Obstructive sleep apnea and ambulatory blood pressure abnormalities in children with chronic kidney disease

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Background **Obstructive sleep apnea (OSA) and hypertension are common complications in children with chronic kidney disease (CKD). Progression of CKD can aggravate OSA and hypertension whereas worsening sleep apnea can make hypertension difficult to treat in CKD patients. We, therefore, conducted a prospective study to evaluate the association between OSA and hypertension in pediatric patients with CKD.**

Method **In this prospective observational study consecutive children with CKD stage 3–5 (nondialysis dependent) underwent overnight polysomnography and 24-h ambulatory blood pressure monitoring (ABPM). The detailed clinical features and investigations were recorded in a prestructured performa.**

Results **Twenty-two children completed overnight polysomnography and 24-h ABPM was performed within 48 h of performing polysomnography. The median (IQR) age of the study population was 11 (8.5–15.5) years, with an age range of 5–18 years. Moderate-severe OSA defined as apnea-hypopnea index (AHI ≥5) was seen in 14 (63.6%) children, periodic limb movement syndrome in 20 (91%) and poor sleep efficacy in 9 (40.9%) children. Ambulatory blood pressure was abnormal in 15 (68.2%) children with CKD. Of them, 4 (18.2%) had ambulatory hypertension, 9 (40.9%) had severe ambulatory hypertension and 2 (9.1%) had masked hypertension. A statistically significant correlation of sleep efficiency with nighttime DBP SD score/Z score (SDS/Z) (r=−0.47; P=0.02); estimated glomerular filtration rate with SBP loads (r=−0.61; P<0.012); DBP loads (r=−0.63; P<) and BMI with SBP load (r=0.46; P=0.012) was found.**

Conclusion **Our preliminary findings suggest that ambulatory blood pressure abnormalities, OSA, periodic limb movement syndrome and poor sleep efficiency are highly prevalent in children with CKD stages 3–5. *Blood Press Monit* 28: 129–133**

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Keywords: ambulatory blood pressure monitoring, chronic kidney disease, hypertension, obstructive sleep apnea, polysomnography

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Introduction

Chronic kidney disease (CKD) is a state of irreversible kidney damage associated with a progressive reduction in kidney function over time [1]. Several risk factors have been implicated for the progression of CKD such as hypertension, proteinuria, anemia, high uric acid levels and hyperphosphatemia [1–3] Recently, studies in adult CKD patients have shown obstructive sleep apnea (OSA) as an important risk factor for the progression of CKD [4,5]. Moreover, evidence from recent observational studies have shown a high prevalence of OSA in adult CKD patients varying from 30 to 54% [6–8]. The factors implicated for an increased prevalence of OSA are: increased apnoeic threshold secondary to uremia, uremic neuropathy causing decreased upper airway muscle tone and extracellular fluid shifts. There is a potential bidirectional relationship between CKD and OSA [9]. OSA and hypertension have an additive impact on the progression of CKD [6].

Studies of the prevalence of OSA and blood pressure in pediatric CKD are lacking. We hypothesized that both OSA and ambulatory blood pressure (ABP) abnormalities are more prevalent in children with CKD as these two entities share common pathophysiological mechanisms and are often interlinked [9]. The present study was performed to evaluate the proportion of children with CKD (stage 3–5) having OSA and its association with ABP abnormalities.

Materials and methods

Study design

This is a single-center, prospective observational study conducted in the pediatric nephrology clinic of a tertiary care teaching hospital. Children with CKD (stage 3–5) and nondialysis dependent were enrolled after taking written informed consent from the parents. Children with CKD stage 1 or 2, children on dialysis and children

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with estimated glomerular filtration rate (eGFR) <5 ml/min per 1.73 m^2 were excluded. The formal sample size was not calculated and a convenience sample was taken. The study was approved by the Institutional human ethical committee.

