## ORIGINAL PAPER

# Effect of renal Doppler ultrasound on the detection of nutcracker syndrome in children with hematuria

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Abstract To assess the detection rate of nutcracker syndrome in children with isolated hematuria, renal Doppler ultrasound examinations were routinely performed on 216 consecutive children (176 microscopic hematuria and 40 gross hematuria). Renal Doppler ultrasound was also performed on 32 healthy normal children. The peak velocity (PV) was measured at the hilar portion of the left renal vein (LRV) and at the LRV between the aorta and the superior mesenteric artery. The PV at the aortomesenteric portion (P=0.003) and the PV ratios of the LRV (P=0.003) were significantly higher in children with hematuria than in normal children, while the PV at the hilar portion was not different. If a PV ratio of the LRV of at least 4.1 (the cut-off level set at the mean  $\pm 2$  SD of the value for the normal children) was defined as abnormal, 72 cases (33.3%) in children with hematuria and no cases in normal children were diagnosed as having nutcracker syndrome. The prevalence of nutcracker syndrome is relatively high in

children with isolated hematuria, and the inclusion of renal Doppler ultrasound as a screening examination has a substantial effect on the detection of nutcracker syndrome.

**Keywords** Nutcracker syndrome · Hematuria · Renal Doppler ultrasound · Screening examination

## Introduction

Hematuria is a common urinary abnormality with a prevalence of 0.5–2.0% among school-aged children [5]. In South Korea, mass urinary screening was started in school-aged children in 1998, and therefore the incidence of patients with asymptomatic microscopic hematuria has been increasing. When routine diagnostic tests for hematuria are used, approximately 40% of children with isolated hematuria are classified as being idiopathic [14, 17].

The prevalence of nutcracker syndrome in children with hematuria is unknown, because evaluation of nutcracker syndrome has not been routinely performed in children with isolated hematuria. This might be due to the absence of both reliable and easily applicable diagnostic methods in diagnosing nutcracker syndrome in children. Recently, however, renal Doppler ultrasound has been developed to diagnose nutcracker syndrome, and it is now possible to apply this diagnostic method to children [10–12].

Therefore, we carried out a prospective study of routine renal Doppler ultrasound in children presenting with isolated hematuria at our Nephrology Unit. The main aim was to assess the detection rate of nutcracker syndrome by renal Doppler ultrasound as a screening examination.

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### Methods

## **Patients**

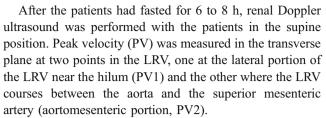
All consecutive 221 children with isolated hematuria (gross and microscopic) who visited our Nephrology Unit between 1 January 2002 and 31 December 2004 were routinely offered a renal Doppler ultrasound to detect cases of nutcracker syndrome in addition to a complete blood cell count, electrolytes, biochemistry, coagulation profile, serology for hepatitis B, antinuclear antibody, anti-streptococcal O titer, complement C3 and C4, urine culture, urinary calcium/creatinine, two-dimensional ultrasonography and excretory urography.

Hematuria was defined as the presence of at least five red blood cells (RBCs) in a centrifuged specimen. A urine sample from each parent and sibling was examined for hematuria, and a family history of urolithiasis was considered positive if a sibling, parent, grandparent, or parental sibling had a history of renal-stone disease. We excluded proteinuria by urinalysis in most patients, but also collected 24-h urine collections if proteinuria was suspected by urinalysis in some patients with gross hematuria. We collected 24-h calcium and creatinine if the urinary calcium/creatinine ratio was more than 0.2. Hypercalciuria was defined when 24-h calcium excretion was more than 4 mg/kg. Children with a documented urinary tract infection (n=2), Henoch-Schoenlein purpura (n=1), and systemic lupus erythematosus (n=2) were excluded, because the causes of hematuria were evident in these patients.

Therefore, 216 patients were included in this study: 176 showed microscopic hematuria on several examinations (170 through mass urinary screening and 6 through routine urinalysis during admission due to other diseases) and 40 gross hematuria. The hematuria was intermittent in 19 patients and permanent in 197. Blood pressure was normal in all patients. Also, 32 age- and sex-matched normal healthy children with no evidence of renal disease or other chronic diseases were selected for comparison. This study was approved by the institutional review board and the research ethics committee of Yonsei Severance Hospital.

