Nutcracker syndrome: diagnosis and therapy

Marcin K. Kolber¹, Zhonghao Cui², Christine K. Chen¹, Peiman Habibollahi¹, Sanjeeva P. Kalva³

¹Division of Interventional Radiology, Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA; ²University of Texas Southwestern School of Medicine, Dallas, TX, USA; ³Division of Interventional Radiology, Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

Contributions: (I) Conception and design: MK Kolber, S Kalva; (II) Administrative support: MK Kolber, S Kalva; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: MK Kolber, Z Cui, S Kalva; (V) Data analysis and interpretation: MK Kolber, Z Cui, S Kalva; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Marcin K. Kolber, MD. Division of Interventional Radiology, Department of Radiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8834, USA. Email: Marcin.Kolber@UTSouthwestern.edu.

Abstract: Nutcracker syndrome (NCS) is an extrinsic compression of the left renal vein (LRV) by the superior mesenteric artery (SMA) anteriorly and aorta posteriorly resulting in renal vascular congestion manifesting as hematuria, proteinuria, orthostatic hypotension, pain, or even renal dysfunction. Long-standing venous compression can encourage collateral drainage pathways through gonadal and pelvic veins, which may explain reported symptom and syndrome overlap with pelvic congestion syndrome. Diagnosis can be challenging and variable, frequently involving a combination of ultrasound Doppler, cross-sectional, and invasive imaging. Often, intravascular pressure measurements are required to prove a renocaval pressure gradient to aid in a definitive diagnosis. Conservative management is appropriate, especially in children, who tend to outgrow the disorder. In the interim, medical management with angiotensin converting enzyme inhibitors (ACEIs) is a useful therapy to manage orthostatic hypotension in the pediatric population. In adults, invasive therapies are more frequently pursued. These are aimed at relieving the extrinsic compression on the LRV. The standard of care is renal vein transposition, with renal autotransplantation reserved for recalcitrant cases. Endovascular stenting is a less invasive option. Laparoscopic placement of an exovascular stent is a newer therapy intended to minimize trauma to the LRV. In this review, we will discuss the clinical manifestations, diagnostic criterion, imaging features, and conservative and surgical therapies for this condition.

Keywords: Nutcracker syndrome (NCS); left renal vein (LRV); vascular compression; hematuria

doi: 10.21037/cdt-20-160
View this article at: http://dx.doi.org/10.21037/cdt-20-160

Introduction

Nutcracker syndrome (NCS) was first coined in 1972 (1) to describe the effect of a narrow angle between the superior mesenteric artery (SMA) and aorta compressing the left renal vein (LRV), as viewed in the sagittal orientation (Figure 1). An aortomesenteric (AM) angle of <35–39 degrees is generally agreed upon as required for the syndrome to manifest, but NCS is considered a diagnosis of exclusion and various imaging and physiologic metrics are utilized for confirmation (2,3). Given the variety of diagnostic criterion, the exact prevalence of NCS is unknown. Peak age of incidence is second decade to middle-age (ranging from childhood to seventh decade) (4). Though classically believed to have a slight female predilection (5), more recent studies suggest equal prevalence between genders (3,4).

Etiology

Classic NCS is infrequently referred to as anterior NCS to differentiate from a less common variant, Posterior...
NCS, which occurs in the presence of a retroaortic LRV compressed by the vertebral column posteriorly and aorta anteriorly (6,7), but results in similar symptoms. Combined (anterior and posterior) NCS has also been reported, resulting from a circumaortic or duplicated LRV with both components stenosed by extrinsic compression (8). Still rarer etiologies of LRV compression include compression by adjacent lymphadenopathy or malignancy (9), severe lordosis (10), pregnancy (11), intestinal malrotation (12), and rapid weight loss (13).

NCS has a suspected correlation to low body mass index (BMI), with some authors noting that symptoms resolve with increasing BMI (14). One explanation is a lack of supporting mesenteric fat, which otherwise lifts the bowel and raises the angle of the SMA. Another suggestion is a correlation to renal ptosis, a condition in which the kidney descends within the retroperitoneum upon position change from supine to upright, has been implicated in LRV “stretching” over the aorta and subsequent venous congestion (15). A lack of supporting retroperitoneal fat in these patients may contribute to renal “descent” (16).

