

Nutcracker syndrome in childhood

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ABSTRACT

Nutcracker phenomenon (NP) is defined as the compression of the left renal vein, often occurring between the aorta and the superior mesenteric artery (SMA). Patients with symptoms associated with the Nutcracker anatomy are called “Nutcracker syndrome” (NCS). Renal vein compression results in venous congestion, outlet obstruction, and increased pressure in the left renal vein. The clinical manifestations of NCS in children vary widely depending on the severity of compression. It can range from being asymptomatic to presenting with intermittent or persistent micro or macrohematuria, orthostatic proteinuria, renovascular hypertension, abdominal pain, left-sided flank pain, dysmenorrhea, pain in the testicles or scrotum, and left varicocele. Hematuria, proteinuria, and flank pain are prevalent symptoms. The anatomical and physiological degree of compression of the left renal vein can be diagnosed through Doppler ultrasound (DUS), computer tomography (CT) scan, or magnetic resonance imaging (MRI). In cases with mild symptoms, conservative treatment is an appropriate option, and ACE inhibitors can be used for patients with proteinuria. In more severe cases where conservative approaches and medical treatment fail to yield satisfactory results, endovascular, laparoscopic, or open surgical interventions are employed.

Keywords: Nutcracker phenomenon, Nutcracker syndrome, left renal vein entrapment, hematuria, orthostatic proteinuria

INTRODUCTION

The Nutcracker phenomenon (NP) is defined as the compression of the left renal vein, often between the aorta and the superior mesenteric artery (SMA). The anatomical variation was first described by El Sadr et al.¹ in 1950 and later termed the “Nutcracker phenomenon” by De Schepper in 1972.² This phenomenon is characterised by the obstruction of flow from the left renal vein to the inferior vena cava (IVC) due to external compression. Patients with symptoms associated with nutcracker anatomy are referred to as having “Nutcracker syndrome” (NCS).³

NCS is typically diagnosed in adults in the third and fourth decades of life and is known to be more common in females.⁴ There is limited data on the incidence and prevalence of NCS in

childhood. Still, it is known to increase in frequency between the ages of 10 and 14.⁵ Although NCS is not considered a hereditary disease, siblings have reported incidental cases.⁶ During adolescence, the angle between the SMA and the aorta narrows due to growth, potentially exacerbating symptoms.

ETIOLOGY

Compression of the left renal vein between the aorta and SMA is termed “anterior NP”⁷, while a less common compression type between the left renal vein and the vertebral column is termed “posterior NP”.⁸ A third type of NP has been identified, where a “circumaortic” left renal vein surrounds the aorta in addition to both anterior and posterior NP.⁹ Types of NP are shown in Figure 1.



