design: Prospective, questionnaire-based, cross-sectional study.

Setting: Tertiary pediatric nephrology center.

Participants: Children aged 6 to 18 years with non–dialysis-dependent CKD. Those with renal transplants were also considered to have CKD and were included, provided it was at least 3 months after the transplant.

Interventions: A validated pediatric sleep questionnaire.

Outcome Measures: Four domains of sleep disturbance were assessed: sleep-disordered breathing, restless leg syndrome/paroxysmal leg movement (RLS/PLM), insomnia, and excessive daytime sleepiness. Positive responses to any of these signified the presence of a sleep disorder.

Results: A total of 49 non–dialysis-dependent children (30 with non–renal transplant CKD and 19 with post–renal transplant CKD; median age, 14 years; interquartile range, 6-18 years) were administered the pediatric sleep questionnaire; 71% (n=35) of the patients were male; 37% (n=18) were identified as having a sleep disorder; 40% (n=12) were in the nontransplant CKD group and 32% (n=6) in the transplant CKD group. The most common type of sleep disorder was RLS/PLM, affecting 27% (n=8) in the nontransplant CKD group and 32% (n=6) in the transplant CKD group. There was no correlation between stage of CKD and prevalence of sleep problems ($P=.22$).

Conclusions: Disordered sleep was identified in more than one-third of our study population, and the most common type was RLS/PLM. Pediatricians should be aware of the relatively high incidence of sleep disorder among children and adolescents with CKD.

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THE MEAN INCIDENCE OF chronic kidney disease (CKD) among the pediatric population is estimated at 12.1 cases per million (range, 8.8-13.9), with prevalence at 74.7 per million in the age-related population[1]; this is likely an underestimate. Increasing awareness of CKD has resulted in a steady rise in the number of children and adolescents diagnosed with CKD.[2] Recently there has been a sustained shift of focus to encompass the issue of quality of life in the treatment of both adults and children with CKD.[3,4] The presence of a sleep disorder is an important contributing factor to morbidity in the general pediatric population, as it has been associated with behavioral problems, inattention, poor school performance, and reduced quality of life.[5] Although it has been reported to be common among adults with CKD,[6,7] studies on sleep disturbance in children with CKD are lacking.[8] The only published pediatric study to date focused on a population receiving dialysis that, similar to the adult dialysis population, identified a high incidence of sleep disorder.[8] To the best of our knowledge, such a study has not been published for the pediatric non–dialysis-dependent CKD population. This is important, as early assessment and appropriate interventions might result in improvement of quality of life in this population.

The goal of the present study was to describe the prevalence of sleep disorders among a cohort of children and adolescents with non–dialysis-dependent CKD. We hypothesized that the morbidity is common and underrecognized in this patient population.

Table 1. Population Characteristics

Characteristic	No. (%) NRT-CKD	No. (%) RT-CKD	*P* Value
Total	30	19	
Median age, y (IQR)	14 (12-16)	14 (11-16)	.98
Male	23 (77)	12 (63)	.39
Race/ethnicity			
White	24 (80)	11 (58)	.09
Aboriginal	2 (7)	3 (16)	.3
Other	4 (13)	5 (26)	.25
Etiology			
Congenital	23 (77)	10 (53)	.08
Acquired	6 (20)	8 (42)	.09
Unknown	1 (3)	1 (5)	.74
Family history of sleep disorder	2 (7)	4 (21)	.13
Medication			
Asthma	3 (10)	1 (5)	.55
Antidepressant	1 (3)	0 (0)	.42
Behavioral	2 (7)	2 (11)	.63
Iron supplement	10 (34)	5 (26)	.6
Median Hb, g/dL (IQR)	13.05 (12.2-14.0)	11.4 (10.9-12.6)	.05
Anemic, Hb <5th percentile	9 (30)	14 (74)	.003

Abbreviations: Hb, mean corpuscular hemoglobin; IQR, interquartile range; NRT-CKD, chronic kidney disease without renal transplant; RT-CKD, chronic kidney disease with renal transplant.

SI conversion factor: To convert to grams per liter, multiply by 10.

METHODS

STUDY POPULATION

The study was conducted at British Columbia's Children's Hospital, which has the only pediatric renal referral center for the province of British Columbia. The study was done between December 2007 and May 2008 and was approved by the University of British Columbia Clinical Research Ethics Board and the Children and Women's Hospital Review Committee.

The study inclusion criteria were age of 6 to 18 years with non–dialysis-dependent CKD and ability to understand English. Per the Kidney Disease Improving Global Outcome advisory,[9] children with renal transplant were considered to have CKD and were included in our study provided the transplant was at least 3 months earlier and they had stable graft function. Children younger than 6 years were excluded for (1) inability to comprehend survey questions about restless leg syndrome/paroxysmal leg movements (RLS/PLM) symptoms and (2) daytime napping, an indicator of excessive daytime sleepiness, which is considered part of the normal sleep/wake behavior in this age group. Patients were also excluded if they had any mental or physical impairment severe enough to preclude interpretation of collected behavioral information.

