Original article

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NUTCRACKER SYNDROME IN CHILDREN: A SINGLE CENTRE EXPERIENCE

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Nutcracker syndrome (NS) is a rare cause of hematuria and/or proteinuria defined as the left renal vein entrapment between the abdominal aorta and the superior mesenteric artery. The majority of patients, mostly females, are diagnosed in puberty age. We report eight children diagnosed with NS analyzing their clinical features, diagnostics approaches, disease evolution and treatment outcomes.

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Key words: *nutcracker syndrome, hematuria, orthostatic proteinuria, left renal vein entrapment*

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Introduction

Nutcracker syndrome (NS) is a rare clinical condition where the renal vein is compressed between the abdominal aorta and the superior mesenteric artery (anterior type) (Figure 1 and Figure 2), or between the aorta and the vertebral column (posterior type) causing various symptoms in the patient. The existence of this state without expressing any symptoms is referred to as nutcracker phenomenon (1). The prevalence is not well known because this conditionis very frequently misdiagnosed. It is believed that NS is more frequently spread among young female population with a thin constitution. The prevalence of posterior NCS, also called pseudo-nutcracker syndrome, is much lower than the anterior one, ranging between 0.1% and 3.2% (2).

Most frequently patients experience one of the following symptoms or a combination of these symptoms: hematuria, proteinuria, left flank pain, chronic fatigue. The anatomical position of the left renal vein is going through the spine angle formed by the abdominal aorta and the superior mesenteric artery. If the angle is less than 45 degrees, as it is the case in thin, tall, young girls lacking fat tissue, then the left renal vein is entrapped within it causing proximal part of the vein dilatation following increased vein pressure (3). This condition is followed up by the interruption of the small vessels in the renal fornix causing hematuria, more likely microscopic than macroscopic. Renal vein congestion causes kidney swelling and stretching of the renal capsule, so some patients complain of left flank pain. The exact mechanism of proteinuria is unclear, but it is believed that vein obstruction changes renal hemodynamics. Renal venous stasis and venous hypertension decrease renal blood flow, which causes angiotensin II activation. Renin and aldosterone levels rise, resulting in an increase in efferent arteriolar resistance, which stimulates protein filtration (4).

As there are not precise diagnostic criteria for NS, before determining a diagnosis, it is necessary to exclude all other causes of hematuria or proteinuria (3). Radiology examinations must be performed to confirm the NS diagnosis. First choice should be renal Doppler ultrasound (5) as a non-invasive technique with sensitivity of 69 – 90% and specificity of 89 – 100% (6) after which a diagnostic approach could be completed with computed tomography (CT) and magnetic resonance imaging (MRI) (3, 1, 7).

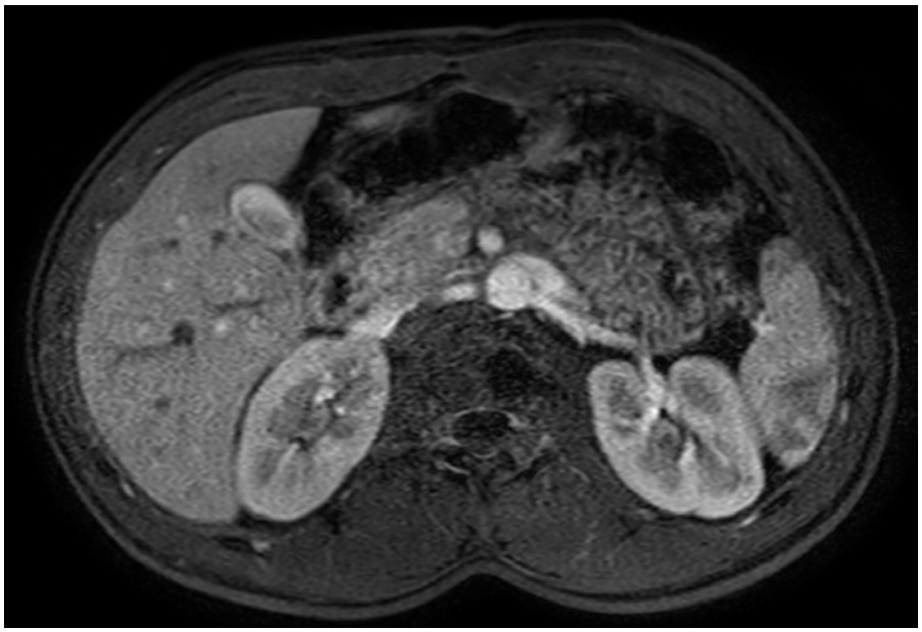

Figure 1. MRI angiography: proximal dilatation of the left renal vein, entrapped between the aorta and the superior mesenteric artery (transversal scan)