## Renal Doppler ultrasound

Renal Doppler ultrasound was performed at the first visit by one experienced radiologist, not knowing whether the subjects had hematuria or were control subjects. A HDI 5000 sonography system with 5- to 8- and 4- to 6-MHz convex transducers (Philips, Ultrasound, Bothell, Wash.) was used, and the Doppler spectrum could be successfully obtained in most cases, except in one with a retroaortic left renal vein.



Doppler spectra of the LRV at the hilum were obtained with the transducer placed on the middle of the upper abdomen. Doppler spectra of the LRV at the aortomesenteric angle were obtained with the transducer placed on the right or left subcostal area for keeping the Doppler angle of the LRV less than 60°. It was relatively easy to obtain the PV at the hilar portion of the LRV with the Doppler angle of less than 60°, but there were some patients in whom the measurements of the PV at or beyond the aortomesenteric portion of the LRV were somewhat difficult with the Doppler angle of 60°. The median Doppler angle was 60° (range 32–66°) at the hilar portion and 60° (range 56–70°) at the aortomesenteric portion of the LRV. Ratios of the PV of the LRV between the two portions (Aortomesenteric PV/Hilar PV, PV2/PV1) were calculated.

## Statistical analysis

Statistical analysis was performed with Student's t-test and chi-square test, using SPSS for Windows (version 11.0). The mean  $\pm 2$  SD of PV2/PV1 ratios was calculated for normal controls and was used as the cut-off value for diagnosing nutcracker syndrome. A P value of 0.05 or less was defined as significant.

## Results

Figure 1 shows Doppler images of a patient with nutcracker syndrome (a, b) and a normal child (c, d). Color Doppler imaging of all LRVs showed blood flow from the renal hilum to the aortomesenteric portion.

Doppler velocimetric findings in children with hematuria and the control subjects are summarized in Table 1. In children with hematuria, the median PV2 and PV1 were 75.4 (range 23.9–288.0) cm/s and 23.8 (range 7.3–40.7) cm/s, respectively. In normal children, the median PV2 and PV1 were 60.2 (range 20–133.7) cm/s and 23.9 (range 10.7–36.8) cm/s, respectively. There were no differences in the PV1, PV2, and PV2/PV1 ratios between children with gross hematuria and those with microscopic hematuria. The median PV2/PV1 ratio was 3.14 (range 1.18–16.44) in children with hematuria and 2.56 (range 1.21–3.87) in normal children. The PV2 (P=0.003) and PV2/PV1 ratios (P=0.003) were significantly higher and had a wider distribution (Fig. 2) in children with hematuria than in



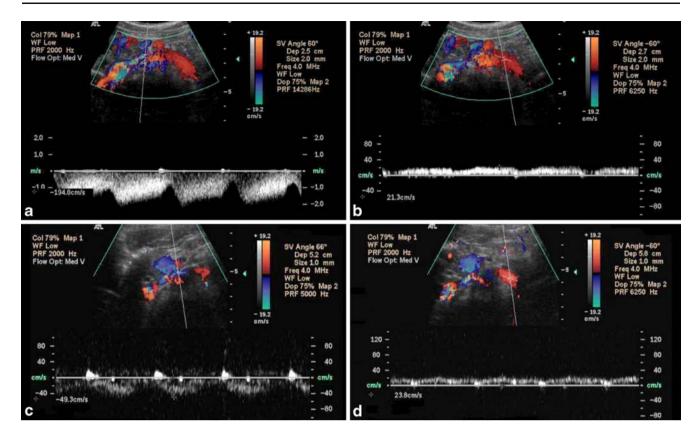


Fig. 1 Renal Doppler ultrasound of the left renal vein in a patient with nutcracker syndrome (a, b) and a normal child (c, d). (a) The peak velocity was 194.8 cm/s in the aortomesenteric entrapped

portion. (b) The peak velocity was 21.3 cm/s in the hilar portion (c). The peak velocity was 49.3 cm/s in the aortomesenteric portion. (d) The peak velocity was 23.8 cm/s in the hilar portion

normal children. On the basis of these data, we set the cutoff levels of the PV2/PV1 ratios for diagnosing nutcracker syndrome at the mean  $\pm 2$  SD of the value for the normal children. The calculated cut-off levels were 4.1. When these Doppler sonographic diagnostic criteria were applied, 72 cases (33.3%) in children with hematuria and no cases in normal children were diagnosed as having nutcracker syndrome. In the 72 children with nutcracker syndrome, the PV2/PV1 ratios were 6.82±2.51 (median 6.46, range 4.1–16.44) as compared with 2.57±0.74 (median 2.56, range 1.21–3.87) in normal children (P<0.0001) (Tables 1, 2). Collateral vessels around the LRV were observed in two

