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ORIGINAL ARTICLE

Nutcracker syndrome in pediatrics: initial findings and long-term follow-up results

Iryna Akdemir[1] · Ece Mekik Akar[2] · Songül Yılmaz[2] · Nilgün Çakar[2] · Suat Fitöz[3] · Zeynep Birsin Özçakar[2]

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Abstract

Background Nutcracker syndrome (NCS) describes a set of symptoms and signs resulting from compression of the left renal vein (LRV). There is a lack of knowledge about its natural course, diagnosis, and management, especially in children. Herein, we present our single-center experience with a large number of patients who have long-term follow-up results.

Methods All patients with NCS diagnosed between January 2011 and March 2021 were included and their data were obtained retrospectively.

Results A total of 123 NCS patients (85 females) were included. The median age at the time of diagnosis was 12 (IQR 10–14) years, and BMI percentiles were below 5% in 38% of the cases. At the time of diagnosis, two-thirds of the patients were asymptomatic. The most common laboratory finding was nephritic proteinuria (98%), followed by microscopic hematuria (16%). Signs of LRV compression were significantly more evident in upright position Doppler ultrasonography (DUS) examination. All patients have been followed conservatively; hematuria and/or proteinuria resolved in 43 of the 108 patients (40%) within 35.8 ± 25.8 months of follow-up. Control DUS was performed in 52 patients after a mean period of 39.1 ± 21.3 months. The median peak velocity and diameter ratios of the LRV in the upright position were found to be decreased significantly when compared to the initial assessment ($p < 0.05$). Normal DUS findings were noted in 13 patients at the final evaluation.

Conclusions In unexplained proteinuria and/or hematuria, NCS should be considered, especially in asthenic adolescents. Our results support conservative management in children as the first-line treatment approach.

Keywords Nutcracker syndrome · Left renal vein entrapment · Hematuria · Proteinuria · Doppler ultrasonography

Introduction

Extrinsic compression of the left renal vein (LRV) followed by mesoaortic narrowing with hilar dilatation was first described anatomically by Grant in 1937 [1] and termed as "nutcracker phenomenon" by De Schepper in 1972 [2]. Nutcracker syndrome (NCS) is defined as LRV entrapment accompanied by clinical findings. Typically, the compression of LRV is between the aorta and the superior mesenteric artery (SMA) and is called "anterior nutcracker." Less frequently, in the presence of a retroaortic or circumaortic LRV, compression occurs between the aorta and the vertebral body and is referred to as "posterior nutcracker" [3]. The true prevalence of NCS is unknown due to the wide variety of clinical manifestations and the lack of consensus on diagnostic criteria [4].

Major theories regarding the etiopathogenesis of NCS include an abnormally high course of LRV, left renal ptosis causing stretching of LRV over the abdominal aorta, abnormal SMA branching from the aorta, and reduced retroperitoneal and mesenteric adipose tissue. All these conditions result in narrowing of the angle between the aorta and the SMA, known as the aortomesenteric angle (AMA), which is normally between 38 and 65°, but less than 35° in patients with NCS [5]. Entrapment of the LRV in the narrow AMA causes venous hypertension in the antecedent LRV segment and varicosities in the renal pelvic and ureteral vessels and gonadal vein tributaries. As a result, patients with NCS can present with hematuria,

✉ Zeynep Birsin Özçakar
zbozcakar@yahoo.com

[1] Department of Pediatrics, Ankara University School of Medicine, Ankara, Turkey

[2] Division of Pediatric Nephrology, Department of Pediatrics, Ankara University School of Medicine, Ankara, Turkey

[3] Division of Pediatric Radiology, Department of Radiology, Ankara University School of Medicine, Ankara, Turkey

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proteinuria, left flank/abdominal pain, left varicocele in males, and pelvic congestion syndrome in females. Typically these symptoms worsen with physical activity and in upright position, as the AMA becomes narrower with gravity-induced visceral proptosis [6]. Rupture of engorged periureteral and peripelvic varices within the renal collecting system results in microscopic and macroscopic hematuria. On the other hand, proteinuria is believed to result from venous hypertension within the nephron, causing an exaggerated physiologic response to the subclinical immune cascade in the vessel wall, and local release of norepinephrine and angiotensin II upon standing [7].

