

Effect of renal Doppler ultrasound on the detection of nutcracker syndrome in children presenting orthostatic proteinuria

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Purpose: To compare the Doppler sonographic findings of the left renal vein (LRV) of children diagnosed with nutcracker syndrome with and without orthostatic proteinuria.

Methods: Fifty and 53 consecutive children with and without orthostatic proteinuria, respectively, underwent renal Doppler ultrasonography examinations. The peak velocity (PV) was measured at the hilar portion of the LRV and between the aorta and superior mesenteric artery. Renal Doppler ultrasonography findings and clinical data including urine protein-to-creatinine ratio (UPCR) were compared according to the presence or absence of orthostatic proteinuria.

Results: Between the two groups, no significant differences were observed in terms of age or sex. The PV ratio between the aortomesenteric and hilar portions was 7.79 ± 2.65 and 6.32 ± 3.01 in children with and without orthostatic proteinuria, respectively ($P=0.009$). No significant differences were observed between the two groups in terms of the UPCR in the first morning urine sample. However, the UPCR in the afternoon urine sample was significantly higher in children with orthostatic proteinuria than in those without orthostatic proteinuria (0.49 ± 0.46 mg/mg vs. 0.11 ± 0.04 mg/mg, $P<0.001$). Furthermore, the PV ratio between the aortomesenteric and hilar portions revealed a positive correlation with the ratio of UPCR of the afternoon to that of first morning urine samples ($R=0.21$, $P=0.034$).

Conclusions: This study suggests that there can be a significant correlation of the PV ratio between the aortomesenteric and hilar portion of the LRV with orthostatic proteinuria in pediatric patients with nutcracker syndrome.

Keywords: Proteinuria; Renal nutcracker syndrome; Ultrasonography, Doppler

Received: May 17, 2024; Revised: June 9, 2024; Accepted: June 11, 2024

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Introduction

Nutcracker syndrome encompasses the clinical symptoms caused by the compression of the left renal vein (LRV) between the superior mesenteric artery and aorta [1]. In children with nutcracker syndrome, the predominant symptoms are hematuria (both microscopic and macroscopic), orthostatic proteinuria, and flank pain [2]. The range of symptoms also includes pelvic pain, flank pain, orthostatic hypotension, hematuria, proteinuria, and varicocele, though some patients may not exhibit any symptoms [1]. The prevalence of nutcracker syndrome is low; however, its exact prevalence remains unknown owing to the lack of definitive diagnostic criteria and the variability in clinical symptoms [1]. Nutcracker syndrome is associated with morbidity, including the risk of chronic kidney disease from LRV hypertension and the risk of LRV thrombosis; consequently, prompt diagnosis is necessary [1]. Nutcracker syndrome is diagnosed based on the medical history and the findings of clinical and imaging examinations. Various imaging techniques have been used to diagnose nutcracker syndrome; however, renal Doppler ultrasonography remains the most used modality [1,3]. Renal Doppler ultrasonography can infer the degree of compression of the renal vein based on the ratio of the peak velocity (PV) of the aorta and the hilum of the LRV [3]. Previous studies investigating the relationship between LRV compression and orthostatic proteinuria revealed that renal Doppler sonography can be used to determine whether nutcracker syndrome is a cause of orthostatic proteinuria [4-11]. The hypothesis of our study is that there will be a correlation between orthostatic proteinuria and PV ratio in the nutcracker syndrome patient group. Therefore, the purpose of this study was to identify the correlation between orthostatic proteinuria and PV ratio in nutcracker syndrome patient group through renal Doppler ultrasonography. The relationship between nutcracker syndrome and orthostatic proteinuria was quantitatively analyzed in this study by determining the urine protein-to-creatinine ratio (UPCR) in the morning and afternoon urine samples. In addition, the data of patients with the diagnosis of nutcracker syndrome confirmed via renal Doppler ultrasonography who visited the pediatric nephrology clinic at the Severance Hospital were analyzed.

Methods

Patients

Patients with nutcracker syndrome who visited the pediatric nephrology clinic at the Severance Hospital between October 1, 2018, and April 30, 2023, were identified by retrospectively analyzing the medical records. The inclusion criteria were age between 2 and 17 years and the diagnosis of nutcracker syndrome confirmed via renal Doppler ultrasonography. Patients with any other kidney diseases were excluded. A total of 103 patients were enrolled in this study.