Clinical, laboratory and study procedure

A detailed history, clinical examination and detailed laboratory investigations were performed. Three resting BP measurements were obtained from the right upper arm using an aneroid sphygmomanometer. The office BP was classified as per the 2017 American Academy of Pediatrics updated guidelines. Participants underwent ambulatory blood pressure monitoring (ABPM) for 24 h with an appropriate size cuff. Ambulatory hypertension was diagnosed based on the subject's age, sex and height according to American Heart Association (AHA) 2022 updated ABPM classification (9). Hemogram, fasting blood sugar, lipid profile, thyroid profile, serum creatinine and bicarbonate levels were also obtained.

Ambulatory blood pressure monitoring method

ABPM for 24 h was performed in eligible children with a portable noninvasive validated oscillometric BP recorder (spacelabs 90227, USA). The device was applied to nondominant arm with an appropriate-sized cuff. The ABPM was programmed to take BP automatically at 20 min interval during the day time and 30-min interval during the night. Caregivers were explained to maintain a diary of daily activities, sleeping time and intake of antihypertensive medications. Following ABPM variables were recorded: mean SBP, mean DBP over 24 h, daytime and nighttime BPs, BP loads (percentage of readings above the ambulatory 95th percentile) and percentage dipping. On each occasion, three serial measurements of BP were taken by auscultatory method for the classification of office BP. Based on the office BP and ABP readings criteria laid by the American Heart Association (AHA) for the staging of ABPM were used [7].

Ambulatory hypertension was defined when the average ambulatory SBP or DBP for day or night was >95th percentile for age, height and sex as per the normative values for ABPM in children >5 years [7]. Dippers were classified as having a decrease in average SBP and DBP greater than or equal to 10% during sleep and nondippers as less than 10% dipping during sleep [7]. White-coat hypertension was defined as office BP ≥95th percentile and normal ABPM, whereas masked hypertension was defined as normal office BP with ambulatory hypertension [7]. ABPM was performed within 48 h of polysomnography in the eligible children.

Polysomnography

Consecutive patients of CKD underwent full night diagnostic Level I Polysomnograph (Alice 6, Philips Respironics, USA) at the Sleep laboratory [8]. The following parameters were monitored during polysomnography: electroencephalogram: frontal, central and occipital, electrooculogram (C3-A2, C4-A1, O1-A2 and O2-A1), sub-mentalis electromyogram (chin and anterior tibialis), nasal and oral airflow, body position and electrocardiogram. Additionally, thoracic and abdominal movements were recorded by inductance plethysmography. All patients underwent $EtCO_2$ monitoring during sleep to detect hypoventilation according to American Academy of Sleep Medicine (AASM) rules. Scoring of events was carried out according to AASM scoring manual version 2012 [8]. OSA was classified into two categories based on the apnea-hypopnea index (AHI): mild (1–4.9) and moderate-severe (AHI ≥5).

Statistical methods

Epi-Info 7 and R software were used for data analysis. Mean with SD or median with interquartile range were used to summarize numerical data and count and percentage for summarizing nominal data. ABPM values were converted to SD scores (SDS/Z-scores). L (lambda), M (Mu) and S (Sigma) values using equation from Wühl *et al*. [10].study to calculate SDS/Z-scores for a given age and BP. It was calculated by using the following formula:

$$SDS = \left[\{Y/M(t)\}^{L(t)} - 1\right] / \{L(t)\ X\ S(t)\}]$$

We used Spearman's correlation coefficient (r) to estimate the correlation between numerical variables. Two-tailed $P < 0.05$ was considered as significant.

Results

Participants and disease characteristics

A total of 30 children were screened, of whom 22 children underwent level I polysomnography and ABPM. Eight children were excluded from the study as they were less than 5 years of age. The median (IQR) age of the study population was 11 years, with an age range of 5–18 years.

Of 22 participants, 4 (18.2%) participants had CKD stage-3, 10 (45.5%) had CKD stage-4 and 8 (36.4%) had CKD stage 5. Their mean (SD) eGFR at the time of sleep study was 21.69 ± 11.56 ml/min/1.73 m^2. The detailed characteristics of the included children are shown in Table 1.

Overnight polysomnography results

The polysomnography results are summarized in Table 2. Overnight polysomnography showed OSA in 21/22 (95.5%) participants with seven each had mild (AHI 1–5), moderate-severe grade of OSA (AHI ≥5). Twenty (91%) participants had periodic limb movement syndrome (PLMS). Poor sleep efficiency (defined as sleep efficiency of ≤85%) was present in 9 (40.9%) participants. A negative correlation was observed between sleep efficiency and nighttime SDS DBP ($r = -0.47$; $P = 0.02$) (Fig. 1).