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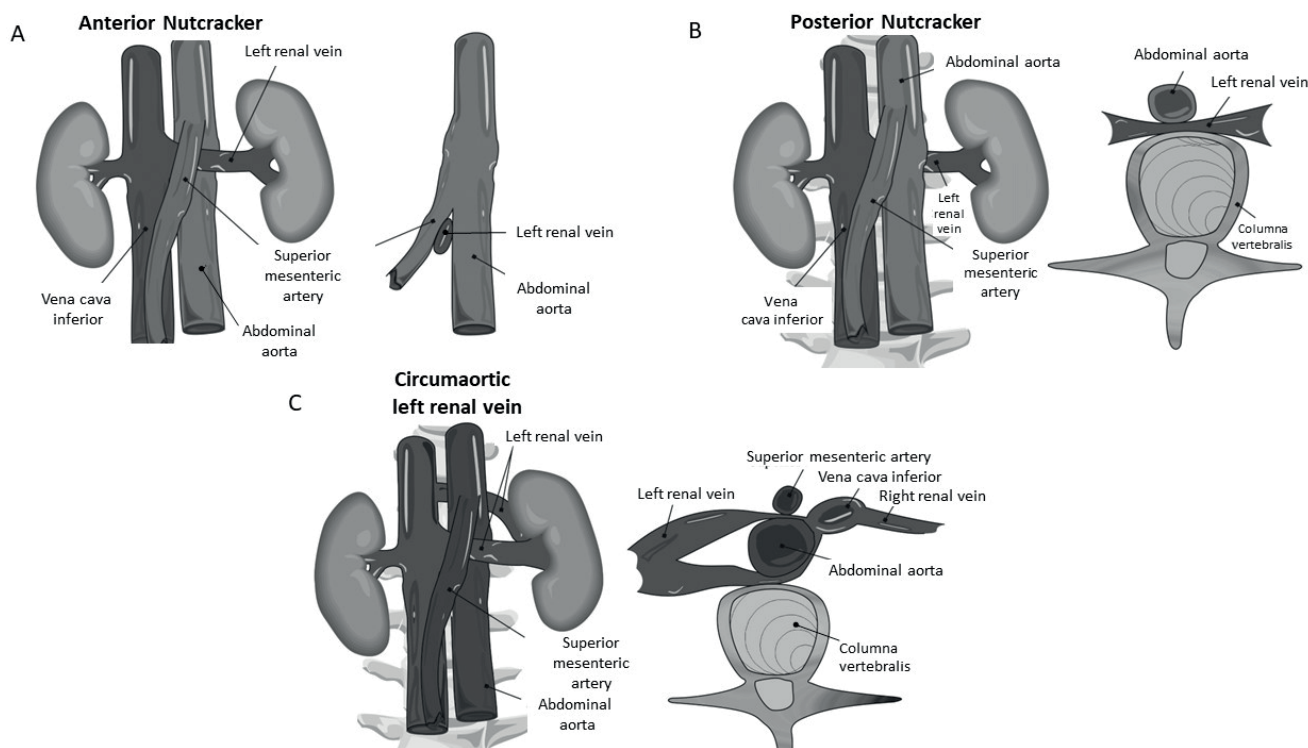


Figure 1. Types of NP. (A) Anterior NP; (B) Posterior NP; (C) Circumaortic left renal vein NP. NP: Nutcracker phenomenon.

Paraaortic lymphadenopathy, retroperitoneal mass, abdominal aortic aneurysm, duplication of the left renal vein, ectopic ventral right renal artery, left renal ptosis, severe lordosis, pregnancy, intestinal malrotation, and rapid weight loss are some of the less common etiologies of the left renal vein.^{3,10}

NCS is thought to be associated with a low body mass index (BMI). The angle between the aorta and SMA is generally between 38° and 65°, surrounded by lymph nodes, mesenteric fat tissue, and other soft tissues.¹¹ The absence of supportive mesenteric fat tissue can displace the intestines downward, narrowing the SMA angle. Another view suggests that the “stretching” of the left renal vein over the aorta occurs when transitioning from a supine to an upright position, resulting in venous compression.¹⁰ Studies indicate that symptoms associated with NCS improve with an increase in BMI.¹²

All anatomical variations causing renal vein compression result in outlet obstruction. This obstruction leads to increased pressure in the left renal vein with a measurable renocaval gradient. The average pressure difference between the distal renal vein and the IVC is <1 mmHg. A renocaval gradient of ≥3 mmHg suggests NP. Increased pressure in the left renal vein leads to the

formation of varices and collaterals. These varices and collaterals create venous sinuses adjacent to the renal calyx, causing clinical manifestations such as proteinuria and hematuria.¹³

CLINICAL FINDINGS

The clinical manifestations of NCS in children vary widely depending on the hemodynamic consequences of anatomical changes. Asymptomatic cases can coexist with micro or macroscopic hematuria (intermittent or persistent), orthostatic proteinuria, renovascular hypertension, abdominal pain, left-sided flank pain, dysmenorrhea, testicular or scrotal pain, left varicocele, nephrolithiasis, hypercalciuria, and fatigue. Recently, a systematic review of 423 children with NCS and a mean age of 12 years found that hematuria emerged as the primary symptom at presentation (55.5%), followed by proteinuria (49.9%). Notably, only 19.1% of the patients exhibited flank pain.⁵ Another systematic review of 159 patients ≤17 years of age with NCS reported that two-thirds were asymptomatic. In children with NCS, painless microscopic hematuria is more common compared to adults.^{14,15} Anecdotal cases have reported acute blood transfusion due to secondary severe anaemia resulting from hematuria.^{3,15}