Diagnostic criteria

Based on the presence of orthostatic proteinuria, the patients with nutcracker syndrome were divided into the orthostatic proteinuria and no orthostatic proteinuria groups ($n=50$ and $n=53$, respectively). Orthostatic proteinuria was characterized by the presence of elevated protein excretion in the ambulatory position (afternoon urine sample) and normal protein excretion in the recumbent position (first morning urine sample) [12]. Elevated proteinuria in the urine sample was defined as a UPCR of ≥ 0.2 mg/mg [12]. In renal Doppler ultrasonography, cutoff value of more than 4.2 for the ratio of anterior to posterior diameter or 4.0 for the ratio of PV between distal and aortomesenteric portion of LRV was considered the diagnostic criterion for nutcracker syndrome [4,13]. Data regarding age, sex, height, weight, body mass index (BMI), body surface area, systolic blood pressure, diastolic blood pressure, and pulse rate were collected. Furthermore, the proteinuria ratio was calculated by dividing the UPCR of the afternoon urine sample by that of the morning urine sample. The PV ratio was determined by dividing the aortic velocity ratio by the hilar velocity measured using renal Doppler ultrasonography. Lastly, the prevalence of symptoms such as flank pain, orthostatic hypotension, and varicocele among the male patients in the two groups was compared.

Statistical analysis

Continuous and categorical variables were compared between the two groups using the Student *t*-test and chi-square test, respectively. Correlation between two variables was assessed by Spearman's rank correlation test. All statistical analyses were performed using MedCalc version 15.8 software (MedCalc Software) and SPSS (version 18.0; SPSS Inc.). Statistical significance was set at $P<0.05$.

Results

Baseline characteristics of the patients with nutcracker syndrome

Table 1 presents the baseline characteristics and clinical manifestations of the patients with nutcracker syndrome. The mean age, sex ratio (male/female), mean height showed no significant difference between the two patient groups. The BMI, calculated by dividing weight by height squared, was also compared between the two groups. Lean patients were expected to exhibit more severe symptoms and signs as lower body fat mass was predicted to result in greater LRV compression [4,14]. However, no significant differences were observed between the two groups in terms of weight and BMI in the present study ($P=0.903$ and $P=0.385$, respectively). Also, no significant differences were observed between the two groups in terms of body surface area, systolic blood pressure, diastolic blood pressure, and pulse rate. The prevalence of symptoms and signs, such as flank

pain, orthostatic hypotension, and varicocele (applicable only to male patients), was also compared to determine whether children with orthostatic proteinuria had more severe symptoms than did those without orthostatic proteinuria. No significant differences were observed between the two groups in terms of symptom severity (flank pain, $P=0.172$; orthostatic hypotension, $P=0.324$; varicocele, $P=0.848$).

Urinalysis findings in patients with nutcracker syndrome

Table 2 presents the urinalysis findings of the two groups. Urinalysis was performed using the first morning and afternoon urine samples. The afternoon UPCR and the proteinuria ratio of the UPCR of the afternoon urine sample to that of the morning urine sample were higher in the orthostatic proteinuria group than in the no orthostatic proteinuria group ($P<0.001$).

Table 1. Baseline characteristics and clinical manifestations of the patients with nutcracker syndrome

Variable	Patients with orthostatic proteinuria (n=50)	Patients without orthostatic proteinuria (n=53)	P-value
Baseline characteristic			
Age (yr)	12.0±3.16	11.8±3.09	0.666
Sex (male/female)	26/24	32/21	0.393
Height (cm)	153.4±20.1	151.7±18.1	0.664
Weight (kg)	41.6±14.1	41.3±13.3	0.903
BMI (kg/m ²)	17.0±2.50	17.4±2.45	0.385
BSA (m ²)	1.32±0.31	1.31±0.28	0.848
SBP (mmHg)	111.9±12.8	108.3±13.5	0.373
DBP (mmHg)	63.9±9.11	61.9±9.99	0.486
Pulse rate (bpm)	81.5±18.4	88.0±22.4	0.397
Symptoms and signs			
Flank pain	27 (54.0)	22 (41.5)	0.172
Orthostatic hypotension	27 (54.0)	24 (45.3)	0.324
Varicocele ^{a)}	13 (50.0)	16 (50.0)	0.848

Values are presented as mean±standard deviation or number (%).

BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute.

^{a)}Applicable only to male patients.

Table 2. Urinalysis findings in patients with nutcracker syndrome

Finding	Patients with orthostatic proteinuria (n=50)	Patients without orthostatic proteinuria (n=53)	P-value
Urine protein-to-creatinine ratio (mg/mg)			
First morning urine	0.09±0.03	0.08±0.02	0.144
Afternoon urine	0.49±0.46	0.11±0.04	<0.001
Proteinuria ratio ^{a)}	6.24±6.76	1.31±0.46	<0.001

Values are presented as mean±standard deviation.

^{a)}Ratio between the afternoon and first morning urine samples.