DATA COLLECTION AND QUESTIONNAIRES

This was a questionnaire-based cross-sectional study. Families who agreed to participate were asked to complete the relevant questionnaire. Parents or legal guardians were allowed to assist the child with obtaining proper answers when age appropriate.

The following baseline information was collected for each participant: age, sex, self-identified ethnicity, underlying renal disease, medication history, mean corpuscular hemoglobin concentration, serum creatinine level, ferritin level, transferrin saturation, mean corpuscular volume (MCV), date of transplant, number of transplants, graft function in transplant, and estimated glomerular filtration rate. Estimated glomerular filtration was determined by the Schwartz formula[10] for children and adolescents: Glomerular filtration (mL/min/1.73 m^2) = k × height (cm) / serum creatinine (mg/dL), where k = 0.55 for girls and boys aged 2 to 12 years and k = 0.7 for boys older than13 years.

A validated pediatric sleep questionnaire[11-13] was used to identify 4 parameters of sleep disorders: sleep-disordered breathing, insomnia, excess daytime sleepiness, and RLS/PLM. Positive responses to any of the 4 symptom domains signified the presence of a sleep disorder. Anemia and CKD were defined per the Kidney Disease Outcome Quality Initiative guideline.[14,15] Iron deficiency was defined as appropriate for the CKD population as ferritin lower than 100 µg/L or transferrin saturation lower than 20%.[16]

STATISTICAL ANALYSIS

Clinical variables were compared for those with and without a sleep disorder using the Mann-Whitney *U* test for continuous variables and χ^2 test for categorical variables. Values are expressed as means (standard deviation) for variables with distribution in the reference range and as median and interquartile range (IQR) for all other variables. Differences were considered significant for $P < .05$.

RESULTS

Over the study period we approached 71 families who met our inclusion criteria, of whom 59 agreed to participate. The final study population comprised 49 (83%) children who returned the completed questionnaires. Nineteen children had had renal transplant and 30 were anticipating renal transplant.

The baseline characteristics of the group are summarized in **Table 1**. The median posttransplant duration was 3.8 years (IQR, 1.2-6.5 years). All but 1 were recipi-

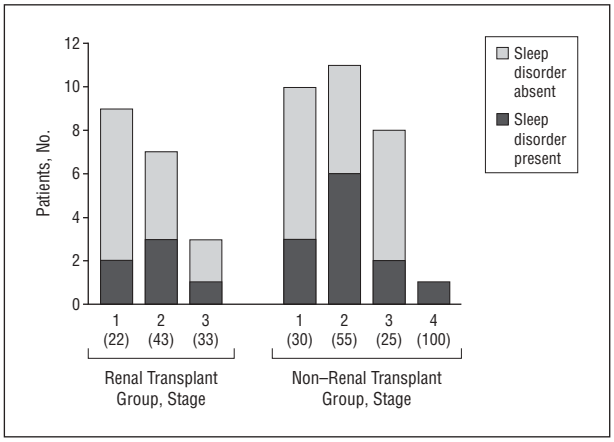

Figure. Sleep disorders across stages of chronic kidney disease. Numbers in parentheses indicate the percentage of patients in each stage who have a sleep disorder.

ents of a primary transplant. Staging of CKD per the National Kidney Foundation Disease Outcomes Quality Initiative revealed that 39% of the study population (n=19) were in stage 1; 37% (n=18), stage 2; 22% (n=11), stage 3; and 2% (n=1), stage 4 CKD. Sleep disorder was identified across all stages of CKD and no significant increase in sleep disorders was noticed across the stages (**Figure**).

Symptoms of sleep disorders were identified in 37% (n=18) of children. The distribution of the subgroups of sleep disorder is shown in **Table 2**. Of the 4 domains of sleep disorders that were assessed, RLS/PLM was overwhelmingly the most common (29%). Although sleep disorder was slightly more common in the nontransplant CKD group (40%) than in the transplant CKD group (32%), the difference did not reach statistical significance.

Overall, there were no differences in hemoglobin levels between those with a sleep disorder (median, 12.75 g/dL [to convert to grams per liter, multiply by 10]; IQR, 11.2-13.2 g/dL) and those without a sleep disorder (median, 12.4 g/dL; IQR 11.4-14.0 g/dL; $P=.5$). Of those with anemia in the nontransplant CKD subgroup, one-third (3 of 9) had a sleep disorder but 43% of those without anemia (9 of 21) also had sleep disorder. Patients with CKD with anemia who had a transplant had a higher percentage of sleep disorder (43%; 6 of 14) compared with nonanemic patients (0%; 0 of 5) but the difference was not statistically significant ($P=.07$).

