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Evaluation of Anterior Nutcracker Syndrome in Children: One Center Experience

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ABSTRACT

Objective: Nutcracker syndrome (NCS), caused by the compression of the left renal vein (LRV) between the superior mesenteric artery (SMA) and the abdominal aorta, is a rare clinical condition. While renal Doppler ultrasonography has been used to diagnose NCS, there have been few studies linking LRV compression measurements to symptoms in pediatric patients. This long-term retrospective study aimed to evaluate the clinical characteristics of NCS and its Doppler ultrasonographic measurements in children.

Material and Methods: Demographic, clinic, and laboratory data were collected from the medical records of patients with NCS. All renal Doppler ultrasonography (DUS) findings of the study population were also reviewed.

Results: A total of 50 patients with NCS were identified with a mean follow-up of 6.3 years. The proportion of proteinuria was 70%, and 36% of the patients exhibited symptoms of hematuria. Varicocele was also observed in 55.5% of male patients. While patients with hematuria were diagnosed earlier, patients with varicocele and proteinuria were diagnosed later in life. The mean SMA angle of patients in the supine position was significantly lower patients with varicocele (23.80±3.04° vs 27.87±4.49°, p=0.049). The estimated glomerular filtration rate (eGFR) did not differ in patients with hematuria and in patients with variocele. On the other hand, patients with proteinuria had a lower eGFR than those without (129.85±18.48 ml/min/1.73 m^2 vs 141.82±20.72 ml/min/1.73 m^2, p=0.030). The Doppler ultrasonographic parameters of the LRV did not change according to the gender, but the SMA angle decreases significantly with aging.

Conclusion: Although hematuria seems to be common, proteinuria is also common in NCS and SMA angle should thought to be important in children with varicocele.

Keywords: Doppler ultrasonography, Hematuria, Nutcracker syndrome, Proteinuria, Varicocele

INTRODUCTION

Nutcracker syndrome (NCS) is characterized by the anterior compression of the left renal vein (LRV) between the superior mesenteric artery (SMA) and the abdominal aorta (1-4). However certain variations of this condition have been described, the most common form is anterior nutcracker syndrome (2).

Nutcracker syndrome, typically presents as abdominal and/or flank pain, hematuria, proteinuria and varicocele. The prevalence of this condition is not exactly known because of the variability of symptoms at presentations and undefined diagnostic criteria (5,6).

The diagnosis is generally made by clinical presentation and also by imaging methods such as renal Doppler ultrasonography (RDUS), computed tomography (CT), magnetic resonance (MR), angiography and venography. Doppler ultrasonography is the most common used noninvasive method for the diagnosis of NCS because of its sensitivity (69–90%) and specificity (89–100%) (7-12). While RDUS has been used to diagnose NCS, there have been

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Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. The study için was approved by the Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Hospital (15.10.2018/2018-151).

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few studies linking LRV compression measurements to symptoms in pediatric patients (7,13-16). Therefore, we carried out a study to evaluate the clinical characteristics and its Doppler sonographic measurements in children with anterior NCS.

MATERIALS and METHODS

A study was conducted on children diagnosed with anterior NCS between January 2014 and December 2018. The study was approved by the Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Hospital (15.10.2018/2018-151).

Patients with malignencies, neurological diseases, posterior NCS or other atypical variation of LRV were excluded from the study. Clinical characteristics, symptoms, positive findings on physical examination, radiologic findings, serum-urine laboratory examinations, estimated glomerular filtration rate (eGFR), body mass index (BMI) and clinical course of the patients were retrospectively analyzed.

The diagnosis of NCS was based on RDUS which showed the LRV compression in both upright and supine position in children with the presence of clinical and laboratory findings.

The cut-off value of >5.15 for the upright PV ratio (%100 sensitivity, %88.5 specificity); and >4.23 for the supine PV ratio (%69.60 sensitivity, %76.90 specificity) were used for diagnosis as stated by Fitoz et al (10). In addition, the cut-off value of <21 for the upright SMA angle (%87 sensitivity, %76.90 specificity) and <41 for the supine SMA angle were also used (10).