Table 3. Renal Doppler ultrasound findings in patients with nutcracker syndrome

Variable	Patients with orthostatic proteinuria (n=50)	Patients without orthostatic proteinuria (n=53)	P-value
Aortomesenteric velocity	146.8±35.2	133.6±37.0	0.069
Hilar velocity	20.2±6.35	23.2±6.68	0.026
Peak velocity ratio ^{a)}	7.79±2.65	6.32±3.01	0.009

Values are presented as mean±standard deviation.

^{a)}Ratio between the aortomesenteric and hilar portion of the left renal vein.

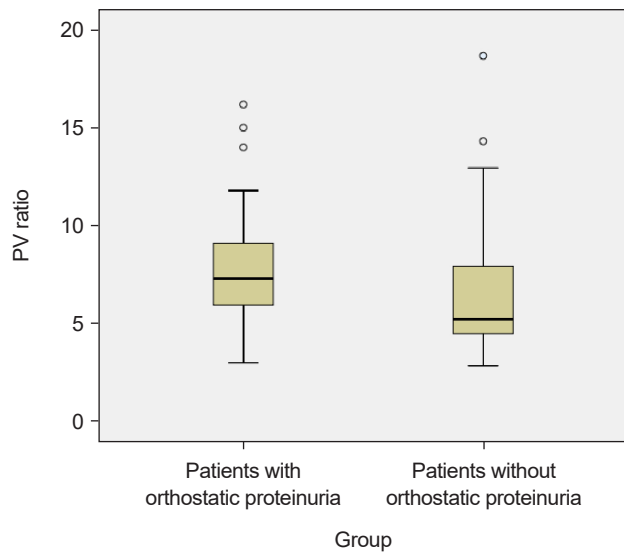


Fig. 1. Differences in the peak velocity (PV) ratio according to the presence of orthostatic proteinuria ($P=0.009$).

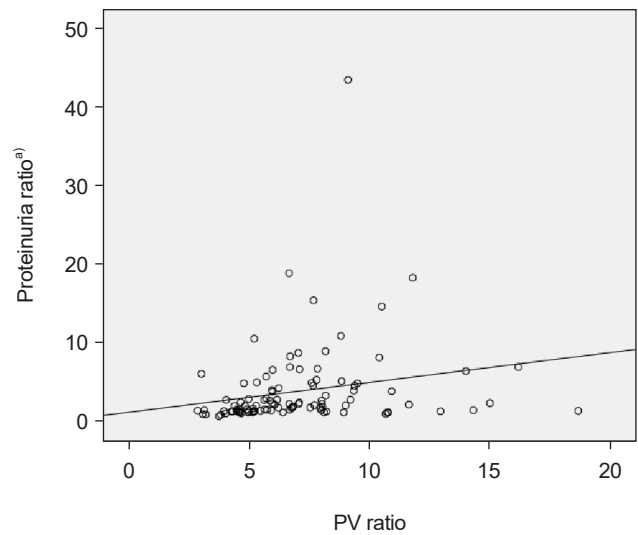


Fig. 2. Correlation curve of the proteinuria ratio with peak velocity (PV) ratio ($R=0.21$, $P=0.034$). ^{a)}Protein-to-creatinine ratio between the afternoon urine and the first morning urine.

Renal Doppler ultrasound findings in patients with nutcracker syndrome

Table 3 presents the renal Doppler ultrasonography findings of the two groups. The hilar velocity was significantly lower ($P=0.026$), whereas the PV ratio was significantly higher ($P=0.009$) in the orthostatic proteinuria group than in the no orthostatic proteinuria group. Fig. 1 presents a box plot depicting the comparison between the PV ratios of the two groups.

Fig. 2 presents the correlation curve between the proteinuria ratio and PV ratio. A higher PV ratio shows a significant association with a higher proteinuria ratio ($P=0.034$). Furthermore, orthostatic proteinuria and PV ratio showed a positive correlation ($R=0.21$), indicating that patients with orthostatic proteinuria tended to exhibit a higher PV ratio.

Discussion

El-Sadr and Mina [15] first described LRV compression between

the superior mesenteric artery and aorta in 1950. De Schep- per [16] termed this condition "nutcracker syndrome" in 1972. Symptoms such as renal venous hypertension, renal hilar and gonadal vein varices, and flank pain are observed in patients with nutcracker syndrome owing to LRV compression [17]. Furthermore, nutcracker syndrome can result in abnormal urinalysis findings such as hematuria and orthostatic proteinuria [11].