Data on ferritin level and transferrin saturation were available only for patients with CKD without transplant. The median ferritin level of those with a sleep disorder in this subgroup was 0.065 ng/mL (to convert to picomoles per liter, multiply by 2.247) (IQR, 0.022-0.212 ng/mL), whereas it was 0.034 ng/mL (IQR, 0.021-0.065 ng/mL) for those without a sleep disorder ($P=.4$). Iron deficiency was found in 5 of 8 (63%) children with RLS/PLM in the nontransplant CKD group.

The MCV correlated poorly with iron deficiency. Despite 77% of children in the nontransplant CKD group being iron deficient, only 1 child had an MCV lower than the age-appropriate range. Even of children with CKD and a transplant with 74% anemia, only 1 child had a low MCV.

Most of the patients with a transplant were receiving triple immunosuppressant medications (74%; n=14), which were mycophenolate mofetil and prednisolone with tacrolimus or sirolimus. Five patients were receiving dual therapy of prednisolone with either tacrolimus (n=1) or sirolimus (n=1), tacrolimus and mycophenolate mofetil (n=1), mycophenolate mofetil and sirolimus (n=1), or mycophenolate mofetil and prednisolone (n=1). The incidence of sleep disorders in the triple- and dual-therapy patients was 36% and 40%, respectively.

Nine children were taking medications other than those used for CKD management or immunosuppression (Table 1). Incidence of sleep disorder was similar among those taking these medications (44%; n=4) compared with patients not taking them (35%; n=14). In total, 15 children were receiving iron supplements; of them, 3 (20%) had RLS/PLM, showing little difference from the incidence of RLS/PLM among those not taking an iron supplement (15%).

COMMENT

To the best of our knowledge, this study is the first to detail sleep problems in non–dialysis-dependent children with CKD. Previously, a single-center analysis of a small group of pediatric dialysis-dependent patients reported sleep disturbance in 86% of the study population.[8] In the current study we showed a high incidence of sleep disorders (37%) even among the pediatric non–dialysis-dependent CKD population.

Sleep hygiene, defined as behavioral and environmental factors that precede and influence sleep,[17] is an important component of health and well-being, and its disturbance can have a significant effect on quality of life in adults and children. For example, poor sleep has been shown to have a negative effect on growth, cardiovascular health, cognitive function, and daytime behavior.[18-21] Sleep disorder in children has also been linked with increased stress in parents, a negative effect on parental sleep, and even marital disruption.[22]

There have been a number of studies on sleep disorder in adults with CKD that have resulted in an appreciation of its importance in the overall treatment of patients with CKD.[7,23] The prevalence of sleep disorder among adults with CKD ranges from 40% to 80%, depending on the assessment method and type of population studied.[24-30] Poor sleep quality has also been reported in adult patients with renal transplant despite better-preserved renal function.[31,32]

Children with chronic disease in general carry a higher risk of sleep disturbances[13] but little is known about the incidence of sleep disorders in children with CKD. Our overall incidence of 37%, though lower than the frequency in the pediatric dialysis group, is comparable with previous adult studies involving a nondialysis CKD population[6] and is considerably higher than the reported rates among the general pediatric population.[11,22,33] In a study of 14 372 English and Scottish school children, Rona et al[22] described sleep problems in only 6% at 11 years of age. In another study based on school children, 16% of

Table 2. Distribution of Subtypes of Sleep Disorder

Study Population	No. (%)				
	RLS/PLM	SDB	EDS	Insomnia	Children With Sleep Disorder
RT-CKD (n = 19)	6 (32)	0 (0)	3 (16)	1 (5)	6 (32)
NRT-CKD (n = 30)	8 (27)	3 (10)	3 (10)	4 (13)	12 (40)
Total (n = 49)	14 (29)	3 (6)	6 (12)	5 (10)	18 (37)

Abbreviations: EDS, excessive daytime sleepiness; NRT-CKD, chronic kidney disease without renal transplant; RLS/PLM, restless leg syndrome/paroxysmal leg movements; RT-CKD, chronic kidney disease with renal transplant; SDB, sleep-disordered breathing.

parents sampled reported that their children aged 4 to 11 years "sometimes" and 5% "usually" have difficulty falling asleep.[33] Incidence of sleep disorder can vary with the type of questionnaire used but, using the same pediatric sleep questionnaire as the present study, Chervin et al[11] previously described a 12% prevalence of sleep disorder in a nonselected pediatric population attending community-based general pediatric clinics.