Table 1 Renal Doppler findings and anthropometric parameters (median values and ranges)

	Gross hematuria (n=40)	Microhematuria (n=176)	Total hematuria (n=216)	Control (n=32)	P-value
Doppler findings					
PV at AM portion (PV2, cm/s)	72.2 (23.9–207)	76.2 (30.1–288)	75.4 (23.9–288)	60.2 (20–133.7)	0.003
PV at hilar portion (PV1, cm/s)	22.6 (11.5–40.7)	24.1 (7.3–38.4)	23.8 (7.3–40.7)	23.9 (10.7–36.8)	NS
PV2/PV1 ratio	3.06 (1.18-10.34)	3.19 (1.2–16.44)	3.14 (1.18–16.44)	2.56 (1.21-3.87)	0.003
PV ratio >4.1*	9 (22.5%)	63 (35.8%)	72 (33%)	0 (0%)	< 0.0001
Anthropometric findings					
Height (cm)	132 (72–183)	134 (88–171)	133 (72–183)	133 (109–164)	NS
Weight (kg)	31.5 (13.5–71)	30 (12–74)	30 (12–74)	30 (18–56)	NS
BSA (m <sup>2</sup> )	1.09 (0.53-1.78)	1.06 (0.54–1.86)	1.06 (0.53–1.86)	1.05 (0.74–1.6)	NS
BMI (kg/m <sup>2</sup> )	17.24 (12.98–27.23)	16.88 (13.13–25.97)	17.05 (12.98–27.73)	17.09 (15.15–20.82)	NS

<sup>\*</sup>Data are number (%)

PV= peak velocity, AM= aortomesenteric, BSA= body surface area, BMI= body mass index, and NS= not significant (P>0.05) There were no differences between gross and microscopic hematuria



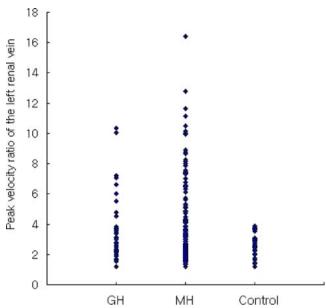


Fig. 2 The peak velocity ratios of the left renal vein in children with gross (GH) or microscopic hematuria (MH) and normal controls

patients with nutcracker syndrome. The body mass index was significantly lower in the nutcracker group than in the non-nutcracker group (P=0.006) (Table 2).

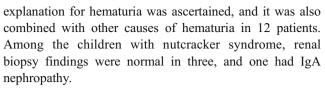
Clinical characteristics and diagnoses of 216 children with hematuria with or without nutcracker syndrome are listed in Table 3. The median age and gender did not differ between the two groups. The incidence of gross hematuria, abdominal or flank pain and a family history of urolithiasis were also similar in both groups. Nutcracker syndrome was present in 60 of the 149 children (40%) in whom no other

**Table 2** Renal Doppler findings and anthropometric parameters in 216 children with and without nutcracker syndrome

	Nutcracker group (PV ratio >4.1: n=72)	Non-nutcracker group (PV ratio <4.1: n=144)	P-value		
Doppler findings					
PV at AM portion, PV2	129 (69.8–288)*	63.9 (23.9–113)	<0.0001		
(cm/s) PV at hilar	20.1 (7.3–30.1)	26.3 (14.2–40.7)	< 0.0001		
portion, PV1 (cm/s)	20.1 (7.3–30.1)	20.3 (14.2–40.7)	<b>\0.0001</b>		
PV2/PV1 ratio	6.46 (4.1–16.44)	2.45 (1.18-4.0)	< 0.0001		
Anthropometric findings					
Height (cm)	137 (72–183)	132 (90–171)	0.031		
Weight (kg)	32 (12–67)	30 (13–74)	NS		
BSA (m <sup>2</sup> )	1.1 (0.53–1.78)	1.05 (0.58-1.86)	NS		
BMI (kg/m <sup>2</sup> )	16.12 (13.42–27.01)	17.24 (12.98–27.73)	0.006		

<sup>\*</sup>Median and ranges

PV= peak velocity, AM= aortomesenteric, BSA= body surface area, BMI= body mass index, and NS= not significant (P>0.05)



