

Clinical Profile and Renal Ultrasound Characteristics of Children With Nutcracker Syndrome in Turkey

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Received: February 19, 2021;

Initial review: April 08, 2021;

Accepted: June 21, 2021.

Objective: We aimed to evaluate the clinical profile and radiological findings of children with nutcracker syndrome (NCS) and to assess the association between the parameters. **Methods:** A retrospective analysis of the clinical, laboratory and radiological parameters of children diagnosed with NCS between January, 2011 and October, 2017 was done. **Results:** Of a total of 29 patients [19 girls, 65.5%] with NCS, having a mean (SD) age of 10.8 years, 72.4% had BMI <-2SD. Approximately half of the patients (51.7%) were asymptomatic. Left flank pain was commonest (9/29; 31%) symptom, followed by macroscopic hematuria (4/29; 13.8%). Isolated proteinuria was seen in 9 children. There was no significant difference between the symptomatic and asymptomatic patients in terms of Doppler ultrasonography findings. All patients were followed up conservatively, 5 received enalapril therapy for moderate proteinuria. **Conclusion:** NCS should be considered in children, especially with low BMI, presenting with orthostatic proteinuria and hematuria, with or without left flank pain after ruling out the common causes.

Keywords: Flank pain, Hematuria, Left renal vein, Proteinuria, Doppler ultrasound.

Nutcracker phenomenon refers to compression of the left renal vein (LRV) most commonly between aorta and superior mesenteric artery [1], resulting in dilatation of LRV and increased venous pressure. Nutcracker syndrome (NCS) or left renal vein entrapment syndrome may be anterior NCS resulting from compression of the renal vein between the aorta and mesenteric artery, and posterior NCS resulting from compression of the LRV between the aorta and corpus vertebrae [1,2]. Patients with NCS often remain asymptomatic and are usually diagnosed incidentally during radiological examination. However, in some cases, it may manifest as macroscopic hematuria, moderate to severe proteinuria, severe flank pain and varicocele [3]. Autonomic disturbances and gonadal vein syndrome (dysmenorrhea, dyspareunia and varicocele) have rarely been reported [4].

The diagnosis of NCS, may be confirmed by renal vein Doppler ultrasonography (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA) or renal venography (RV). Though renal vein DUS is an easy and non-invasive method with a sensitivity of 70-90% and a specificity of 89-100% [5,6], there is no clear consensus on the measurement values, thereby making the assessment partially subjective.

This study was done to describe the clinical, laboratory and radiological findings of children diagnosed with NCS

and to assess the relationship between the clinical features and the radiological measurements.

METHODS

This retrospective study included children from 0-18 years of age, presenting to our child nephrology outpatient clinic between January, 2011 and October, 2017, who were diagnosed with NCS. Clinical symptoms and investigation details were retrieved from records. Cases had been diagnosed with NCS based on their symptoms, clinical findings and left renal vein DUS findings. The study was approved by the ethical board of our hospital.

Findings of urinalysis were interpreted as per standard recommendations [7]. Radionuclide scintigraphy was done to rule out scars in patients with proteinuria and recurrent urinary tract infection.

In children suspected to have NCS, the diagnosis had been confirmed using pre-defined criteria of DUS [3,8] viz., hilar/aortomesenteric diameter ratio of left renal vein ≥ 4 ; angle between the superior mesenteric artery and the aorta $< 45^\circ$; collateral formation between renal hilum and retroperitoneum; and, peak velocity ratios between aorto-mesenteric and renal hilum portions ≥ 5 . DUS was done using ultrasonography device (Toshiba Aplio 500, Toshiba Medical Systems) with high frequency linear and convex probe. In a small number of cases in which adequate data

could not be generated by DUS, CTA or MRA methods were used.

Statistical analysis: IBM SPSS Statistics 24 program (IBM Corp.) was used for statistical analysis. The relationships between continuous variables were examined by correlation analysis. Comparison of independent groups was done using Mann Whitney U test. The significance level was taken as 95% CI and a P value <0.05 .

RESULTS

A total of 29 patients [19 girls, 65.5%] with NCS, having a mean (SD) age of 10.8 (3.2) years were included. The mean (SD) time of follow-up was 39 months. The mean BMI was 15.8 kg/m^2 (**Table I**), with 72.4% having a BMI $<-2\text{SD}$; nearly half (51.7%) were asymptomatic. While the most common symptom was left flank pain in 9 (31%) children, isolated proteinuria was the most frequent abnormality in urine in 9 (31%) children (**Table I**). There were no patients with extrarenal symptoms. The mean (SD) 24-hour urine protein excretion was $9.1 \text{ mg/m}^2/\text{h}$. None had nephrotic-range proteinuria ($>40 \text{ mg/m}^2/\text{hr}$). Majority 27/29 (93.1%) had anterior NCS