Of the 4 domains of sleep disorders examined, RLS/PLM was the most common type. Its incidence rate of 29% is much higher than the general population's rate of 2.7% among teenagers and even greater than the 10% to 15% incidence among adults.[34,35] This is similar to the 30% incidence reported in the pediatric dialysis-dependent population and also similar to the incidence reported among both dialysis- and non–dialysis-dependent adults with CKD.[8,26,28,36-39] Per the Kidney Disease Improving Global Outcome guideline, we included children who had renal transplant in our CKD population, and though our numbers were small, the presence of sleep disorder in nearly one-third was striking. Our finding is comparable with the 50% incidence of disturbed sleep reported for adult renal transplant recipients[32] but lower than the 80% incidence reported for 25 pediatric renal transplant recipients in Cleveland, Ohio.[40] Restless leg syndrome/paroxysmal leg movements was the most common abnormal sleep domain in patients with CKD who had not had a transplant (27%) as well as patients with CKD who had a transplant (32%). In fact, it was identified in all of those with sleep disorders in the transplant group. Previous studies have described variable incidence of RLS/PLM among adult renal transplants ranging from 4%[41,42] to 37%.[32]

Although the exact pathophysiology of RLS/PLM remains unknown, iron metabolism appears to play an important role.[43] Recent evidence points toward an abnormality in brain iron metabolism reflected by low ferritin levels in the cerebrospinal fluid and low iron signal in the substantia nigra demonstrated by magnetic resonance imaging of patients with RLS/PLM.[44,45] Cerebrospinal fluid ferritin level might not always correlate with serum ferritin level,[46] and it has been demonstrated that serum ferritin level does not always reflect iron responsiveness in children with RLS.[47] Although some studies have shown a ferritin level lower than 50 µg/L to be associated with increased prevalence of RLS,[43] this is unlikely to be true for patients with CKD because of their inherent chronic inflammatory state, which can result in a higher ferritin level. All of this, to a large extent, might explain our inability to show any relation between ferritin levels and the presence of RLS/PLM in our nontransplant CKD population, although most (63%) patients with RLS/PLM were iron deficient. Unfortunately, owing to a lack of ferritin level data in our renal transplant CKD group, we could not determine whether there was any correlation in this subgroup. We also collected data on MCV but, similar to Kotagal et al,[48] found it to correlate poorly with serum ferritin level or anemia.

The high prevalence of anemia in the CKD population might be a contributing factor to their higher prevalence of sleep disorder.[49,50] Though this was not reflected in our nontransplant CKD group, a higher incidence of sleep disorder was seen in our patients with CKD and transplant with anemia than those without anemia.

In contrast to RLS/PLM, other domains of sleep did not seem to be a major problem. The overall incidence of sleep-disordered breathing (6%) was only slightly higher than the 2% prevalence reported in American children for the general population.[28] Similarly, the incidence of excess daytime sleepiness and insomnia also was just marginally higher than the general pediatric population.[11]

Similar to some adult studies, we did not observe any differences in the incidence of sleep disorders across the stages of CKD.[6,51] Interestingly, similar to the adult experience, we also found sleep problems to be common even in early stages of CKD.[52,53]

The increased frequency of sleep disorders might reflect some undetermined underlying pathogenesis inherent in CKD or might be secondary to various associated comorbidities. In fact, adult studies have suggested that the sleep problems of patients with CKD and those receiving chronic intermittent daytime hemodialysis may have different etiologies.[53,54] Functional and psychological factors may play a more prominent role in the non–dialysis-dependent CKD group,[53] while intrinsic sleep disruption (arousals, apneas, and limb movements) secondary to the effects of chronic intermittent dialysis may play a more significant role in the dialysis population.[53,54] This postulated different mechanism may explain the presence of sleep disorder in patients with early CKD in which psychosocial factors could be an important contributing factor.

Despite being the first pediatric study to look at sleep disorder in non–dialysis-dependent CKD and renal transplant patients, our study has some limitations. One is our small sample size, although we believe our findings are

representative of the pediatric CKD population for our province because our hospital manages all pediatric patients with CKD in the province of British Columbia. Multicenter pediatric studies ensuring adequate representation of CKD, dialysis, and post–renal transplant patients would be the logical next step. Studies should also try to corroborate the questionnaire-based findings with objective measurements using actigraphy or polysomnography and should correlate the effect of poor sleep on quality of life and associated comorbidities in children and adolescents with CKD because adult studies have confirmed that sleep disorders contribute to poor quality of life.[29,55]

Our study highlights the high incidence of sleep disorders in the pediatric CKD population and emphasizes the need to query for symptoms at routine clinic visits. Early identification with appropriate intervention might lead to an improvement in the quality of life of children with CKD.

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