The diagnosis of NCS is based on demonstrating LRV compression via imaging techniques in conjunction with the patient's clinical and laboratory examinations. Doppler ultrasonography (DUS) is recommended as a first-line diagnostic test as it shows both anatomical and physiological features of LRV without radiation exposure [3].

The treatment decision should be made according to the clinical findings of the patient. Conservative management is the best approach for the pediatric population with mild and tolerable symptoms, given the fact that the majority would resolve spontaneously. On the other hand, patients with severe flank pain, renal dysfunction, recurrent macroscopic hematuria, persistent anemia, and orthostatic proteinuria that persists or worsens after 24 months of conservative follow-up may require surgical treatment [3–9].

Thus far, the published data on NCS mostly consists of case reports and single-center studies with a limited number of patients. Given the rarity and diverse manifestation of NCS, there is no consensus on diagnosis, management, and course of the disease, especially in children. Herein, we present our single-center experience with the highest number of NCS patients who have a long-term follow-up to the best of our knowledge.

Methods

All patients who were diagnosed and followed up with NCS in our outpatient pediatric nephrology clinic between January 2011 and March 2021 were included in this retrospective observational study. Patients with concomitant diseases ($n=4$) that could affect the results of the study were excluded. Patients' data regarding demographic features, anthropometry, comorbidities, presenting symptoms, laboratory, and radiological findings at diagnosis and follow-up were obtained from hospital records retrospectively.

Patients were diagnosed with NCS if they have typical DUS features of LRV entrapment (SMA angle < 35° [5] and/or LRV diameter ratio > 4.2 [10] and/or LRV peak velocity ratio > 4.7 [11]) in the supine or upright position accompanied by clinical symptoms (left flank and/or abdominal pain, macroscopic hematuria) and/or laboratory (microscopic hematuria and proteinuria) findings. Patients who had laboratory findings without clinical symptoms were considered asymptomatic. Visible blood in the urine was accepted as "macroscopic hematuria" while the presence of at least 5 red blood cells per mm^3 in centrifuged urine was defined as "microscopic hematuria." Protein excretion above 4 $mg/m^2/h$ in the 24-h urine samples and spot urine protein/creatinine ratios greater than 0.2 mg/mg were considered as proteinuria. Nephrotic range proteinuria was defined as proteinuria more than 40 $mg/m^2/h$ in 24-h urine samples and spot urine protein/creatinine ratio of over 2 mg/mg. Glomerular filtration rate (GFR) was calculated from 24-h urine specimens.

Doppler ultrasonography studies were performed with an Aplio (Toshiba Medical Systems Co, Ltd, Tokyo, Japan) and iU22 (Philips Healthcare Ultrasound, Amsterdam, the Netherlands) using 1–5.5 MHz convex transducers. All 123 patients went through supine DUS examination while upright DUS could not be performed in 4 of them, due to posterior NCS in three and gas superposition in one patient. The angle of SMA, LRV diameter, and peak velocity (PV) were measured in both supine and upright positions. The anteroposterior diameter and PV of the LRV were measured at two points, one in the lateral or proximal segment of the LRV near the hilum and the other where the LRV passes between the aorta and the SMA (aortomesenteric (AM) portion). Diameter and PV ratios were calculated between both regions. As DUS examination provided sufficient radiological information to lead to the diagnosis in all cases, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) was not used in any patient for diagnostic purposes.

In descriptive statistics, mean, standard deviation, median, and interquartile range (IQR) values were given for continuous data, and percentage values were given for discrete data. Kolmogorov–Smirnov test was used to examine the conformity of the data to normal distribution. In the comparison of continuous data in two groups, independent samples *t*-test was used for data with normal distribution, and Mann–Whitney *U* test was used for data that did not fit normal distribution. Chi-square and Fisher's exact tests were used for group comparisons (cross tables) of nominal variables. In the comparison of the baseline and follow-up values of the continuous data, the *t*-test was used in the dependent groups for data with normal distribution, and the Wilcoxon test was used for data that did not comply with the normal distribution. McNemar test was used to compare baseline and follow-up values of nominal variables. IBM SPSS Statistics 21 was used for the statistical analyses and a p value < 0.05 was considered statistically significant.

