

Is Nutcracker Syndrome Innocent?

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Citation: Bozbeyoğlu SG, Gökna N. Is Nutcracker Syndrome innocent? Çocuk Dergisi - Journal of Child 2024;24(1):11-14. <https://doi.org/10.26650/jchild.2024.1393387>

ABSTRACT

Objective: Nutcracker syndrome (NS) is defined by the compression of the left renal vein by the superior mesenteric artery. The incidence of NS and the exact treatment protocols are not well known. The objective of this study is to analyze children with NS and evaluate the prognosis in follow-up.

Methods: All patients were referred to the pediatric nephrology clinic by pediatricians because of proteinuria. The study includes 74 patients (52 girls, 22 boys) with a mean age of 13.15 ± 2.32 and records the presenting symptoms, degree of proteinuria, and radiologic findings. The diameter ratios of the left renal vein before and after stenosis and peak systolic velocity (PSV) ratios were calculated with a Doppler ultrasound, with a peak systolic ratio of 3.0:1 or greater was accepted as the diagnostic criterion for NS.

Results: The mean age was 13.15 ± 2.32 (5.33-17.42) years, while the mean follow-up duration was 14.6 ± 9.1 months. Proteinuria was not correlated with the degree of compression. Most patients had a good prognosis, and none of them required medical or surgical treatment. A significant reduction or complete normalization of proteinuria was seen in more than half of the patients under conservative management.

Conclusions: Based on our findings, NS seems to have a good prognosis in children who present with isolated proteinuria.

Keywords: Proteinuria, nutcracker syndrome, renal Doppler ultrasound

INTRODUCTION

Classical anterior nutcracker syndrome (NS) results from the compression of the left renal vein (LRV) by the superior mesenteric artery (SMA) as it passes between the SMA and the abdominal aorta, thereby reducing the outflow of blood from the renal vein. Posterior nutcracker syndrome results from compression of the LRV between the aorta and the lumbar spine. This can lead to venous hypertension in the left renal vein, with the rupture of thin-walled venous structures into the collecting system able to cause repeated hematuria [1,2]. Although NS is asymptomatic in most patients, especially in children, it can also cause various symptoms and signs such as proteinuria, left flank pain, left varicocele, and pelvic congestion [2,3]. Unlike NS, the nutcracker phenomenon refers to the presence of radiological findings with no clinical and laboratory symptoms and signs. To diagnose NS in children, the primary examination to be performed is noninvasive renal Doppler ultrasound (RDUS), which is easily accessible and contains no ionizing radiation. Angiographic venous imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and digital subtraction angiography (DSA) can also be performed to show

compression in the left renal vein, but these are expensive, laborious, time-consuming, and most importantly apart from MRI, radiation-based examinations. Orthostatic proteinuria, also called daytime proteinuria, is a common finding in NS involving the absence of proteinuria at night (i.e., while in the supine position). Treatment of NS should remain conservative in children, except in cases with severe symptoms. In addition, surgical treatment is rarely required in severe cases [4,5].

The prevalence of NS is not well known, and data about prognosis is limited. This study retrospectively compares imaging findings of pediatric patients with RDUS to their clinical and laboratory findings and aims to evaluate whether a correlation exists between the amount of isolated proteinuria and degree of renal vein stenosis. The study also analyzes the prognosis of these patients in terms of proteinuria and presenting symptoms.

MATERIAL AND METHODS

The study was conducted retrospectively. Institutional ethical committee approval was obtained beforehand (ID:2023/0123). All renal venous Doppler examinations performed on patients

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Submitted: 20.11.2023 • Revision Requested: 16.01.2024 • Last Revision Received: 18.01.2024 • Accepted: 24.01.2024



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who were under 18 years of age between 2018-2023 were included in the database. Children diagnosed with NS by Doppler examination were the patients whose proteinuria etiology had been investigated in the pediatric nephrology outpatient clinic or who had been followed up for various reasons such as microscopic hematuria or hydronephrosis. The study excluded renal venous Doppler patients presenting with renal vein thrombus who also had malignancy and coagulation disorders. Renal Doppler ultrasound measurements were performed by the same radiologist with a 3.5 MHz convex array transducer using Aplio 500 (Toshiba, Otawara, Japan) in the supine position. The AP diameter (mm) and peak systolic velocity (PSV; cm/sec) of the left renal vein at its widest point, the diameter (mm) of the left renal vein in the mesoaortic segment between the SMA and the aorta, and its PSV (cm/sec) at this level were measured using the renal Doppler. The diameter ratios of the left renal vein before and after stenosis and PSV ratios were calculated, with a PSV ratio of 3.0:1 or higher being accepted as the diagnostic criterion for NS. As a result of the complete urinalysis, protein values were recorded as trace, 1+, 2+, and 3+. Age, sex, and symptoms were recorded. The presence or absence of hematuria, spot protein-to-creatinine (mg/mg) ratio, and 24-hour urine protein (mg/m²/day) were noted in the complete urinalysis. In addition, serum creatinine, complement levels, antinuclear antibody results, coagulation parameters, normal blood count, and urine culture results were recorded. Body mass index (BMI) was also calculated from the height and weight of the children. The analysis investigates the correlation between left renal vein PSV, mesoaortic PSV, flow rates, left renal vein diameter and diameter at the mesoaortic level, spot protein-to-creatinine ratio, and 24-hour urinary protein. Urinalysis and spot protein-to-creatinine ratio were performed based on first-morning urine.