Another significant finding in NCS is orthostatic proteinuria, with a higher incidence during puberty. It is estimated to affect 2-5% of children and young adults, with the majority having a benign course.¹⁶ The exact pathogenesis and mechanism of orthostatic proteinuria is still unknown. It is thought that venous hypertension induces a subclinical immune cascade in the vessel wall within the nephron¹⁷, leading to excessive release of norepinephrine and angiotensin II during upright posture.¹⁶ An enhanced physiological response to sudden changes in renal hemodynamics is thought to contribute to orthostatic proteinuria.¹⁰

Atypical left-sided pain is observed in one-third of pediatric NCS patients, often explained as visceral pain secondary to the dilation of the left renal vein. It is a well-known “triad” symptom, along with hematuria and proteinuria.^{18,19} Approximately 10% of pediatric cases may present with atypical diffuse abdominal pain secondary to pelvic venous compression.^{3,18-20} Both flank and abdominal pain may occur in these patients due to the activation of the inflammatory cascade triggered by venous hypertension.⁴

Hypertension is not a classic symptom of NCS, and only a few cases of NCS associated with hypertension have been identified in children. NCS should be considered as a potential cause in patients with unexplained hypertension, especially those who do not respond to antihypertensive medication. The underlying mechanism is not well understood, but increased plasma renin activity and aldosterone levels in the peripheral blood may explain it without renal artery stenosis or a renin-secreting tumour.²¹

In addition to renal symptoms, varicocele in males (usually on the left) and painful menstrual periods in pubertal girls may occur as a result of the development of gonadal venous varices in NCS. Chronic fatigue syndrome and symptoms of autonomic dysfunction such as hypotension, syncope, and tachycardia may rarely occur in patients with high renal vein and IVC pressure gradients in NCS.^{3,19}

DIAGNOSIS

Due to the lack of standard diagnostic criteria, the diagnosis of NCS can be challenging, even in patients with a suspicious clinical history. The presence of clinical features forms the basis for diagnosis. A detailed history and physical examination are essential, and in cases where NCS is suspected, comprehensive diagnostic procedures are necessary to confirm the diagnosis. Urinalysis and renal imaging should be performed. Various imaging modalities such as Doppler ultrasonography (DUS), computed tomography (CT), magnetic resonance imaging

(MRI), and retrograde venography are used for the diagnosis of NCS.^{5,22,23}

DUS, being non-invasive and radiation-free, is the first-line imaging modality in suspected cases of NCS. It has high sensitivity (69-90%) and specificity (89-100%) for diagnosing NCS.²⁴ The normal SMA originates from the back of the pancreatic neck and typically forms a sharp angle where it exits the aorta. In children, the average SMA angle is $45.8 \pm 18.2^\circ$ in males and $45.3 \pm 21.6^\circ$ in females, while the SMA-aorta distance is 11.5 ± 5.3 mm in males and 11.5 ± 4.5 mm in females.²⁵ The ultrasound diagnostic criteria of NCS were defined by Zhang et al.²⁶: 1) the flow rate of the LRV stenosis accelerates significantly in the supine position, and acceleration exceeding 100 cm/s is more pronounced after the patient has stood for 15 minutes; 2) the ratio of the inner diameter between the renal hilum and the stenotic segment of the left renal vein is >3 in the supine position and >5 after the patient has been standing for 15 minutes. However, using these criteria in children is limited because the measurements change with the patient's position and because of technical challenges due to a tiny sampling area.^{3,24} Additionally, the peak flow velocity ratio on DUS is above 4-5 between the compressed narrowed part of the renal vein and the noncompressed dilated renal hilar vein, offering a sensitivity of 80% and specificity close to 95% for NCS.⁷ In cases where DUS is not diagnostic, axial imaging may be required. Both CT and MRI can show compression of the left renal vein in the fork formed by the SMA and abdominal aorta, as well as dilation of the gonadal veins and pelvic congestion. However, neither CT nor MRI is a dynamic modality, so they cannot accurately measure flow rate and orientation. The most specific finding on CT for NCS is a left renal vein hilum/aorto-mesenteric diameter ratio ≥ 4.9 (100% specificity). However, the highest diagnostic accuracy observed on axial CT images is achieved by combining the “beak sign” and the left renal vein diameter ratio (AUC 0.903 for both). Although non-invasive, CT carries the risk of radiation exposure and the use of contrast agents. MRI is radiation-free and has the advantage of better visualisation of soft tissue anatomy in the compression area.²⁴