The study was approved by the Ethics Committee of Ankara University School of Medicine with a report numbered I5-338–21.

Results

A total of 123 NCS patients with a mean follow-up duration of 31.7 ± 26.6 months were included in the study and the female/male ratio was 2.2. The median age at the time of diagnosis was 12 (IQR 10–14) years, and 68% ($n = 84$) of the patients were between the ages of 10–15, while 19% ($n = 23$) were < 10, and 13% ($n = 16$) were > 15 years old. Comorbidities were detected in 46% of the patients, the most prevalent being familial Mediterranean fever (FMF). Percentiles of BMI were below 5% in 38% of the patients, below 50% in 84%, and none of them had a BMI above 95%.

At the time of diagnosis, 68% ($n = 83$) of the patients were asymptomatic. Symptomatic patients presented with left flank and/or abdominal pain (24%), macroscopic hematuria (6%), dysuria (5%), and varicocele (2%). The most common laboratory finding was proteinuria (98%), followed by microscopic hematuria (16%). Seven of 20 patients with microscopic hematuria also had macroscopic hematuria and 5 of them had accompanying left flank and/or abdominal pain. Only one patient with concomitant kidney cysts had impaired kidney function tests. The demographic, clinical, and laboratory features of the patients are detailed in Table 1. Patients with proteinuria had median protein excretion of 8.4 (IQR 5.9–12.3) mg/m^2/h in 24-h urine samples and a median spot protein/creatinine ratio of 0.57 (IQR 0.34–1.01) mg/mg. Nephrotic range proteinuria was detected in 8 of 121 patients with proteinuria according to spot urine samples, but none of them had protein excretion over 40 mg/m^2/h in 24-h urine specimens. The patients' median GFR was 142.8 (IQR 119.5–183) ml/min/1.73 m^2. Kidney biopsy was performed in 6 patients (5%); 4 had proteinuria above 25 mg/m^2/h, and 2 had proteinuria along with macroscopic hematuria. Pathology results were evaluated as normal in 4 patients. The histopathological findings of 2 patients with FMF showed minimal thickening of the basement membrane and focal dilatation of the lamina rara interna in the other. No amyloid deposition was detected in either biopsy.

Doppler ultrasonography studies showed posterior NCS in 3 patients, 2 of them were circumaortic LRV, and one was retroaortic LRV. Detailed data of DUS findings in both supine and upright positions at the time of diagnosis are presented in Table 2. The difference between vertical and supine DUS measurements was statistically significant in all parameters of DUS ($p < 0.001$). It was demonstrated that ratios of diameter and PV between the two portions of LRV were higher, and SMA angles were lower in the upright than in the supine position, indicating a more evident compression of the LRV. The comparison of the DUS features of the patients with and without symptoms showed no statistically significant difference between groups, except for the PV in the LRV at hilar portion and the PV ratios between AM and hilar portions, which were higher in symptomatic patients in the upright position ($p = 0.017$ and $p = 0.043$, respectively). Likewise, there was no correlation between the patients' DUS parameters and 24-h urine proteinuria levels (Table 3).