Office blood pressure and ambulatory blood pressure monitoring results

Office BP was abnormal in 11 patients; two had stage 1 hypertension; nine had stage 2 hypertension. Ambulatory hypertension was present in 15 children (15/22); 13 had ambulatory hypertension; 2 (9%) had masked hypertension and 1 (4.5%) had white-coat hypertension. Despite on antihypertensive (calcium channel blockers), all seven children had ambulatory hypertension. Approximately 60% of the participants in this study population were nondippers. A statistically significant correlation of eGFR with SBP load ($r = -0.61$; $P < 0.050$); DBP load ($r = -0.63$; $P < 0.05$); creatinine with SBP load ($r = 0.64$; $P < 0.05$); DBP load ($r = 0.61$; $P < 0.05$); BMI with SBP load ($r = 0.46$; $P = 0.04$) was found in the present study (Fig. 1).

Out of seven children with normal ABP, 1 (14.3%) had mild, 3 (42.8%) had moderate and 2 (28.6%) had a severe grade of OSA. Out of 15 children having abnormal ABP, 6 (40%) had mild, 4 (26.7%) had moderate and 5 (33.3%) had severe grade of OSA.

Overall, only one child had no OSA (who had white-coat hypertension with normal 24-h ABP). Of 21 children with OSA, seven children each had a mild, moderate and severe grade of OSA. Six children had normal ABP while 15 (68.2) had abnormal ABP [4 (18.2%) had ambulatory hypertension, 9 (40.9%) had severe ambulatory hypertension and 2 (9.1%) had masked hypertension].

Discussion

The present study revealed a high prevalence of moderate-severe OSA (63.6%) in children with CKD stage 3–5 (nondialysis dependent) diagnosed by using gold standard level I polysomnography; of them, 33.3% each had a mild, moderate and severe grade of OSA. The prevalence of OSA diagnosed by overnight polysomnography in our study was higher than that has been reported in previous studies involving pediatric CKD patients [11,12].

There is a paucity of literature exploring OSA and ABPM abnormalities in children with CKD. Amin *et al* [12] reported a 16% prevalence of OSA in children with CKD stage 3–5 who were dialysis dependent. In another pediatric study [11] which included children with CKD stage 2–5 who were nondialysis dependent, none of the children had OSA. The possible explanation for the high prevalence of OSA in our study could be due to a higher number of CKD stage 4 and 5 (82%) enrolled in the present study compared to those enrolled in the study by Tsampalieros *et al* [11], in which 60% of the children had CKD stage 2. Moreover, one-third of the study population by Tsampalieros *et al* [11] included post-transplant

Table 1 Characteristics of the patients included in study

Clinical characteristics	All participants (n=22)	CKD stage III (n=4)	CKD stage IV (n=10)	CKD stage V (n=8)
Age (years; SD)	11.50 (±3.70)	7.75 (±3.77)	11.50 (±3.66)	13.38 (±2.38)
Sex [Male, n(%)]	18 (82%)	4 (18%)	9 (41%)	5 (23%)
BMI (kg/m^2;SD)	14.93 (±1.91)	13.82 (±1.08)	14.98 (±1.46)	15.44 (±2.60)
Antihypertensive	7 (32%)	0	3 (14%)	4 (18%)
eGFR (ml/min/1.73m^2)	21.69 (±11.86)	40.72 (±8.92)	23.17 (±3.98)	10.33 (±3.15)
Hemoglobin (g/dl)	9.58 (±1.88)	10.7 (±0.41)	9.83 (±2.13)	8.70 (±1.75)
Ca++ (mg/dl)	8.43 (1.28)	9.52 (0.34)	8.85 (1.18)	7.37 (0.96)
Uric acid (mg/dl)	5.94 (1.74)	4.79 (1.27)	6.54 (2.01)	5.77 (0.96)
TG (mg/dl)	138.31 (82.23)	97.29 (20.68)	152.24 (82.40)	141.40 (100.62)
Albumin (g/dl)	3.71 (0.49)	4.17 (0.45)	3.65 (0.44)	3.55 (0.48)