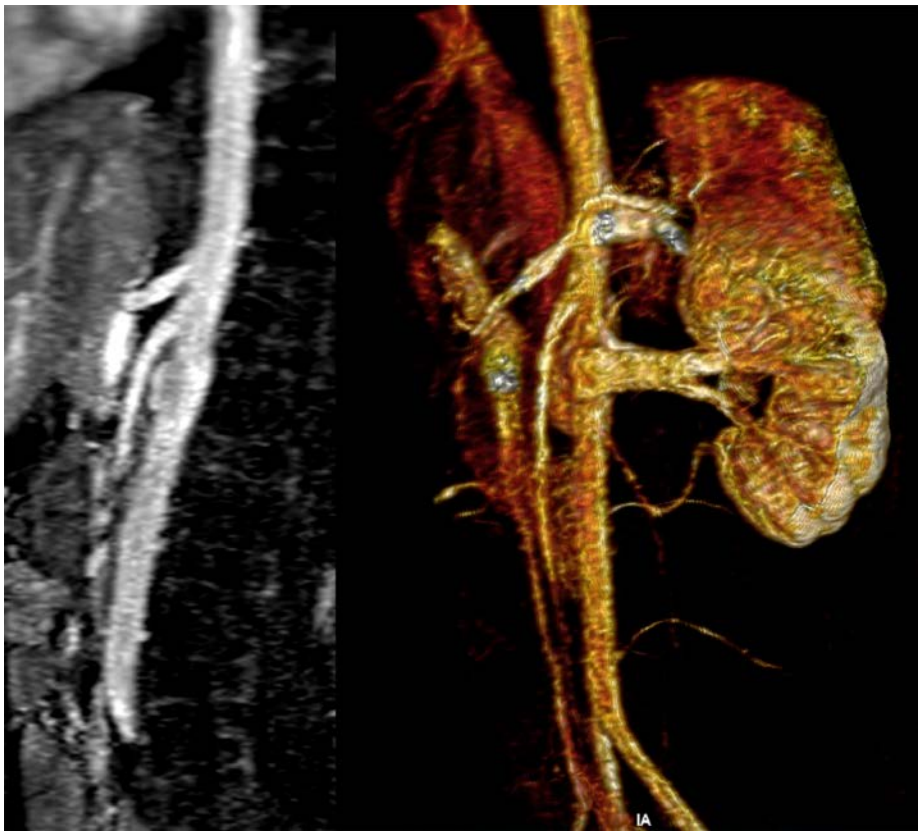

Figure 2. MRI angiography: proximal dilatation of the left renal vein, entrapped between the aorta and the superior mesenteric artery (axial scan)

The treatment of patients depends on severity of complaints and clinical features and can range from conservative methods to surgical approaches including balloon dilatation, LRV bypass, LRV transposition with or without wedge insertion between aorta and superior mesenteric artery, superior mesenteric artery transposition and, in the worst case, nephrectomy (1).

Material and Methods

We retrospectively reviewed eight adolescents, six females and two males, who were diagnosed with NS on MRI at the University Clinic Center Niš from January 2015 to December 2022. Their ages ranged from 13 to 17 years. All patients underwent physical examination, blood and urine analysis and radiologic examination (abdominal ultrasound, renal Doppler ultrasound and MRI angiography).

Results

Our study included eight patients who were diagnosed with NS at the Clinic of Pediatrics, University Clinical Centre Niš. Two of them were male (25%) and six (75%) were female. Their mean age was 14.87 years at diagnosis. Average body mass index was 19.8 kg/m^2. All patients were followed up for at least 15 months up to three years.

Clinical features of patients at diagnosis were analyzed (Table 1). Six (75%) patients showed isolated proteinuria with characteristics of orthostatic type and not nephrotic range. Five (83%) of them had daily proteinuria less than 500 mg, in one (17%) girl, the maximum value of proteinuria was 900 mg. Out of these six patients, three (50%) complained of occasional left flank pain, especially after excessive physical effort and they showed positive left renal succession. It is interesting that all patients presenting with isolated proteinuria were female.

Two patients had persistent microscopic hematuria with no episodes of macroscopic hematuria. They had no other symptoms and hematuria was revealed after routine urine sampling. Both patients were male.

Physical examination was normal in all patients, except for positive left renal succession in three girls with occasional left flank pain.