The presence of at least five red blood cells per high-power microscopic field in a centrifugated urine sample was classified as hematuria. Proteinuria was defined as urine protein levels greater than 4 mg/m^2/h. The eGFR (ml/min per 1.73 m^2) was calculated using the Schwartz equation. BMI was calculated as kilograms per square meter. Additionally, scrotal sonography has performed in male patients in order to evaluate the presence of varicocele.

Statistical Analysis

The data were statistically analyzed using IBM SPSS Statistics for Windows, version 11.5 (IBM Corp., Armonk, N.Y., USA) . For categorical variables, frequencies and percentages are provided as descriptive statistics, while for continuous variables, mean and standard deviation (SD) is presented. The study population was grouped based on the presence of hematuria and proteinuria, while male participants were further categorized according to the presence of varicocele. To compare two groups, the independent samples t-test was used for continuous variables with normal distribution, whereas the Mann-Whitney U test was applied for continuous variables have not normal distrubution. Categorical variables were evaluated using the Chi-square test, and correlation analysis was performed using Pearson's correlation test. A significance level of $p < 0.050$ was applied in all statistical tests.

RESULTS

A total of 50 children with anterior NCS were retrospectively analyzed. Among them 32 (64%) were female, and 18 (36%) were male. The female/male ratio was ~1.8. Age at diagnosis was 11.00 ±2.40 years for all children; 11.50±2.20 years for female patients and 10.10±2.60 years for male patients (Table I). No significant difference was found between male and female in terms of age at diagnosis (p=0.132). The most frequent symptoms were abdominal pain (48%) and dysmenorrhea (44%). Ten (55.50%) of 18 male patients had varicocele. Proteinuria was present in 35 (70%) patients and hematuria in 18 (36%). Three (6%) patients had both proteinuria and hematuria. All patients with proteinuria in the study had non-nephrotic proteinuria. The mean spot urine protein/creatinine ratio (mg/mg) of the patients at the time of diagnosis was 0.50±0.68 (0.04-3.40). Age of diagnosis was significantly higher in patients with proteinuria (11.50±1.80 vs 9.70±3.10 years, p=0.013)

Table I: The demographic features of patients with Nutcracker syndrome (n=50)

Characteristic Features	Values
Gender*	
Female	32 (64)
Male	18 (36)
Age at diagnosis (year)†	
All Patients	11.00±2.40
Female	11.50±2.20
Male	10.10±2.60
With proteinuria	11.50±1.80
Without proteinuria	9.70±3.00
With hematuria	10.10±3.10
Without hematuria	11.40±1.80
With varicocele	11.50±1.90
Without varicocele	8.30±2.50
Clinical features*	
Abdominal pain	24 (48)
Flank Pain	5 (10)
Dysmenorrhea	14 (43.8)
Varicocele	10 (55.5)

***:** *n(%),* **†:** *mean±SD*

Table II: Comparison of Doppler ultrasonographic parameters of the LRV according to the gender

Parameters	Female (n=32)	Male (n=18)	p
Supine SMA angle*	25.69±6.96°	25.37±4.21°	0.857†
Upright SMA angle*	17.59±3.47°	17.16±1.92°	0.618†
Supine PV ratio*	4.80±1.71	4.66±1.18	0.754†
Upright PV ratio*	5.81±1.64	5.49±1.26	0.480†

***:** *mean±SD,* **†:** *Independent samples t-test*

Table III: The correlation of Doppler ultrasonographic parameters with age

Parameters	Age	
	r	p*
Supine SMA angle	-0.519	0.001
Upright SMA angle	-0.380	0.006
Supin PV ratio	0.196	0.173
Upright pPV ratio	0.265	0.063

***:** *Pearson moment product correlation*

Table IV: The descriptive values for age-corrected and actual values

Parameters	Actual	Age-Corrected
Supine SMA* agle	25.57±6.04° (13.73-37.41°)	25.69±5.16° (15.58-35.80°)
Upright SMA* angle	17.43±2.97° (11.61-23.25°)	17.47±2.75° (12.08-22.86°)
Supin PV ratio*	4.75±1.52 (1.77-7.73)	4.74±1.50 (1.80-7.68)
Upright PV ratio*	5.69±1.51 (2.73-8.65)	5.68±1.46 (2.82-8.54)