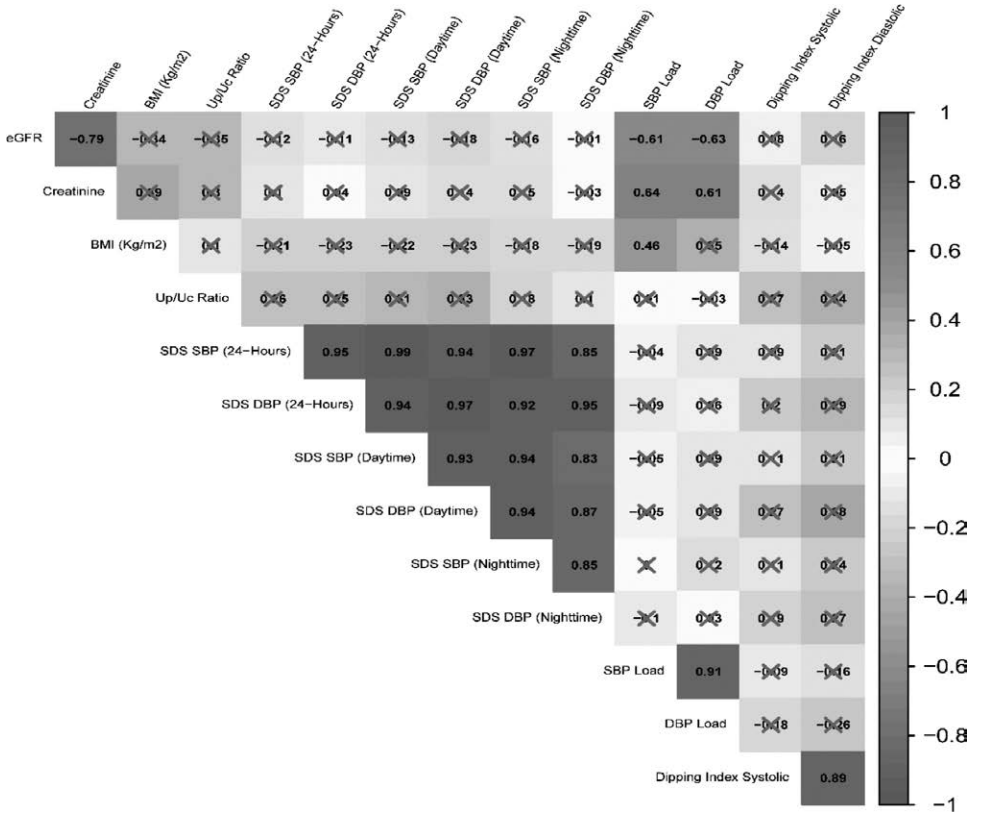
CKD, chronic kidney disease.

Table 2 Results of overnight polysomnography

Measurements	All participants	CKD stage III	CKD stage IV	CKD stage V
OSA (n) (%)	21 (95.5%)	4 (18.2%)	10 (45.5%)	7 (31.8%)
Sleep efficiency (%) (SD)	83.74 (0.11)	85.40 (0.11)	82.13 (0.12)	84.91 (0.13)
Total sleep time (h) (SD)	6.53 (1.25)	6.81 (1.22)	6.54 (1.24)	6.38 (1.42)
Total AHI (mean) (SD)	8.57 (6.38)	9.83 (3.17)	9.70 (4.78)	6.53 (9.00)
REM AHI (mean) (SD)	9.30 (10.58)	6.38 (7.02)	10.58 (10.24)	9.15 (13.13)
NREM AHI (mean)(SD)	7.69 (6.30)	9.78 (3.79)	8.47 (5.24)	5.66 (8.33)
PLMS (n)(%)	20 (91%)	3 (14%)	10 (45%)	7 (32%)
Arousal Index (events/h) (SD)	8.59 (4.81)	13.55 (4.02)	7.6 (4.97)	7.35 (3.67)
Lowest O_2 (%)	82.95 (12.22)	90.25 (4.50)	81.70 (10.76)	80.87 (15.90)
ODI	6.05 (5.40)	4.82 (0.95)	5.31 (5.26)	7.60 (6.87)

AHI, Apnea-hypopnea index; NREM, nonrapid eye movement; OSA, obstructive sleep apnea; PLMS, periodic limb movement syndrome; REM, rapid eye movement; ODI, oxygen desaturation index.