The results of the diagnostic studies are included in Table 4. Complete blood count, electrolytes, biochemistry, and the coagulation profile were normal in all patients. Positive antinuclear antibody was detected in 13 patients (1:40 weak positive), but repeat testing and anti-ds DNA showed no evidence of autoimmune diseases. Serum C3 concentrations were low (more than 10% below the lower limit of normal) in four patients. Hypercalciuria was found in 26 patients (12%). Ninety-five percent of the twodimensional ultrasonography and 97% of the excretory urography showed no abnormal findings. Of the 11 abnormal ultrasounds (2 increased echogenecity, 3 thickened bladder wall, 1 mild dilatation of the renal pelvis, and 5 urolithiasis) and 7 urographic examinations (2 duplications of the ureter, 1 aberrant small right upper calyx, and 4 bifid collecting systems), no finding was clinically significant. The detection rate of nutcracker syndrome by renal Doppler ultrasound was highest among all diagnostic tests for hematuria.

## **Discussion**

According to Stapleton et al. [14], the cause of isolated hematuria was defined in only 27% of their patients when routine diagnostic tests for hematuria were performed. However, they found that idiopathic hypercalciuria was the most common cause of hematuria with a prevalence of 26% in children with isolated hematuria by the routine evaluation of urinary calcium excretion. Nevertheless, the cause of hematuria in the remaining 47% of the patients could not be explained.

In the present study, we could not identify the cause of hematuria in 149 (69%) of the 216 patients when renal Doppler ultrasound was not performed, but 40 percent was found to have nutcracker syndrome by renal Doppler ultrasound. Thus, nutcracker syndrome was the most common cause of isolated hematuria in children without urinary tract infection or proteinuria in our study, and we speculate that childhood nutcracker syndrome might have been underestimated in the past.

Compression of the LRV between the aorta and the SMA by a mechanism similar to that of a nutcracker has been recognized by anatomists for about 70 years [6, 8]. However, the prevalence of this syndrome is unknown in both children and adults with hematuria. Even current textbooks of pediatrics rarely describe this syndrome [1, 5]. It is known that nutcracker syndrome is an uncommon cause



**Table 3** Clinical characteristics and diagnoses of 216 children with hematuria with and without nutcracker syndrome

	PV ratios of the LRV		
	Nutcracker group (PV ratio >4.1: n=72)	Non-nutcracker group (PV ratio <4.1: n=144)	
Clinical characteristics*			
Age (years)	9 (2–16)	9 (3–15)	
Sex (M/F)	37:35	76:68	
Gross hematuria**	9	31	
Abdominal or flank pain	11	17	
Familial history of urolithiasis	4	10	
Clinical diagnoses†			
IgA nephropathy	1 (1)	1 (1)	
Thin GBM disease		5 (5)	
Hereditary nephritis with deafness		2	
Proliferative glomerulonephritis		1 (1)	
Postinfectious glomerulonephritis		4	
Familial hematuria	3	20	
Cystitis		3	
Trauma		1	
Hypercalciuria	8	18	
Hematuria unexplained	60 (3)‡	89 (5)‡	

<sup>\*</sup>There were no differences between the two groups (\*\*P=0.107)

of gross or microscopic hematuria from non-glomerular origin and may cause orthostatic or variable degrees of proteinuria [4, 9, 12]. Hematuria is believed to be caused by LRV hypertension, which may result in minute rupture of thin-walled collateral veins into the calyceal fornix [9, 10].

Left renal venography with measurement of the pressure gradient between the inferior vena cava and LRV has been used to confirm nutcracker syndrome in selected cases [10]. However, this procedure is invasive, time-consuming, and therefore not indicated if there are no severe symptoms. In addition, there were no reliable and easily-applicable noninvasive diagnostic methods in diagnosing childhood nutcracker syndrome in the past. Consequently, it has been thought that screening nutcracker syndrome in all children with hematuria is unnecessary and irrational, and therefore, the prevalence of nutcracker syndrome has not been evaluated. Recently, however, the introduction of renal Doppler ultrasound with color flow has improved functional diagnostic capabilities by showing the blood flow velocity of the LRV [10-12]. Compression of the LRV between the aorta and the SMA may cause an increase in flow velocity in the LRV at the aortomesenteric angle, and this flow can be measured noninvasively by using Doppler ultrasound. Although anatomical definition of nutcracker syndrome is the compression between the aorta and the SMA, the changes (narrowing at the aortomesenteric portion and dilatation at the hilar portion) in diameters of LRV are variable according to the stage of nutcracker syndrome. This would be the reason that Doppler ultrasound had been developed to detect nutcracker syndrome in both adults and children.

