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Diagnosis And Treatment in Children With Nutcracker Syndrome: A Single-Center Experience

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ABSTRACT

Objective: It has been aimed to report the experience of our center regarding diagnosis and treatment experience in children with Nutcracker syndrome (NCS).

Materials and Methods: The medical records of seven patients who have admitted to the Department of Pediatric Nephrology of our hospital between February 2017 and March 2020 were evaluated retrospectively. The diagnosis of NCS was confirmed with renal Doppler ultrasound (RDUS) and magnetic resonance angiography (MRA) in these patients who have admitted with the complaints of hematuria and proteinuria. The patients' data such as clinical characteristics, radiological findings, radiological signs and information about medical treatment at baseline and last control were recorded.

Results: The mean levels of 24-h urine protein excretion in all patients at baseline and last control were 15,25±9,19 mg/m2/h and 9,8±3,94 mg/m2/h, respectively. The mean levels of 24-h urine protein excretion in patients treated with ACE (angiotensin converting enzyme) inhibitors at baseline and last control were 20±11,53 mg/m2/h and 9,6±6,44 mg/m2/h, respectively. (p=0,073). The mean levels of 24-h urine protein excretion were 11.7±6.39 mg/m2/h and 9.95±1.84 mg/m2/h in patients not receiving ACE inhibitor treatment, at baseline and the last control respectively (p= 0,61). The mean angle value of the left renal vein in the aortomesenteric distance measured by RDUS examination performed in the upright position was 14,71±4,46 degrees. The anteroposterior diameter of the left renal vein (hilar/aortomesenteric) measured in the upright position was 6,4.

Conclusion: The benign nature of NCS in young patients requires maintaining conservative approach.

Keywords: Nutcracker syndrome, orthostatic proteinuria, renal vein

Nutcracker Sendromlu Çocuklarda Tanı ve Tedavi: Tek Merkez Deneyimi

ÖZET

Amaç: Merkezimizin Nutcracker sendromlu (NCS) çocuklardaki tanı ve tedavi deneyiminin paylaşılması istenmiştir.

Gereç ve Yöntemler: Hastanemizin çocuk nefroloji bölümüne Şubat 2017 ile Mart 2020 tarihleri arasında başvuran yedi hastanın medikal kayıtları geriye dönük olarak değerlendirildi. Hematüri ve proteinüri yakınmalarıyla başvuran bu hastalarda NCS tanısı renal doppler ultrasonografi (RDUS) ve MR anjiografi (MRA) ile doğrulandı. Hastaların başvuru ve son kontroldeki klinik özellikleri, radyolojik bulguları, laboratuvar tetkikleri ve medikal tedavileri değerlendirildi.

Bulgular: Hastaların başlangıç ve son kontrolde 24 saatlik idrarda protein atılımı sırasıyla ortalama 15,25±9,19 mg/m2/saat ve 9,8±3,94 mg/m2/saat idi. Anjiotensin dönüştürücü enzim inhibitörü (ACE inhibitörü) kullanılan hastalarda başlangıç ve son kontrolde, 24 saatlik idrarda protein atılımı sırasıyla ortalama 20±11,53 mg/m2/saat ve 9,6±6,44 mg/m2/saat bulundu (p=0,073). Anjiotensin dönüştürücü enzim inhibitörü kullanmayan hastalarda başlangıç ve son kontrolde 24 saatlik idrarda protein atılımı sırasıyla ortalama 11,7±6,39 mg/m2/saat ve 9,95±1,84 mg/m2/saat saptandı (p= 0,61). Ayakta yapılan RDUS incelemede sol renin aortomesenterik mesafede açı ortalaması 14,71 ± 4,46 derece idi. Ayakta ölçülen sol renal ven antero-posterior çap oranı (hiler/Aortomesenteric) ortalama 6,4 bulundu.

Görüş: Genç hastalarda NCS'nun selim seyirli olması tedavide konservatif kalınmayı gerektirir.