In selected and rare cases, measuring the pressure gradient between the left renal vein and the IVC through catheterisation may be considered an invasive evaluation. In the normal population, the pressure difference between the left renal vein and the IVC is less than 1 mm Hg, and a pressure difference greater than 3 mm Hg may suggest NCS. Retrograde venography, although an invasive test, is the most informative method and is considered the gold standard for the diagnosis of NCS. It not only confirms anatomical changes but also shows a pressure gradient along the compression zone. It is not commonly performed in patients without severe symptoms.^{3,23,24}

TREATMENT

Management of NCS in childhood is primarily based on clinical findings and the severity of the left renal vein hypertension. A conservative approach (e.g., “watch and wait” strategy) is strongly supported as the first-line treatment in patients with mild symptoms.^{12,27} In addition, it has been observed that NCS in children may resolve spontaneously due to the development of adipose tissue or the reduction of the pressure gradient in the left renal vein by the development of collaterals.¹⁸ The best option is to start with at least two years of observation and a conservative approach without medication in patients under the age of 18. Complete resolution occurs in 75% of patients with hematuria during this period. Angiotensin-converting enzyme inhibitors (ACEIs) may be effective, particularly in patients with severe and prolonged orthostatic proteinuria.^{10,24,27}

Surgery and more invasive treatment methods, such as endovascular techniques, may be required in rare and selected cases presenting with severe abdominal or (left) flank pain, recurrent macroscopic hematuria, renal dysfunction, left varicocele, anaemia, and persistent symptoms after 24 months of conservative treatment.^{5,24} Renal autograft or non-autograft left renal vein transposition is the most preferred surgical technique. The left renal vein is dissected from the IVC and reimplanted distally to the SMA.⁴ Other possible surgical techniques for the surgical treatment of NCS include SMA transposition, nephropexy, nephrectomy, renocaval bypass, left gonadal vein transposition, or laparoscopic procedures (laparoscopic splenorenal venous bypass and laparoscopic left renal vein-IVC transposition). Another option is the endovascular approach, in which a self-expanding stent is placed in the left renal vein. Although less invasive, endovascular treatment is not preferred because of the potential risks associated with stent displacement and the challenging management of anticoagulant therapy in children.^{24,28-30}

In light of current literature data, a conservative approach should be considered the first-line treatment for children. In selected cases that do not benefit from a conservative approach and medical management, clinicians should consider other interventional treatment options after conducting a careful risk-benefit assessment.

CONCLUSION

NCS should be considered in patients with unexplained hematuria, proteinuria, and pelvic and/or flank pain. The left renal vein's anatomical and physiological degree of compression can be assessed with DUS, CT, or MRI. DUS has additional

diagnostic value in determining the highest velocity ratios in the same positions. In mild cases, conservative treatment is an appropriate option, and ACEIs may be used in patients with proteinuria. In more severe cases that do not benefit from conservative and medical treatment, endovascular, laparoscopic, and open surgical treatments are used. As it is a rare disease, no clinical studies compare treatments. Larger-scale and longer-term studies are needed for further evaluation of these treatments.

Author contribution

Concept: EGÖ, BG; Design: EGÖ, BG; Data Collection or Processing: EGÖ, BG; Analysis or Interpretation: EGÖ, BG; Literature Search: EGÖ, BG; Writing: EGÖ, BG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

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