The ratio of left renal hilum diameter to aortomesenteric diameter varied between 1.4-7.7 with a mean value of 5.0. In addition, the mean value of the velocity ratio of aortomesenteric and hilar portions of LRV was 4.0. The mean (SD) aortomesenteric angle (AMA) value was $29.8 (8.5)^\circ$. The hilum/aortomesenteric region diameter ratio [$5.2 (2.0-7.5)$ vs $4.5 (1.4-7.7)$; $P=0.12$], aortomesenteric region /hilum velocity ratio [$4.5 (1.0-10.0)$ vs $3.4 (2.0-6.0)$; $P=0.71$], and the aortomesenteric angle [$30.5 (18.0-49.0)$ vs $30.0 (9.0-42.0)$]

Table I Clinical and Laboratory Characteristics of Children With Nutcracker Syndrome

Characteristics	Value
Girls, n (%)	19 (65.5)
Age (y); mean (SD)	10.8 (3.2)
BMI z-score, median (IQR)	-1.0 (-3.2, -1.4)
Symptomatic, ^a n (%)	14 (48.3)
Left flank pain	9 (31)
Macroscopic hematuria	4 (13.8)
Urinary findings, ^b n (%)	
Isolated proteinuria	9 (31)
Isolated microscopic hematuria	3 (10.3)
Isolated macroscopic hematuria	4 (13.8)
Microscopic hematuria and proteinuria	5 (17.3)
Tenderness and microscopic hematuria	5 (17.3)
Tenderness and proteinuria	2 (6.9)

BMI: Body mass index. ^aOne child had pelvic pain. ^bOne child had pelvic pain, microscopic hematuria and proteinuria.

degree; $P=0.56$] were not significantly different between symptomatic and asymptomatic children, respectively with nutcracker syndrome.

All patients were followed conservatively and none of the patients required surgical treatment. Five patients received enalapril for proteinuria. Enalapril was also used in two patients having type 1 diabetes besides NCS.

DISCUSSION

Nutcracker syndrome has been described as one of the less known causes of hematuria and proteinuria in individuals of all ages from late childhood to middle-aged adults. Though rare, it is possible that many patients investigated for hematuria or proteinuria, could have had underlying NCS, which was missed due to lack of awareness.

As reported in literature, our study also found that NCS is found commonly in and around the pubertal age group [3,5], with a higher frequency among females [9]. It is thought that venous congestion in the pelvic region due to the vasodilator effect of progesterone, increases pain, and women are more symptomatic and thus more easily diagnosed [8]. However, the symptom frequency was similar in both genders in our study. With rapid increase in length and hence low BMI during puberty, the angle between the superior mesenteric artery (SMA) and the aorta is narrowed, and this may cause a compression of LRV and NCS [8]. Our study showed a high proportion (72.4%) of children having low BMI.

In our study, almost similar proportions of children were present in the symptomatic and asymptomatic groups. Consistent with previous reports [10], the abdominal or left flank pain was not severe and did not need treatment. Our study re-confirms that proteinuria in these children is usually mild. There was no evidence of renal impairment in any of our patients over the follow-up period. NCS usually does not lead to chronic kidney disease because it affects one kidney and entrapment symptoms improve with age.

As per recommendations, DUS was performed as the first imaging modality in our study. It is known to have a 69-90% sensitivity and 89-100% specificity for the diagnosis of NCS [5,11-13]. To the best of our knowledge, there are as yet no accepted radiological criteria for diagnosing NCS in children. Measurements during childhood vary due to age, LRV sampling area is smaller and the AMA value is wider compared to adults [5,6,14]. Due to the high sensitivity and specificity of AMA measurements [14], there is no requirement to meet all diagnostic criteria in pediatric patients for the diagnosis of NCS. In our study, though all patients did not meet all the diagnostic criteria completely, but the majority of them were diagnosed with NCS using DUS. In contrast to some previous studies, we found that the hilum/

WHAT THIS STUDY ADDS?

- No difference was found in Doppler ultrasound measurement parameters between symptomatic and asymptomatic children with nutcracker syndrome.

aortomesenteric diameter and aortomesenteric/hilum velocity ratio was not higher in the symptomatic group. [9,12].

With increasing age and weight of the children, up to 75% decrease in clinical symptoms is reported, and the need for surgery is extremely low [15]. None of the patients with NCS in our study required surgical treatment.

The main limitations of our study are that it is single-center and retrospective. Since the study was retrospective, the association between exercise and the patients' symptoms other than proteinuria could not be assessed.

To conclude, NCS should be considered in children, especially with low BMI, presenting with orthostatic proteinuria and hematuria, with or without left flank pain. After common causes of hematuria and proteinuria are reasonably ruled out by clinical history, examination and urinalysis, it is prudent to radiologically evaluate for NCS before subjecting the patient to invasive procedures including renal biopsy. NCS is a relatively benign cause of proteinuria and hematuria, which can be managed conservatively with close follow up, depending on the severity of symptoms.

Ethics clearance: Institutional Ethics Committee of Health Science University, Kecioren Training and Research Hospital; No.1540 dated 10/2017.

Contributors: EGB: concept and designed the study and analyzed data; ACY: concept and designed the study and drafted the manuscript; OG: collected the data and helped in data analysis; ACT, BB: conducted behavioral assessments. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

Funding: None; *Competing interests:* None stated.

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