All patients underwent complete laboratory examination. Blood urea nitrogen, creatinine, electrolytes (sodium, potassium, calcium, phosphorus and magnesium), total protein, albumin, transaminases, C-reactive protein and vitamin D levels were within normal range. Calcium excretion and coagulation parameters were normal. Immunoglobulin A, M and G, antistreptolysin titer antibody, complement components C3 and C4 results were within referent range; antinuclear antibodies, anti-double stranded DNA antibodies and antineutrophil cytoplasmic antibodies results were negative.

Renal and urinary bladder ultrasonography revealed no pathological findings.

At the end, MRI was performed in all patients. MRI scan showed left renal vein narrowing in aortomesenteric clamp with diameter ratio before and after entrapment greater than 4.9 and angle between the abdominal aorta and the superior mesenteric artery was less than 30 degrees. Therefore, the NS diagnosis was confirmed with MRIafter ruling out other renal factors that may cause proteinuria and/or hematuria.

Table 1. Clinical characteristic of patients´

	Genderf-female m-male	Age (years)	BMI (kg/m^2)	Symptom	Clinical findings	24-hour urine protein excretion (mg)	Treatment	Disease evolution
1	f	14	19.0	none	proteinuria	440	conservative	no progression
2	f	15	19.4	left flank pain	proteinuria	500	conservative	no progression
3	f	17	20.9	none	proteinuria	850	conservative	improvement after weight gain
4	f	16	21.4	left flank pain	proteinuria	450	conservative	no progression
5	f	13	18.5	none	proteinuria	280	conservative	nephrotic syndrome
6	f	15	19.7	none	proteinuria	350	conservative	focal segmental glomerulosclerosis
7	m	15	18.7	none	microscopic hematuria	normal	conservative	no progression
8	m	14	21.1	none	microscopic hematuria	normal	conservative	no progression

The treatment of all patients was conservative. No medication was administrated after diagnosis. The follow-ups were done every three months and six of them showed no progression in clinical and laboratory findings. Two boys maintained microscopic hematuria with no other complications. Four girls showed no increase in proteinuria above 1 g daily during the following-up of two years. Two girls showed renal disease progression. One girl developed complete nephrotic syndrome shortly after being diagnosed with NS. The other girl showed up after 15 months with peripheral edema, hypertension, 2 g proteinuria daily and glomerular filtration rate of 78 ml/m^2/min; she underwent a renal biopsy, which confirmed focal segmental glomerulosclerosis. In both girls the treatment was started with corticosteroids, as they were diagnosed with glomerulopathy. The other six children were observed every three months without any medication and there was no disease progression in any of the cases.

Discussion

Nutcracker syndrome is a clinical phenomenon which occurs when the left renal vein is entrapped between the abdominal aorta and the superior mesenteric artery (anterior type), as well as between the aorta and the lumbarvertebral body (posterior type, pseudo-nutcracker syndrome) causing various symptoms, dominantly haematuria and/or proteinuria. The first type is much more frequent than the second one (8).

The exact prevalence of this state is unknown because of the lack of precise diagnostic criteria. It is believed that NS is more often diagnosed in female than in male, like in our study (75% of female versus 25% of male patients), although in some groups of patients the opposite proportion is described(9).

NS is diagnosed between the second and the seventh decade of life with the highest incidence in adolescents and young adults. This distribution is probably the consequence of rapid increase in body height in adolescence resulting in anatomical changes such as decreasing the angle between the abdominal aorta and the superior mesenteric artery. This is why thin, tall persons with low body mass index are more often diagnosed with NS (7). Some data suggest a positive correlation between low body mass index and NS (1). It is consistent with our result, where average BMI is below 20 kg/m^2.

The usual clinical features are hematuria, more likely microscopic, orthostatic proteinuria and left flank pain. Left renal entrapment leads to venous stasis and renal venous hypertension, which causes the rupture of the small veins into the renal calices. Macrohematuria is usually intermittent and mostly physical effort induced (9). In our group of patients, there were no evidence of macroscopic hematuria. Two patients (25%) had persistent microscopic hematuria following no complains and it was confirmed with a routine urine test.

Proteinuria presents mostly as orthostatic type and it is diagnosed witharoutine urine test. The exact mechanism of proteinuria is unclear, but it is believed that vein obstruction changes renal hemodynamics. Renal venous stasis and venous hypertension decrease renal blood flow, which causes the activation of angiotensin II. Renin and aldosterone levels rise resulting in an increase in the efferent arteriole resistance, which stimulates protein filtration (4). In our group of patients, isolated proteinuria was present in four (50%) patients, three (75%) of the mhad proteinuria less than 500 mg/24 h, in one girl (25%) it was 900 mg/24 h. Two patients had periodical left flank pain, most often exercise induced, two other patients had no complains. According to review studies data, proteinuria is present in non-nephrotic range, mostly below 1 g daily (5, 9).