Anahtar kelimeler: Nutcracker Sendromu, ortostatik proteinüri, renal ven

Nutcracker Syndrome (NCS) is a clinical picture that emerges due to compression of the left renal vein accompanied with clinical, laboratory and radiological findings. Its most frequent type is termed as "anterior NCS" resulting from the compression of the left renal vein between the aorta and the superior mesenteric artery and its frequency has been reported as 0.8-7.1% (1,2). Less frequently, "posterior type NCS" is observed as a result of the compression between the aorta and the vertebral corpus in the retroaortic field. Pressure on the left renal vein leads to the obstruction of blood flow and increased intrarenal venous pressure (1,2). On the other side, Nutcracker phenomenon, differently from the syndrome, refers to the presence of radiological findings due to the compression of the left renal vein without accompanying clinical and laboratory symptoms and findings (3-5).

The clinical and laboratory findings of Nutcracker Syndrome may present a wide variety. Its common symptoms are microscopic or macroscopic hematuria, orthostatic proteinuria and flank pain. It may be also presented as varicocele, dysmenorrhea, fatigue and orthostatic intolerance in some patients. However, it courses asymptomatically in most patients, particularly in children (6).

Orthostatic proteinuria is defined as the non-detection of protein in the collected urine in the supine position whereas the presence of proteinuria in the collected urine in the upright position.

The diagnosis is established by the clinical findings supported by the specific changes for NCS encountered by the imaging techniques. Nutcracker Syndrome can be diagnosed with various imaging techniques such as renal Doppler ultrasonography (RDUS), MR angiography (MRA) and catheter angiography (7). Although, catheter angiography provides more definite results in the diagnosis of NCS, it is preferred only in the cases in whom diagnostic problems are experienced due to its invasive character. Renal Doppler ultrasonography is preferred for non-invasive nature, non-exposure to radiation and easy applicability. However, operator-dependency and the difficulty of viewing the retroperitoneal area are the disadvantages of this technique (8). The non-invasive and three-dimensional morphological imaging has become possible with the progressively improving cross-sectional imaging techniques (CTA and MRA).

The treatment of Nutcracker Syndrome is controversial except in cases with severe symptoms. Angiotensin converting enzyme inhibitors (ACE inhibitor) may be a treatment option to reduce proteinuria in the patients with orthostatic proteinuria (9,10). In addition, surgical correction may be rarely needed in severe cases (4).

In the present study, we aimed to retrospectively evaluate the clinical, laboratory and imaging findings of the pediatric patients who admitted to the Department of Pediatric Nephrology of our hospital and diagnosed with NCS between 2017 and 2020.

Material and Methods

Totally seven patients who admitted to the Department of Pediatric Nephrology due to proteinuria and/or hematuria and diagnosed with NCS between February 2017 and March 2020 were included in the study. The diagnosis was confirmed with imaging techniques (RDUS and MRA) as well as clinical and laboratory findings. The baseline clinical characteristics, physical examination and radiological findings of the patients at admission, the presence of hematuria at the time of diagnosis and the last control, protein excretion and the use of ACE (angiotensin converting enzyme) inhibitors were recorded. The presence of greater than 5 red cells per mm³ in centrifuged urine was defined as hematuria while detection of protein higher than 4 mg/m²/hour in 24-hour urine collection sample was accepted as proteinuria. The diagnosis of orthostatic proteinuria was established based on absence of protein in the first urine in the morning despite detection of proteinuria in 24-hour urine collection. The study included the patients with blood pressure below 90th percentile. Serum BUN, creatinine, complement levels and urinalysis were tested in all the patients.

Renal doppler ultrasonography examinations were performed by the same pediatric radiologist with convex probe (3.5 MHz frequency) using Acuson S3000 USG device (Siemens, Erlangen, Germany) in the supine position. Antero-posterior (AP) diameter of the left renal vein was measured in the hilar and aortomesenteric segments by RDUS examinations performed in the supine and upright positions.

The hilar and aortomesenteric AP diameter ratios were calculated in the upright position. In addition, the aortomesenteric angles were measured in the supin and upright positions.