Table 1 Demographic, clinical, and laboratory features of the patients

	$n = 123$ (%) Median (IQR)
Age at diagnosis	12 (10–14)
Sex, female	85 (69.1)
Clinical findings	
Left flank and/or abdominal pain	30 (24.3)
Macroscopic hematuria	7 (5.7)
Dysuria	6 (4.9)
Varicocele	3 (2.4)
Hypertension	2 (1.6)
Asymptomatic	83 (67.5)
Anthropometric measurements	
Weight (kg)	40 (30–47)
Height (cm)	156 (140–164)
BMI	16.3 (14.8–18.2)
BMI percentile (%)	11.7 (2.6–35)
Laboratory findings	
Proteinuria only	103 (83.7)
Microscopic hematuria only	2 (1.6)
Proteinuria and microscopic hematuria	18 (14.6)
Impaired kidney function tests	1 (0.8)
Comorbidities	56 (45.5)
Familial Mediterranean fever	26 (21.1)
Growth failure	8 (6.5)
Previous diagnosis of Henoch Schönlein purpura	4 (3.3)
Recurrent urinary tract infections	3 (2.4)
Pelviectasia	2 (1.6)
Nephrolithiasis	2 (1.6)
Celiac disease	2 (1.6)
Asthma	2 (1.6)
Kidney cysts	1 (0.8)
Epilepsy	1 (0.8)
Previous diagnosis of acute rheumatic fever	1 (0.8)
IgA deficiency	1 (0.8)
Raynaud's phenomenon	1 (0.8)
Type 1 diabetes mellitus	1 (0.8)
Type 1 diabetes mellitus and goiter	1 (0.8)

Table 2 Doppler ultrasonography findings of the patients in supine and upright positions

	n	Supine position Median (IQR)	*n*	Upright position Median (IQR)	*p*
Diameter of LRV at AM portion (mm)	123	1.6 (1.2–2.2)	119	1.1 (0.8–1.5)	< 0.001
Diameter of LRV at hilar portion (mm)	123	7.7 (6.2–9)	119	8.6 (7.4–10)	< 0.001
Diameter ratio of LRV (hilar/AM)	123	5 (3.2–6.4)	119	7.6 (5.5–10)	< 0.001
PV of LRV at AM portion (cm/s)	123	94 (58–130)	119	140 (107.7–182.2)	< 0.001
PV of LRV at hilar portion (cm/s)	123	20 (17–25)	119	18 (14.5–21)	< 0.001
PV ratio of LRV (AM/hilar)	123	4.7 (3.3–6)	119	8 (5.8–10.9)	< 0.001
SMA angle (°)	123	26 (20.2–35.7)	119	15 (12–19)	< 0.001

LRV left renal vein, *AM* aortomesenteric, *PV* peak velocity, *SMA* superior mesenteric artery

Table 3 Correlations between the DUS parameters and proteinuria levels

	24-h urine proteinuria levels	
	Spearman's rho coefficient	*p*
Supine position		
Diameter ratio of LRV (hilar/AM)	0.005	0.962
PV ratio of LRV (AM/hilar)	− 0.041	0.661
SMA angle (°)	0.092	0.337
Upright position		
Diameter ratio of LRV (hilar/AM)	− 0.108	0.262
PV ratio of LRV (AM/hilar)	0.071	0.464
SMA angle (°)	0.108	0.263

LRV left renal vein, *AM* aortomesenteric, *PV* peak velocity, *SMA* superior mesenteric artery

Follow-up results

Among 123 patients, 108 were followed for a mean of 35.8 ± 25.8 months. At the last visit, the patients' weight, height, BMI, and BMI percentiles were observed to be increased compared to the baseline, and these increases were statistically significant except for the BMI percentiles (Table 4). Macroscopic hematuria persisted in only one of six patients with initial macroscopic hematuria. Microscopic hematuria was noted to be resolved in 8 out of 17 patients who had microscopic hematuria at baseline. Proteinuria resolved in 46 patients ($p < 0.001$); protein excretion levels in both 24-h and spot urine samples were significantly decreased in the remaining patients (Table 4). Overall, complete recovery of hematuria and/or proteinuria was observed in 43 (40%) of the 108 patients.