In our study, two patients developed glomerulopathies during the follow-up period after being diagnosed with NS. A 13-year-old girl developed the nephrotic syndrome after three months, she was treated with corticosteroids and proteinuria resolved. A 15-year-old girl initially presented with asymptomatic mild proteinuria. Two years after being diagnosed, she developed hypertension and peripheral edema following 24-hour 2 g proteinuria and renal function impairment. However, she never came for a check-up since she did not experience any symptoms. She underwent renal biopsy and focal segmental glomerulosclerosis was proven.

In the literature, there are some reports of superimposed NS with other clinical entities, such as Henoch-Schonlein purpura, IgA nephropathy, membranous nephropathy, hypercalciuria and nephrolitiasis (3). Hirakawa et al. report a 21-year-old woman with coexisting NS and thin basement membrane disease clinically presenting with macrohematuria, proteinuria and left flank pain (10). Medin et al. described a 22-year-old man with IgA nephropathy and previous diagnosed NS in whom all symptoms disappeared and laboratory findings improved after steroid treatment (11). Some studies revealed high prevalence of NS in IgA nephropathies (6.8%), which suggests possible relationship between these two entities, but there have not been found hard evidence yet (12). Although hypertension is not a typical clinical feature of NS, several cases are described. Azhar et al. report a case of an 18-year-old Asian girl who presented with hypertension, hematuria and left flank pain and was diagnosed with NS after ruling out secondary causes of hypertension (13). But the connection between NS and hypertension is more likely in case described by Wang et al. where after the placement of endovascular stent in the left renal vein, blood pressure normalized within three days after surgical intervention (14). Superior mesenteric syndrome, also known as Wilkie's syndrome is a rare benign clinical entity emerging when the transverse part of the duodenum is compressed between aorta and superior

mesenteric artery causing duodenal stasis and gastrointestinal symptoms and it sometimes co-exists with NS (15, 16). So far, there has been no evidence about association of NS and focal segmental glomerulosclerosis in the available literature.

Diagnostic approach of NS must be based on the exclusion of all common causes of proteinuria, hematuria and left flank pain. To confirm the diagnosis, Doppler ultrasound should be performed as a first line radiology imaging method, eventually CT or MRI angiography. In our study, the diagnosis remained unclear after Doppler ultrasonography, so all patients underwent MRI angiography.

Treatment is recommended to be conservative if the clinical features are mild. The best treatment option for children is to follow-up them for at least two years as majority of them spontaneously recover. Some of patients with moderate proteinuria could be treated with ACE-inhibitors (1). In our group of patients, all patients were treated conservatively after diagnosis. Two girls, in whom disease got complicated by glomerulonephritis, were afterwards treated with steroids. The other six patients did not show disease progression. One girl experienced a decrease in moderate proteinuria after gaining weight. Pardinhas et al. reported seven patients diagnosed at adolescent age, all of them were treated conservatively with no medication and no recurrent symptoms reported during follow up (9). If clinical features of NS such as recurrent gross hematuria or severe abdominal pain are not tolerable, surgical treatment should be considered. The most successful surgical approaches include balloon dilatation, LRV bypass, renocaval reimplantation, LRV transposition with or without wedge insertion between aorta and superior mesenteric artery and superior mesenteric artery transposition (3). In the Serbian medical literature, Banzić et al. reported the first case of the NS presented with gross hematuria, which was resolved by reimplantation of the LRV into the more distal inferior vena cava (17).

Conclusion

Nutcracker syndrome is a rare entity accompanied by hematuria, proteinuria and other nonspecific symptoms. Its prevalence and prognosis, as well as possible complications are not well known because the NS is often misdiagnosed. As it most commonly occurs during puberty, pediatricians should consider NS as a possible cause of unexplained persistent or recurrent hematuria and orthostatic proteinuria.

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NUTCRACKER SINDROM KOD DECE – ISKUSTVO JEDNOG CENTRA

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Nutcracker sindrom (engl. *nutcracker syndrome* – NS) predstavlja redak uzrok hematurije i/ili proteinurije, a definisan je kao uklještenje leve bubrežne vene između abdominalne aorte i gornje mezenterične arterije. Kod većine bolesnika dijagnostikuje se u pubertetu, i to uglavnom kod žena. U radu se izveštava o osmoro dece sa dijagnozom NS-a. Analizirane su njihove kliničke karakteristike, kao i dijagnostički pristupi, ishodi lečenja i evolucija bolesti.

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***Ključne reči**: sindrom orašara, hematurija, ortostatska proteinurija, uklještenje leve bubrežne vene*