MRA was performed in all patients to evaluate the morphology more accurately and to reduce operator-dependent

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diagnostic failure. MRA imagings were performed using Optima MR450w 1.5 Tesla device (General Electric, Milwaukee, USA) in the supine position. The antero-posterior diameter of the left renal vein in the hilar and aortomesenteric segments was measured and the ratio between these measurements was calculated in the axial MR images obtained after intravenous administration of contrast agent. The aortomesenteric angles were measured in the postcontrast sagittal images (Figure 1).

i)The aortomesenteric angle less than 39 degrees in the RDUS and MRA in the supine position and/ or ii)detection of a lower value of this angle in RDUS examination in the upright position compared with that measured in the supine position and/or iii) the antero-posterior diameter ratio of the left renal vein (hilar/aortomesenteric) greater than 4.9 in RDUS examination in the upright position were accepted as the diagnostic criteria.

The Ethics Committee Approval by the protocol code 09.2020.466 and informed consent forms from the parents of the patients were obtained for this study.

Statistical Analysis

All data was analyzed using Statistical Software Package for The Social Sciences (SPSS Inc., Chicago, Illinois, USA) Version 21.0. The distribution homogeneity of the data was evaluated by Kolmogorov-Smirnov test. The normally distributed data was expressed as mean±standard deviation. Paired test was used for comparison between the initial and final values. A p value less than 0.05 was accepted as statistically significant.

Results

Of the seven pediatric patients diagnosed with NCS; 2 (28%) were female and 5 (72%) were male. Mean age of the patients was 11,7±2,95 years while mean follow-up duration was 34±6,7 months (Table 1). RDUS and MRA were performed as diagnostic tests in all the patients with suspected Nutcracker Syndrome. The demographic, clinical and laboratory characteristics of the patients were shown in Table 1. The admission complaint was abdominal pain in one patient while all other patients admitted due to coincidentally detected proteinuria and/or microscopic hematuria (Table 1). The mean levels of 24-h urine protein excretion in all patients at baseline and last control were 15,25±9,19 mg/m²/h and 9,8±3,94 mg/m²/h, respectively. ACE inhibitor was used in three patients during follow-up period. The mean levels of 24-h urine protein excretion in the patients treated with ACE inhibitors at baseline and last control were 20±11,53 mg/m²/h and 9,6±6,44 mg/m²/h, respectively. (p=0,073). The mean levels of 24-h urine protein excretion were 11,7±6,39 mg/m²/h and 9,95±1,84 mg/m²/h in the patients not receiving ACE inhibitor treatment, respectively (p= 0,61). Kidney function test results were within normal limits in all patients.

The left RDUS and MRA findings of the patients were presented in Table 2. The mean left renal vein diameters at the level of renal hilus and in the aortomesenteric segment were 8.78±2.62 mm and 1.37±0.40 mm, respectively. These values were 6,85±1,59 mm and 1,81±0,52 mm in the supine position, respectively. The mean left renal vein diameters at the level of renal hilus and in the aortomesenteric segment were found 7,94±1,53 mm and 1,91±0,50 mm in the MR angiography, respectively.
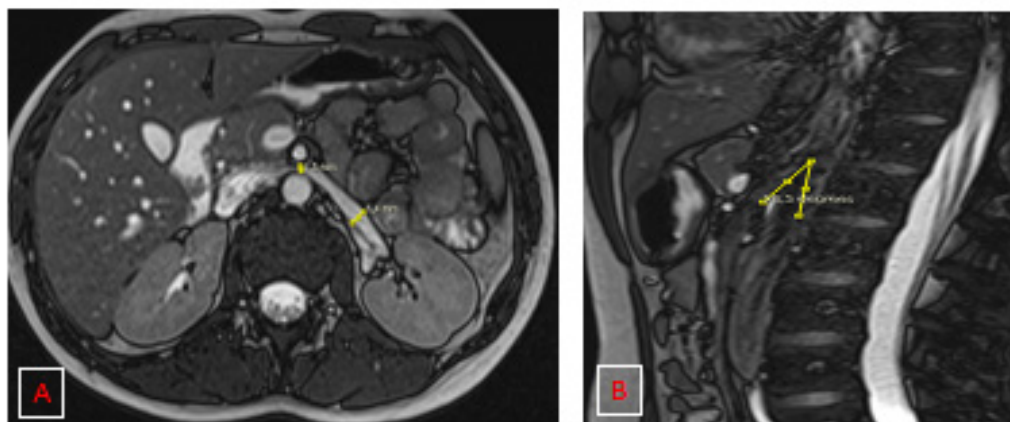