Kim et al. [10] first developed and applied this Doppler technique to adults with nutcracker syndrome confirmed by venography, because the measurements of diameters of the LRV had not been satisfactory [3], and it had been suggested that dilatation in the proximal LRV shown at either 2-dimensional ultrasonography or computed tomography might be a normal variant in both children and adults [3, 18]. Takebayashi et al. also found that nutcracker syndrome can exist in either nondistended or distended LRV, and normal flow also can exist in distended LRV [15]. However, a combination of different parameters might improve the correlation with hematuria [10]. According to the Kim et al.'s study [10], Doppler sonographic findings were comparable to venographic findings, and the sensitivity and specificity of the PV2/PV1 ratios were higher than those of the ratio of LRV diameters (sensitivity 80% vs. 69%; specificity 94% vs. 89%) in adults with nutcracker syndrome. Park et al. [12] had also reported that the mean PV2/PV1 ratios in 26 normal children aged 6-16 years were 2.57±0.70 (range 1.3-3.9), which were similar to those (2.57±0.74, range 1.21-3.87) in our control subjects (4.8–14.5 years). Thus, the Doppler sonographic cut-off value for the PV2/PV1 ratios in our study (4.1) was similar to that of Park et al. [12] (4.0), but lower than that in adults

Table 4 Diagnostic studies

Diagnostic study	Normal result (no. of patients)	Abnormal result (no. of patients)	Positive rate (%)
Complete blood count	216	0	0
Electrolytes and	216	0	0
biochemistry			
Coagulation profile	216	0	0
C3	212	4	1.9
C4	214	2	0.9
Anti-streptococcal O titer	179	37	17
Antinuclear antibody	203	13	6
Hepatitis B surface antigen	215	1	0.5
Urine culture	216	0	0
Urinary calcium/creatinine	190	26	12
Renal/bladder ultrasonography	205	11	5
Excretory urography	209	7	3
Renal Doppler ultrasound	144	72	33



<sup>†</sup>Numbers in parenthesis indicate the number of diagnoses confirmed by renal biopsy

<sup>‡</sup>Results of renal biopsies were normal

[10] (5.0). Kim et al. [10] reported the PV at the hilar portion in hematuric adults with nutcracker syndrome was significantly lower than that in normal adults, suggesting compression of the LRV at the aortomesenteric portion could change the flow pattern in the hilar portion of the LRV. Similarly, our study also demonstrated that the PV at the hilar portion in the nutcracker group is significantly lower than that of the non-nutcracker group, suggesting the entrapment of the LRV might also influence the PV at the hilar portion.

We agree with the previous reports describing the necessity of limited evaluations in children with microscopic hematuria, because the extensive work-up resulted in a low rate of positive findings [7]. Nevertheless, our data suggest that the detection rate of nutcracker syndrome by renal Doppler ultrasound was highest among many other diagnostic tests. Regarding treatment of nutcracker syndrome, surgery should be considered if the patients have severe symptoms [2], but it has been suggested that childhood nutcracker syndrome might be a transient phenomenon resolving spontaneously with time by physical development [13, 16]. Therefore, renal biopsy should be delayed in children with asymptomatic microscopic hematuria if nutcracker syndrome is detected. However, if hematuria persists despite the improvement of Doppler findings, renal biopsy might be necessary to detect other causes of hematuria.

However, our study has some limitations: (1) We did not perform left renal venography because most of our patients had mild renal symptoms, such as asymptomatic microscopic hematuria, detected through mass urinary screening. It was felt to be unethical to perform such an invasive procedure in these patients. (2) Renal Doppler ultrasound was performed by one pediatric radiologist, and we could not show inter-observer reproducibility. (3) We did not perform the urinary RBC morphology as a routine examination. However, a current textbook of pediatrics [5] describes: "Although urinary RBC morphology may be normal with non-glomerular bleeding and dysmorphic from glomerular bleeding, cell morphology does not reliably correlate with the site of hematuria." Kim et al. demonstrated the percentage of isomorphic RBC was considerably variable (range 2-90%) in patients with nutcracker syndrome confirmed by venography [10]. Despite these limitations, our data suggested that nutcracker syndrome might be one of the leading causes of isolated hematuria during childhood.

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