Statistical analysis

Statistical analyses were performed using SPSS 22 for Windows (IBM Corp., Armonk, NY, USA). Standard descriptive statistics were used, with data being expressed as mean and SD, or median depending on whether the variables were normally distributed or not. Spearman correlation was used to examine the relationships between the parameters conforming to the non-normal distributions. Statistical significance was set as p<0.05.

RESULTS

The study includes a total of 74 patients (52 girls, 22 boys). The mean age was 13.15±2.32 (median: 13,25, min-max: 5.33-17.42) years, while the mean follow-up duration was 14.6±9.1 months. All patients had been referred to the pediatric nephrology clinic by pediatricians because of proteinuria. Upon the patients arrival to the pediatric nephrology outpatient clinic, 20 children had 3 positive proteinuria, 21 children had 2 positive proteinuria, 20 children had 1 positive proteinuria, and 3 children had trace amounts of proteinuria. Proteinuria was not observed in 10 children at the first outpatient clinic visit. Microscopic hematuria (27%) was found in 20 children. The spot protein-to-creatinine ratio was 0.70±0.99 mg/mg, creatinine 0.04-5.1 mg. In 32 children, the spot protein-to-

creatinine ratio was between 0.2-2. A spot protein-to-creatinine ratio >2 mg/mg was detected in 6 children. The mean 24-hour urine proteinuria was found to be 9 ± 8.31 mg/m²/h (1.34-32.70) and 271.86±241.75 mg/day (40-1180 mg/day). The mean BMI was found to be 17.88±2.46 (13.6-23.8).

No patient had any clinical history of urinary tract infection, and their serum complement levels, coagulation parameters, blood count, and renal function tests were within normal limits. There was no complement consumption, and autoimmune examinations were found to be normal. Urine cultures were negative.

Table 1 shows the patients’ clinical characteristics. The most common complaint (73%) at the time of admission was incidental proteinuria in asymptomatic patients.

Table 2 presents the patients’ left RDUS findings. The mean left renal vein diameter at its widest point was found to be 8.63±2.12 mm and the mesoaortic level to be 2±0.535 mm.

A minimum compression ratio (CR = P/C) of 3 was found, as well as a maximum CR of 12 and a median CR of 6.

The mean left renal vein PSV was found to be 24.60±5.8 cm/sec and the mean mesoaortic level PSV was found to be 121.8±38.6 cm/sec. Patients with a minimum PSV value of 3.0 or greater

Table 1: The clinical characteristics of the patients

Complaints at the time of admission (n:74)	
Asymptomatic, incidental proteinuria	54 (%73)
Proteinuria with FMF (familial Mediterranean fever)	1 (%1,4)
Hematuria	1 (%1,4)
Detection of hydronephrosis during examination for aberrant vessels	1 (%1,4)
Proteinuria with abdominal pain	9 (%12)
Proteinuria with DM (diabetes mellitus)	2 (2,7)
Nausea	1 (%1,4)
Inability to gain weight, proteinuria	1 (%1,4)

Table 2: BMI values and Renal Doppler ultrasound findings of the patients

	Minimum	Maximum	Mean
BMI	13,6	23,8	17,88±2,46
C-PSV (cm/sec)	10	40	24,6±5,79
P-PSV (cm/sec)	47	241	212,86±3,62
PCV-R: P-PSV/C-PSV	3	12	6,61±3,01
CR: P/C	3	12	5,93±2,65

BMI: Body mass index, PSV: Peak systolic velocity, CR:P/C: minimum compression ratio

were included in the study. The mean PSV ratio of the patients included in the study was found to be 6.6. Fifty-four patients had a 4-fold or more increase in the PSV-R value. Eighteen patients had a 3-to-4-fold increase in the PSV-R value, but they were included in the study because of significant diameter differences.

Compressed peak systolic velocity (C-PSV), peak systolic velocity ratio (PSV-R), pre-compressed peak systolic velocity (P-PSV), compressed ratio (CR), spot protein/creatinine, and 24-hour urine protein were compared with the Spearman correlation test, with a correlation found only between C-PSV and 24-hour urine protein.