Fig. 1



Correlogram: A Correlogram was plotted between different variables, a statistically significant correlation of eGFR with SBP load (r=−0.61; P<0.050); DBP load (r=−0.63; P<0.05); Creatinine with SBP Load (r=0.64; P<0.05); DBP load (r=0.61; P<0.05); BMI with SBP load (r=0.46; P=0.04) was found.

children and data from adult studies have shown that there is improvement in OSA symptoms following renal transplant [13]. This improvement in OSA may begin as early as 3 months post-transplant [13].

Studies in the adult population have shown that the concomitant presence of CKD, OSA and hypertension may have a negative impact with a more rapid progression of CKD [6]. These three entities, though managed separately share a common pathophysiology including chronic volume overload, hyperaldosteronism, endothelial dysfunction, increased sympathetic activity and increased inflammatory markers [9]. Other comorbidities such as obesity, diabetes and hypertension also influence the prevalence of OSA [14].

ABP abnormalities have been previously reported in children with CKD.

Data from multicentric chronic kidney disease (CKiD) in children reported a high prevalence of ABP abnormalities with a strong association with end-stage renal disease [15]. ABP was categorized as a normal, white coat, masked and ambulatory hypertension in 42, 4, 35 and 14%, respectively in the CKiD cohort. The possible causes for the high prevalence of hypertension in CKD patients include volume overload, excessive salt retention, sympathetic overactivity, endothelial dysfunction and hormonal dysregulation responsible for BP control [6].

There is a paucity of literature showing the relationship between OSA and ABP monitoring in children. A retrospective study of the relationship between severe OSA and office BP in 76 patients who underwent polysomnography reported an association of severe OSA with higher office SBP index after adjusting for BMI, age, sex and socio-economic status (β = 0.07; P = 0.014) [16]. However, the association between OSA and ABPM cannot be determined due to the small number of ABPM results available in the severe OSA group (n = 4) [16]. Another cross-sectional study in healthy children with polysomnography-proven OSA reported an increase of 1.162 percentile units in mean nighttime BP per unit increase in AHI [17]. In the present study, a negative correlation between sleep efficiency and nighttime SDS DBP (r = –0.47; P = 0.02) was found.

The strength of the present study are: (1) it is one of the few studies exploring OSA and ABPM abnormalities in

CKD children stage 3–5; (2) we utilized gold standard level 1 polysomnography for diagnosis of OSA.

Our study had a limitation with regard to a smaller sample size owing to specific eligibility criteria within patients of CKD. Thus, we have only reported nonparametric correlations and have not performed any inferential statistical tests or multivariate analyses. Further, adequately powered multicentric longitudinal studies exploring the relationship between declining eGFR and the presence of OSA are required to understand the impact of OSA on children with CKD.

Conclusion

In conclusion, the present study highlights a high prevalence of OSA and ABP abnormalities in children with CKD stage 3–5 (nondialysis dependent). This emphasizes the importance of screening for OSA and ABP abnormalities in children with CKD.

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Conceived and designed the experiments: G.C.B., S.K. and A.G. Performed the experiments: S.K., M.A., A.G., G.C.B., S.M., M.M. and A.K. Analyzed the data: S.K., A.P.P. and G.C.B. Wrote the article, created tables and figures: S.K., M.A., G.C.B., A.G., S.M., M.M., A.K., A.P.P. and R.R.

Due to ethical restrictions imposed by the author's Ethics committee, it is not possible to deposit data to a public repository. Interested researchers are kindly asked to send appropriate requests to the corresponding author at drgcbhatt@gmail.com.

The research has been approved by the Institutional human ethics committee of AIIMS Bhopal (LOP/2019/MD0035).

Conflicts of interest

There are no conflicts of interest.

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