Nutcracker syndrome is an important cause of orthostat- ic proteinuria in children. Park et al. [4] compared the renal Doppler ultrasonography findings of children with orthostatic proteinuria with those of healthy children. In contrast, the pres- ent study analyzed the Doppler ultrasonography findings of patients with nutcracker syndrome and compared the results between patients with nutcracker syndrome who did and did not have orthostatic proteinuria. The PV ratio of the orthostatic proteinuria group was higher than that of the no orthostatic proteinuria group. To the best of our knowledge, no previous

study has performed a comparison between patients already diagnosed with nutcracker syndrome. This relationship was quantitatively analyzed in the present study by determining the UPCR in the first morning and afternoon urine samples. A positive correlation indicates that greater LRV compression results in a higher proteinuria ratio between the afternoon and first morning urine samples. This finding may be attributed to greater LRV compression resulting in the congestion of renal blood flow in patients with nutcracker syndrome, which is most likely to cause orthostatic proteinuria. As shown in Table 3, a statistical difference in the PV ratios was observed based on the presence of orthostatic proteinuria. However, the difference was not large because various biases may have been introduced when measuring the PV ratio.

Previous studies have shown that improvement in the severity of nutcracker syndrome can decrease the severity of hematuria in children with increased BMI [14] as retroperitoneal fat and the third segment of the duodenum play crucial roles in maintaining a wide aortomesenteric angle, which can alleviate renal vein compression [4]. Based on the findings of these studies, it was suspected that the clinical symptoms and orthostatic proteinuria would be more severe in lean patients owing to the lower overall fat mass, resulting in further compression of the LRV before the commencement of the present study. However, the findings of the present study are remarkable in that no significant differences were observed in the incidence and severity of symptoms or orthostatic proteinuria based on body weight and BMI. Different from the findings of previous study that compared patients with and without nutcracker syndrome [14], we compared within nutcracker syndrome group. For this reason, the BMI distribution of patients may not have been sufficiently wide to result in statistically significant differences. In addition, in contrast to previous studies that mostly focused on hematuria, the present study is unique in that it attempted to analyze the relationship between BMI and orthostatic proteinuria.

Before commencing this study, it was suspected that clinical symptoms would be more severe in patients with greater renal vein compression, which shows a positive correlation with orthostatic proteinuria. Previous studies have demonstrated a correlation between the presence of flank pain [18] and varicocele [19] and the diagnosis of nutcracker syndrome; these symptoms improved with improvement in the severity of nutcracker syndrome. However, studies demonstrating a higher likelihood of the presence of symptoms in patients

with nutcracker syndrome and orthostatic proteinuria were difficult to identify. Therefore, the relationship between orthostatic proteinuria and the presence of other symptoms of nutcracker symptoms, such as flank pain, orthostatic hypotension, and varicocele, was analyzed in the present study. Notably, no differences were observed in terms of the prevalence of flank pain, orthostatic hypotension, and varicocele based on the presence of orthostatic proteinuria. The PV ratio of the orthostatic proteinuria group was higher than that of the no orthostatic proteinuria group, which was expected to result in a higher prevalence of clinical symptoms in the former group. A difference in the PV ratio may induce a difference in orthostatic proteinuria; however, the difference may not be sufficient to result in a difference in symptoms. Another reason may be that symptoms are more subjective and difficult to accurately examine in children. Furthermore, testicular ultrasonography examinations to confirm the presence of varicoceles have been performed in a limited number of patients.

The limitations of this study are as follows. Patient activity level affects orthostatic proteinuria; thus, differences in activity level and the resulting impact should be considered. The accuracy of the present study would have been higher if additional considerations were made regarding other factors that can affect proteinuria, such as fever and infection. In addition, the measurement of the PV ratio of LRV was performed by pressing the probe during the renal Doppler ultrasound examination. The measured PV ratio varies if the patient is uncooperative or pressure is applied to the abdomen. Moreover, some variation may be observed among the results obtained by different clinicians as all tests were not performed by the same clinician. Nevertheless, the present study is the first to report the difference in orthostatic proteinuria via the comparison of the PV ratio when all other conditions are similar. As only the presence of orthostatic proteinuria was analyzed in the present study, further studies must be conducted to analyze the differences in hematuria caused by the PV ratio.

In conclusion, we quantitatively analyzed and identified the correlation of the PV ratio between the aortomesenteric and hilar portion of the LRV with the orthostatic proteinuria in nutcracker syndrome pediatric patient group.

Ethical statements

This study was reviewed and approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2023-0940). The

requirement for informed consent was waived because of the nature of the study.

Conflicts of interest

Jae Il Shin and Keum Hwa Lee are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Funding

None.

Author contributions

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Investigation: EJH, JIS, KHL

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Project administration: JHK

Visualization: EJH

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Writing-review & editing: EJH, JHK, MJL, HY, JIS, KHL

All authors read and approved the final manuscript.

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