None of the patients had medical or surgical treatment. A significant reduction or complete normalization of proteinuria was seen in 41 patients (55.4%). In 20 children (27%), proteinuria persisted at the same level. Only two children had increased proteinuria (2.7%). At the final follow-up, proteinuria was observed in 34 children (45.9%), whereas 40 children (54%) had no proteinuria.

DISCUSSION

Nutcracker syndrome and its wide range of symptoms overlap with other clinical entities and cause complexity. As a result, it may be misdiagnosed, or the diagnosis may be delayed. Although the exact prevalence is not known, it is slightly more common in girls [6]. Most pediatric cases of NS were described in adolescent patients, with the mean age in the current study being 13 years and NS being more common in girls, which are consistent with the literature [7,8]. Frequently, NS is associated with the asthenic constitution and reduced retroperitoneal and mesenteric fat. A positive correlation was found between low-weight children and NS due to decreased abdominal fat predisposing to meso-aortic angle changes [9]. According to the variety of the degree of renal venous hypertension, the most common clinical finding is microscopic or macroscopic hematuria [6-9]. Painless microscopic hematuria is more common in NS children compared to adults [10]. Okada et al. showed that NS syndrome may be one of the important causes of hematuria [11]. Only 27% of the current study's patients had microscopic hematuria. Proteinuria was the leading symptom for diagnostic radiology, and the ratio of hematuria was found to be lower than expected. Orthostatic proteinuria is probably caused by increased pressure in the LRV and changes in renal hemodynamics upon standing, altering the release of angiotensin II and norepinephrine [12]. Abdominal pain associated with proteinuria was observed in 12% of this study's subjects, and the literature also states that both flank and abdominal pain could be seen in 10% due to the activation of the inflammatory cascade prompted by venous hypertension [13-15]. Pelvic congestion syndrome characterized by symptoms of lower abdominal pain, dysuria, pelvic and vulvar varices, and varicoceles did not present in the current study group. None of the patients had been referred from pediatric urology clinics.

Left renal Doppler ultrasound has a diagnostic sensitivity of 78% and a specificity of 100% for NS [16]. A cut-off ratio above 2.25 has been reported to have 91% sensitivity and

specificity for the diagnosis of NS [17]. However, Ananthan et al. defined the classic "bird's beak" appearance of NS as a specific finding for the narrowed stenotic segment in CT/MR angiography examinations and accepted this ratio as greater than 4.9 on CT [18]. This bird's beak appearance was present in all our patients diagnosed with NS by Doppler. PSV-R may be more predictive as compression of the transducer in the supine position can produce artifacts, and peak velocities are highly variable depending on the patient's position [19]. When accepting a left renal vein PSV ratio of > 4.7 as the limit for the diagnosis of NS, the sensitivity and specificity of this ratio in children with NS were found to be 100% and 90%, respectively; however, various ratios ranging between 4.0 and 5.0 have been suggested to be important in many studies [20-24]. The current study saw the bird's beak appearance with a PSV ratio of 3.0 and above being accepted as NS.

The current study's patient group seems to be rather lean or even underweight, similar to the literature. One review found a mean BMI of 17.3 [24], while the current study's patients had a mean BMI value of 17.8. Alaygut et al. reported an increase in BMI to be directly correlated with symptom regression in their patient group [12].

The present study's patient group had a good prognosis with most of the children showing improvement in terms of proteinuria and symptoms. Treatment is controversial, and most cases are managed with conservative treatment. Young patients can have spontaneous resolution of symptoms with increased body mass index [12]. Surgery may be needed for gross hematuria and severe symptoms including abdominal pain [25]. Surgical options involved left renal vein transposition, bypass, and SMA transposition. Endovascular treatment options are also present [26]. One systematic review showed approximately 90% of NS patients to be treated conservatively and 94.9% to have had resolution of clinical symptoms [24]. For asymptomatic patients and patients without severe clinical findings, the conservative approach seems to be adequate. The same review recommended a follow-up of 2-3 years due to the possibility of an improvement or resolution over this period.

Knowledge of the presenting symptoms, radiology findings, treatment options, and prognosis has increased in recent years. This study has shown that most NS patients present with proteinuria. In the long term, patients were followed up conservatively, and remission in proteinuria was demonstrated.

Ethics Committee Approval: This study was approved by the ethics committee of İstanbul Medeniyet University (ID:2023/0123).

Informed Consent: The study was conducted retrospectively.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.G.B., N.G.; Data Acquisition- S.G.B.; Data Analysis/Interpretation- S.G.B., N.G. ; Drafting Manuscript- N.G.; Critical Revision of Manuscript- S.G.B., N.G.; Final Approval and Accountability- S.G.B., N.G.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

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