Figure 1: A) Anteroposterior diameter measurements of the left renal vein in the aortomesenteric and hilar regions in the MR angiography, B) Anteroposterior diameter measurement in the MR angiography

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Table 1. The demographic, clinical and laboratory characteristics of the patients	
Age (years) mean ±SD	11,7±2,95
Follow-up duration (months) mean ±SD	34±6,7
Gender n(%)	
Female	2 (28)
Male	5 (72)
Clinical (n)	
Microscopic hematuria+proteinuria	(2)
Microscopic hematuria	(1)
Macroscopic hematuria	(1)
Abdominal pain+proteinuria	(1)
Proteinuria	(2)
Protein in the baseline 24-hour urine sample (mg/m2/h) mean ±SD	15,25 ±9,19
Protein in the 24-hour urine sample in the last visit (mg/m2/h) mean ±SD	9,8 ±3,94
Use of ACE inhibitor n (%)	3 (42)
Protein in the baseline 24-hour urine sample in the patients treated with ACE inhibitor (mg/m2/h) mean ±SD	20±11,53
Protein in the 24-hour urine sample in the patients treated with ACE inhibitor in the last visit (mg/m2/h) mean ±SD	9,6 ±6,44
Complement factor 3 Normal n (%)	7 (100)
Complement factor 4 Normal n (%)	7 (100)

Table 2. Renal Doppler ultrasound and MR Angiography findings of the patients		
	Renal Doppler Ultrasonography mean ±SD	MR angiography mean ±SD
Upright		
Aortomesenteric angle (degrees)	14,71 ± 4,46	
Left renal vein diameter in the aortomesenteric segment (mm)	1,37 ± 0,40	
Left renal vein diameter at the level of renal hilus (mm)	8,78 ± 2,62	
Supine		
Aortomesenteric angle (degrees)	22,14 ± 7,98	22,08 ± 3,27
Left renal vein diameter in the aortomesenteric segment (mm)	1,81 ±0,52	1,91 ± 0,50
Left renal vein diameter at the level of renal hilus (mm)	6,85 ± 1,59	7,94 ± 1,53

Mean aortomesenteric angle values measured by RDUS and MR angiography in the supine position were detected to be 22,14±7,98 and 22,08±3,27 degrees, respectively. RDUS examination performed in the upright position revealed a mean aortomesenteric angle value of 14,71±4,46 degrees. The mean value of left renal vein anteroposterior diameter ratio (hilar/aortomesenteric) measured in the upright position was 6.4.

Discussion

Anterior NCS and more rarely posterior NCS have been an interesting subject with wide variety of their symptoms and their confusability with many other renal diseases (11,12). The other etiological factors of Nutcracker Syndrome include renal ptosis, high osteal location of the left renal vein or narrow-angle exit of the superior mesenteric artery from the aorta, pancreatic masses and lymphadenomegalies. Nutcracker Syndrome may emerge in any age and shows no difference between genders (13). In our study, mean age at diagnosis was found 11,7 years and males were majority. The most commonly reported symptoms for Nutcracker Syndrome are pelvic pain, hematuria and varicocele (3). Orthostatic proteinuria may occur as a result of increased pressure in the left renal vein and the changes in the release of angiotensin II and norepinephrine caused by impaired renal hemodynamics (14-17). It has been also reported that the obstruction of the renal venous circulation causes formation of varicose veins around the renal pelvis and ureter and that the small ruptures and bleedings in these veins are the reasons of particularly hematuria and proteinuria triggered by exercise (18,19). The most common reason for hospital admission among our patients was coincidentally detected proteinuria. This complaint was followed by microscopic hematuria. Macroscopic hematuria was the cause for admission in only one patient.