Control DUS examinations were performed in 52 patients after a mean period of 39.1 ± 21.3 months. Detailed information about follow-up DUS findings and their comparison with initial findings are presented in Table 5. Normal DUS findings were noted in 13 patients at the final evaluation, and the clinical and laboratory features of these patients were completely recovered. Among patients with a follow-up DUS, macroscopic and microscopic hematuria resolved in 4 of 5 and 8 of 15 patients, respectively. Proteinuria resolved in 24 out of 49 patients; moreover, protein excretion levels were observed to be decreased in the remaining patients, though not significantly. At the last visit, their median proteinuria changed from 8.2 (IQR 5.5–11.9) to 5.6 (IQR 5.2–10.1) mg/m^2/h in 24-h urine and from 0.5 (IQR 0.32–1.2) to 0.29 (IQR 0.24–0.6) mg/mg in spot urine ($p = 0.153$ and $p = 0.087$, respectively). The recovery rate from proteinuria and microscopic hematuria was found to be statistically significant ($p < 0.001$ and $p = 0.039$, respectively). Overall, in 23 of 52

Table 4 The comparison of initial and final anthropometry and laboratory data of the patients

	n	At the time of diagnosis Median (IQR)	*n*	At the last visit Median (IQR)	*p*
Weight (kg)	108	38.8 (28.8–47)	108	48.2 (40–56.2)	< 0.001
Height (cm)	108	155 (139–160.7)	108	162 (155–168.7)	< 0.001
BMI (kg/m^2)	108	16.2 (14.8–18.2)	108	18.2 (16–20.3)	< 0.001
BMI percentile (%)	108	13.1 (2.7–36.5)	108	14.3 (2–37.3)	0.844
24-h proteinuria (mg/m^2/h)	102	8.3 (5.9–12.4)	47	5.7 (5.1–10)	0.007
Spot urine protein/creatinine (mg/mg)	78	0.56 (0.34–1.1)	36	0.44 (0.25–0.82)	0.004
GFR (ml/min/1.73 m^2)	92	143 (123–187)	66	137.5 (121.2–163.7)	0.134

BMI body mass index, *GFR* glomerular filtration rate

Table 5 The comparison of initial and follow-up DUS measurements

	Supine position ($n=52$)			Upright position ($n=52$)		
	Initial Median (IQR)	Follow-up Median (IQR)	*p*	Initial Median (IQR)	Follow-up Median (IQR)	*p*
Diameter of LRV at AM portion (mm)	1.5 (1.1–2)	2 (1.5–2.5)	0.007	1 (0.8–1.3)	1.2 (1–2)	0.056
Diameter of LRV at hilar portion (mm)	7.4 (6–9)	7.5 (5.6–9.2)	0.460	8.5 (7.2–9.7)	8.2 (7.4–9.2)	0.749
Diameter ratio of LRV (hilar/AM)	5.1 (3–6.7)	3.7 (2.8–5.1)	0.067	7.8 (6.5–10.6)	6.1 (4.7–9.2)	0.045
PV of LRV at AM portion (cm/s)	99.5 (65.9–137)	85 (66.2–134)	0.567	159 (128.2–192.1)	118 (87.7–140)	<0.001
PV of LRV at hilar portion (cm/s)	20.3 (17–25)	20.2 (14.2–24.7)	0.150	18.1 (15–21.2)	19 (14–21.5)	0.139
PV ratio of LRV (AM/hilar)	5 (3.4–6.4)	4.6 (2.9–7.2)	0.498	8.4 (6.2–11.6)	6.2 (4.4–9.9)	0.041
SMA angle (°)	26.5 (22–37.5)	28 (20–38)	0.708	16 (12–21)	18 (13–24.5)	0.095

LRV left renal vein, *AM* aortomesenteric, *PV* peak velocity, *SMA* superior mesenteric artery

patients (44%), laboratory findings were noted to be normal at the last visit.

All patients have been followed conservatively. Medical treatment was commenced in 8 patients (6.5%) with persistent relatively high proteinuria. The choice of drug was an angiotensin-converting enzyme inhibitor, enalapril, in all cases. Laboratory improvement was observed in 5 patients with treatment.

Discussion

In this study, we present the clinical, laboratory, and imaging findings in a quite large number of pediatric NCS patients. The majority of the patients were diagnosed during proteinuria evaluation with DUS. Hematuria and/or proteinuria resolved in approximately 40% of the patients roughly within 3 years and improvement in DUS findings was also shown during follow-up.