**: mean±SD (95% CI)*

Table V: Comparison of adjusted Doppler utrasonographic parameters of the LRV for age according to the presence of proteinuria

Parameters	Without Proteinuria	With Proteinuria	p
Supin SMA angle*	26.84±5.86°	25.21±4.84°	0.310†
Upright SMA angle*	17.93±4.27°	17.28±1.84°	0.441†
Supin PV ratio*	4.46±0.84	4.86±1.70	0.394†
Upright PV ratio*	5.15±1.37	5.90±1.45	0.096†

**: mean±SD, †: Independent samples t-test*

Table VI: Comparison of adjusted Doppler utrasonographic parameters of the LRV for age according to the presence of hematuria

Parameters	Without Hematuria	With Hematuria	p
Supin SMA angle*	25.02±4.06°	26.90±4.70°	0.218†
Upright SMA angle*	17.33±1.84°	17.76±3.97°	0.607†
Supin PV ratio*	4.70±1.59	4.81±1.34	0.814†
Upright PV ratio*	5.71±1.56	5.61±1.30	0.811†

**: mean±SD, †: Independent samples t-test*

and with varicocele (11.50±1.90 vs 8.30±2.50 years, p=0.010). On the other hand, patients with hematuria were diagnosed in younger age (10.10±3.10 vs 11.40±1.80 years, p = 0.050) (Table I).

Serum urea and creatinine levels were found to be within normal range in all patients. The mean eGFR was 133.40±19.70 ml/min/1.73 m^2 at the end of the follow-up period. eGFR was significantly low in patients with proteinuria (129.85±18.48 ml/min/1.73 m^2 vs 141.82±20.72 ml/min/1.73 m^2, p=0.030). The eGFR did not differ in patients with hematuria (139.55±21.19 ml/min/1.73 m^2 vs 130.53±18.82 ml/min/1.73 m^2; p=0.143) and in patients with variocele (143.70 ±18.01ml/min/1.73 m^2 vs 153.25±26.79 ml/min/1.73 m^2; p=0.405). The Doppler sonographic parameters of the LRV did not change according to the gender, on the other hand the SMA angle decreases significantly with aging (Table II and III). The descriptive values for actual values and age-corrected values are given in the Table IV.

The adjusted Doppler ultrasonographic parameters of the LRV for age according to the presence of proteinuria and hematuria did not change (Table V and VI).

Doppler ultrasonographic parameters in the supine and upright positions of NCS patients with varicocele were summarized in

Table VII: Comparison of Doppler ultasonographic parameters of the LRV according to the presence of varicocele

Parameters	Without Varicocele (n=8)	With Varicocele (n=10)	p
Age at diagnosis (year)*	8.30±2.50	11.50±1.90	0.010†
Supine SMA angle*	27.87±4.49°	23.80±3.04°	0.049†
Upright SMA angle*	17.75±2.25°	16.70±1.70°	0.274†
Supine PV ratio*	5.08±1.06	4.12±1.14	0.088‡
Upright PV ratio*	5.75±1.50	5.16±0.86	0.313‡

**: mean±SD, †: Mann-Whitney U test, ‡: Independent samples t-test*

Table VII. SMA angle in the supine position was lower in patients with varicocele (23.80±3.04° vs 27.87±4.49°, p=0.049).

Five patients (10%) in the study received ACE inhibitors during the follow-up period. However, the majority of patients were treated conservatively, and none developed renal failure during the follow-up.