According to Kim et al.(9); an angle of <39 degrees between SMA and abdominal aorta in the sagittal plane by CT is 92% sensitive and 89% specific for diagnosis of NCS . This angle normally ranges between 45-90 degrees. However, Ananthan et al. (3) have defined a left renal vein diameter ratio (hilar/aortomesenteric) greater than 4.9 in the CT or MR images and classical "bird's beak" view as the most specific findings for NCS. In our study, the aortomesenteric angle less than 39 degrees in the RDUS and MRA in the supine position and/ or detection of a lower value of this angle in RDUS examination in the upright position compared with that measured in the supine position and/or the antero-posterior diameter ratio of the left renal vein (hilar/aortomesenteric) greater than 4.9 in RDUS examination in the upright position were accepted as the diagnostic criteria. We found the aortomesenteric angle values less than 39 degrees in the RDUS and MRA in the supine

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position in all of our patients and mean aortomesenteric angle values measured by RDUS and MR angiography in the supine position were 22,14±7,98 and 22,08±3,27 degrees, respectively. In all of our patients, we found a lower value of the aortomesenteric angle in RDUS examination performed in the upright position compared with that measured in the supine position. In addition, the anteroposterior diameter ratios of the left renal vein (hilar/aortomesenteric) were greater than 4.9 in RDUS examination in the upright position in all of our patients . The mean value of left renal vein anteroposterior diameter ratio (hilar/aortomesenteric) measured in the upright position was 6.4.

There are only a limited number of studies that investigated the clinical course of NCS in children. Tanaka et al. demonstrated that spontaneous remission developed after a 7-year follow-up period in an adolescent patient diagnosed with NCS who had persistent microscopic hematuria (20). None of our patients developed remission in the existing microscopic hematuria. Proteinuria was orthostatic in all of our patients and none of those were at the level of nephrotic range. Orthostatic proteinuria is one of the common causes of asymptomatic proteinuria in the adolescent age group and accepted as a benign condition. The development of spontaneous remission parallelly with continuing growth and weight gain has been reported in many studies (2,14). The possible results of orthostatic proteinuria accompanied with Nutcracker syndrome are not different from the known nephrotoxic effects of proteinuria. However, KDIGO has accepted albuminuria as an indicator of the progression of chronic renal failure in 2012 (21). The use of ACE inhibitor is a treatment option to reduce persistent proteinuria in patients and we initiated the treatment of ACE inhibitor in our patients with protein excretion over 20 mg/m2/h in 24-hour urine sample. As expected the level of baseline proteinuria was higher in our patients initiated with ACE inhibitor treatment. The reduction in the level of proteinuria was remarkable, although statistically not significant, in our patients who used ACE inhibitor (p=0,073). Increased proteinuria was encountered in none of the patients at the end of approximately 3-year follow-up period. The small number of the patients was the limitation of our study. The microscopic examination of urine sediment was performed in all of the patients who admitted due to the complaint of macroscopic or microscopic hematuria and morphic erythrocyte morphology was detected in our patients except one patient. Kidney biopsy was performed in our patient with dysmorphic type of erythrocyte morphology and C3 glomerulopathy was detected in kidney pathology besides the RDUS and MRA findings consistent with NCS. With this example, we aimed to emphasize the importance of microscopic examination of urine sediment in the differential diagnosis of other causes of hematuria.

Conclusion

Nutcracker syndrome should be investigated in the presence of orthostatic proteinuria and/or persistent microscopic/macroscopic hematuria. The benign nature of NCS in young patients requires maintaining conservative approach. The differential diagnosis of other diseases that cause proteinuria and/or hematuria should be made carefully.

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