Nutcracker syndrome describes LRV compression, typically between the aorta and the SMA, accompanied by a set of signs and symptoms. It was reported to be more common in females; however, more recent studies have suggested that there is an equal prevalence between the sexes [4, 12]. It is hypothesized that pelvic venous congestion combined with the vasodilator effect of progesterone increases pain, making women more symptomatic and thus more easily diagnosed [13]. On the other hand, our patient population, of which two-thirds were asymptomatic, had a female/male ratio of 2.2, supporting that NCS is more prevalent in females. Although NCS can be seen at any age, its peak incidence in adolescence has been associated with a rapid increase in height and maturation of the vertebral bodies, narrowing the AMA [14]. Consistent with the data in the literature, in our study, it was observed that 68% of the patients were in the pubertal 10–15 age range. NCS is also reported to be associated with a lower BMI, as reduced retroperitoneal fat causes renal ptosis and narrows the AMA [3, 7, 15]. Accordingly, BMI percentiles were found to be below 50% and 5% in 84% and 38% of our patients, respectively. Therefore, NCS should be suspected in tall and thin adolescents with unexplained hematuria and/or proteinuria.

Despite being accepted as a rare condition, NCS is assumed to be underdiagnosed [16], mostly because children tend to be asymptomatic [4, 12, 17, 18] and are diagnosed incidentally with microscopic hematuria and/or nephritic proteinuria during investigations for other diseases or mass urinalysis screenings [3]. Similarly, two-thirds of our patients were asymptomatic and almost half had a concomitant disease, the most common being FMF (21% of the whole study group). Avar-Aydin et al. investigated the relationship between FMF and NCS and reported that in the colchicine era, NCS was the leading cause of proteinuria in patients with FMF [19]. Therefore, in case of persistent hematuria and proteinuria in patients with FMF or any other disease, the diagnosis of NCS should be excluded with non-invasive and feasible DUS.

Hematuria has been stated as the most common clinical feature in many studies, although, recently, it has been shown that proteinuria is one of the significant findings in children with NCS [4]. Likewise, a review of the literature revealed that LRV entrapment was the most important cause of orthostatic proteinuria [20]. All but two of our patients had proteinuria, while only 20 of 123 had microscopic and/or macroscopic hematuria. This remarkably high proteinuria rate in our study is thought to be because almost all of our patients, who have high comorbidity rates, were diagnosed during investigations for proteinuria etiology. It is also noteworthy that none of them had nephrotic range proteinuria. However, six of our patients went through kidney biopsy because of persistently high levels of proteinuria and proteinuria with recurrent macroscopic hematuria. Even though not detected in this study, the co-existence of NCS with other kidney diseases such as IgA nephropathy and membranous nephropathy has been defined in the literature; thus, it is suggested that patients whose clinical findings cannot only be

explained by the presence of NCS should be evaluated with kidney biopsy for possible glomerular diseases [21–25].

The first-choice imaging modality in the diagnosis of NCS is DUS with sensitivity and specificity of 69–90% and 89–100%, respectively [3]. Although there are no established diagnostic criteria, the latest cut-off values for the diagnosis of NCS have been reported as > 4.2 and > 4.7 for diameter and PV ratios, respectively [10, 11]. Since the diagnosis of NCS was confirmed by DUS examination in all of our patients, neither CTA nor MRA was used for diagnostic purposes. Fitoz et al. demonstrated that DUS in upright position shows more pronounced entrapment findings with higher cut-off values than in supine position [26]. Accordingly, our findings revealed a significant difference between the supine and upright DUS parameters. Therefore, DUS in the upright position is considered to be particularly important in the diagnosis of NCS.