DISCUSSION

The frequency of NCS accompanied by clinical symptoms is not yet known. As the majority of this entrapment is asymptomatic and undiagnosed or only discovered incidentally, it is difficult to assess the exact frequency of this disease (3,17,18). Today, it is not clear why this configuration of LRV produces non-specific, variable clinical findings and why produces symptoms only in a small part of population. The three typical symptoms (hematuria, abdominal pain and flank pain) are the most clinical findings and the diagnosis of NCS may be done generally by exclusion of the other possible causes compatible with the clinical presentation in addition with imagining methods (2,3,5,19). Although venography, MRA and CTA, provide a good quality of diagnosis of this syndrome, it is very expensive and hard to perform as a first-line diagnostic tool for developing coutries and also for pediatric patients (2,7,11,12,20,21). Therefore, the RDUS measurement of the diameter of LRV, SMA angle and the peak flow velocity should be used with significant success for the diagnosis (9-12,20,21). Although most studies have been conducted with hematuric patients, the relationship of radiological compression of LRV with clinical symptoms is still unclear. In this study, 50 patients' ultrasonographic data of NCS were evaluated not only in patients with hematuria but also with other symptoms (proteinuria, varicocele).

In general opinion, NCS is more common in female patients. Although the most symptomatic patients are in their second and third decade of life, affected persons are ranging from children to older people (2). Hematuria was reported as 33.30-78.50% in children as microhematuria which was four times more common than macrohematuria (2,5,17). Although most studies have included hematuric patients, it is well known that NCS was also one of the causes of proteinuria/orthostatic proteinuria (10,22-26). Some researchers demonstrated the association of orthostatic proteinuria and NCS and suggested that NCS may be a possible cause of massive protein excretion (13,15,16). In addition, varicocele also

affects 5.50%-35.71% of men with NCS, which is related with high LRV pressure, collateral circulation leading to high resistance and pressure in the internal gonadal veins (3,17,27,28).

The pathophysiologic characteristics of NCS are not fully understood. While hematuria is due to elevated LRV pressure resulting the rupture of thin-walled veins into the collecting systems or calyceal fornix; proteinuria may due to elevated norepinephrine and angiotensin II and increased hemodynamic response and "subclinical immune injury" (2).

In our study, more than half of the patiens were female (female/male ratio ~1.8) and age of diagnosis was 11.00±2.40 years. In addition, 70% of the patients have proteinuria, %36 have hematuria and 55.50% male patients with NCS have varicocele. Most of the NCS were detected during proteinuria evaluation and the leading symptoms were abdominal and flank pain. Although the age of diagnosis was smaller in patients with hematuria, the age at diagnosis was greater in patients with proteinuria and varicocele. This can be attributed to the fact that the diagnosis of NCS is being considered in patients with hematuria rather than proteinuria and varicocele. It is well established that ruling out other causes of proteinuria requires a significantly longer time frame.

The ultrasonographic criteria for the diagnosis of NCS was reported from different studies as the ratio of the AP diameter >4.20 and as the ratio of PV 4.00-5.00 (3,7,13). On the other hand, Fitoz et al. (10) reported the cut-off value of >5.15 for the upright PV ratio as 100% sensitivity and 88.50% specificity. In addition, the cut-off value of <21 for the upright SMA angle (87% sensitivity, 76.90% specificity) and <41 for the supine SMA angle were also reported (10). However, as we mentioned above, association of RDUS measurements of the LRV with clinical symptoms are still remains unknown.

While no significant differences was reported in children for the PV at the hilar portion between the NCS and normal children, significantly lower PV at the hilar portion was also reported in adults with hematuria (6,11). Again, the degree of compression of the LRV with abdominal pain, hematuria, and proteinuria was also reported as significantly high in NCS (diagnosed with CT) compared with controls (29). As seen, all these studies were generally conducted by comparing NCS with healthy control groups.

In our study, patients were compared according to the presence or absence of proteinuria and hematuria for age, and Doppler ultrasonographic parameters of the LRV did not change. In addition, we have found the mean SMA angle of our patients in the supine position was significantly lower in patients with varicocele.

However, we have also some limitation; first, we have small number of patients with NCS; second, MR imaging, CT, or venography were not used as a reference standard to confirm the diagnosis of NCS.

CONCLUSION

In conclusion, to our knowledge there are few studies in children which compares the RDUS radiological measurements of LRV and the clinical symptoms with NCS. By reporting this study, we would like to emphasize the importance the SMA angle measurement on clinico-radiological correlation. Although hematuria seems to be common, proteinuria is also a common finding and patients with proteinuria and varicocele should also be evatuated for NCS.

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