Considering that there are few studies with limited patient numbers investigating the natural course of NCS, we evaluated our 108 patients with a mean follow-up of 35.8 ± 25.8 months in terms of clinical features. Since conservative management is recommended as first-line treatment in children with mild symptoms, all of our patients were followed up conservatively. Recovery rates for macroscopic and microscopic hematuria, and proteinuria were found to be 83%, 47%, and 43%, respectively. Furthermore, proteinuria levels were significantly reduced in the remaining patients. Physical growth resulting in adipose and fibrous tissue accumulation at the origin of SMA is believed to alleviate LRV compression. Accordingly, the improvement in the clinical features of our patients is thought to be the result of a significant increase in their weight, height, and BMI in nearly 3 years of mean follow-up duration. We reckon that if the follow-up period of the patients were longer, the recovery rate could be higher. A study by Miro et al. demonstrated that after a mean period of 52 months, 76% of their patients achieved resolution of symptoms [8]. Tanaka and Waga reported spontaneous remission of persistent hematuria in an adolescent with NCS with physical growth, particularly in height, in 7 years [27]. The index of BMI was found to be significantly increased in patients with clinical regression in another study [28]. Previous reports and our results suggest that NCS symptoms improve with time and physical growth; therefore, conservative management should be continued for at least 2 years in pediatric patients with NCS [3, 5, 29].

Available data on control DUS measurements in patients with NCS are lacking. In 2005, Shin et al. performed control DUS after an average of 1.4 years in their study group consisting of 20 patients in which 75% of the hematuria resolved spontaneously, and it was observed that PV ratios were significantly decreased in all of them, negatively correlated with the increase in BMI [30]. They also reported a significant reduction in PV ratios of the LRV after a mean period of 1.7 years in 15 patients with NCS whose hematuria dissolved in 2007 [31]. The main limitations of these 2 studies were their low patient numbers, exclusion of patients with proteinuria, and lack of examination of diameter ratios. Milani et al. demonstrated spontaneous resolution of LRV entrapment and postural proteinuria associated with an increase in BMI in 8 of 12 patients with more than 6 years of follow-up [32]. In a more recent study, Taktak et al. performed control DUS on 9 of 63 NCS patients whose hematuria and proteinuria resolved, and they noted a significant increase in upright SMA angles ($p = 0.043$), regardless of the change in their BMI [33]. In this study, control DUS was performed in 52 patients after a mean period of 39.1 ± 21.3 months, and we demonstrated that the diameter and PV ratios of the patients in the upright position were significantly lower than the baseline ($p = 0.045$ and $p = 0.041$, respectively). Moreover, 13 of 52 (25%) of the patients had normal DUS findings, and their clinical and laboratory findings were completely resolved. The recovery rate of proteinuria and microscopic hematuria was found to be statistically significant in patients with control DUS and nearly half of them had a normal laboratory at the last visit. Our findings confirm the radiological improvement with physical growth in children with NCS, which favors the conservative approach as the first-line treatment in this population.

The major limitation of this study is its retrospective nature. Therefore, prospective and comprehensive studies are needed to determine the diagnostic criteria of NCS, define its natural course and prognosis, and establish valid treatment algorithms, especially in children.

Conclusion

Given that children with NCS have a high rate of asymptomatic course, NCS should be considered in the presence of unexplained proteinuria and/or hematuria, especially in asthenic adolescents. Timely diagnosis and proper management of the disease will prevent unnecessary investigations and complications. Doppler sonography should be recommended as the first-line diagnostic test because of its noninvasive nature and high diagnostic value, especially in the upright position. Our single-center study, which presents long-term follow-up results of a large number of patients and especially control Doppler ultrasonography findings in a quite good number of patients, confirms the spontaneous resolution of laboratory findings and improvement in imaging findings of children with NCS.

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Author contribution Iryna Akdemir designed the study, performed data collection, interpreted the results, and drafted the manuscript. Ece Mekik Akar contributed to data collection, performed statistical data analysis, interpreted the results, and drafted the manuscript. Songül Yılmaz contributed to data collection and provided both scientific and grammatical revisions to the manuscript. Nilgün Çakar provided both scientific and grammatical revisions to the manuscript. Suat Fitöz interpreted the results and provided both scientific and grammatical revisions to the manuscript. Zeynep Birsin Özçakar designed the study, interpreted the results, and provided both scientific and grammatical revisions to the manuscript. All authors have read and approved the final version of the manuscript.

Data availability All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval The study was approved by the Ethics Committee of Ankara University School of Medicine with a report numbered I5-338–21.

Conflict of interest The authors declare no competing interests.

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