Clinical manifestations

The hallmark manifestations of NCS—hematuria, proteinuria, and flank/pelvic pain (3)—are probably related to renal venous congestion and increased pressure within the communicating venous structures. Within the renal collecting system, periureteral and peripelvic varices engorge and rupture, resulting in macroscopic or microscopic hematuria (17,18). Isolated left-sided hematuria, identified on cystoscopy as hematuria from the left ureteral orifice only, supports the diagnosis (19).

Within the nephron, venous hypertension is believed to induce a subclinical immune cascade in the wall of the vessel (20), predisposing to a greater-than-necessary local release of norepinephrine and angiotensin II upon standing (21). This exaggerated physiologic response to abrupt changes in renal hemodynamics is thought to result in orthostatic proteinuria (22,23). However, it should be noted that orthostatic proteinuria is relatively common in the pediatric population as a whole, affecting 2–5% of children and young adults, most of whom experience a benign course (21). In addition, severe systemic hypertension has been reported in association with NCS (24).

Extrinsic to the kidney, the LRV communicates most directly with the lumbar venous plexus and the left gonadal vein [in addition to the inferior vena cava (IVC)] (Figure 2), which frequently dilate as they emerge as preferential drainage pathways for the renal vein (Figure 3A) (11). In advanced cases, gonadal vein engorgement can progress to pelvic congestion syndrome (25), a condition defined as noncyclic chronic pelvic pain and/or heaviness attributable to gonadal vein reflux and dilation (Figure 3B) (26). The gonadal vein communicates directly with the ovarian venous plexus and subsequently the uterine venous plexus, eventually draining to the hypogastric vein via visceral tributaries or parietal tributaries via gluteral vulvoperineal.
veins—any of which may contribute to pain, fullness, or discomfort in the pelvis (27). Concomitant NCS has been described in up to 18% of patients with pelvic venous congestion syndrome (28). In males, NCS, as diagnosed by elevated LRV velocities, is frequently associated with varicocele caused by venous hypertension and collateralization (Figure 3C) (29).

Another example of symptom and syndrome overlap with NCS is loin pain hematuria syndrome (LPHS), a rare condition characterized by loin pain radiating to the abdomen, medial thigh, and/or groin, with an estimated prevalence of 0.012% (30,31). It is estimated to be caused by NCS in up to 40% of patients (32).

**Diagnosis**

Even in patients with a straightforward and highly suspicious clinical history, the diagnosis of NCS can be
challenging. Computed tomography (CT), magnetic resonance imaging (MRI) and Doppler ultrasound (DUS) are all reasonable imaging studies in patients with suspected NCS, but frequently invasive assessment with catheter venography and pressure measurement is required for definitive diagnosis (4).

The screening examination of choice is DUS, offering both anatomic and physiologic assessment of the LRV absent radiation. However, the technique can be challenging, requires 6–8 hours fasting, and definitions vary depending on position (supine versus upright) (33). Reference ratios are slightly higher in the upright position, thought to be related to gravity acting on bowel and mesentery, pulling the SMA downward and pronouncing the LRV stenosis. Peak systolic velocity (PSV) is evaluated in the compressed, AM LRV and compared to hilar PSV. Various ratios have been proposed as significant, ranging from 4.0:1 to 5.0:1 (Figure 4) (34-36).

Cross-sectional imaging with CT and MRI relies on vessel diameter and, to a lesser extent, SMA angle to identify pathologic narrowing of the LRV. A normal aorta-to-SMA angle is between 45 and 90 degrees. An angle of 35 degrees in sagittal dimension suggests NCS (37) (Figure 5A). In the axial plane, a characteristic “beak” sign with abrupt narrowing of the LRV at the SMA is reported to have a sensitivity of 91.7% and specificity of 88.9% (38). As normal absolute values vary by patient, studies have focused on the ratio of diameters of the LRV at the renal hilum as compared to those at the narrowed AM segment. On CT, a hilar-to-AM diameter ratio of ≥4.9 has a 66.7% sensitivity and 100% specificity for NCS (Figure 5B) (2).

A separate study demonstrated a 91% sensitivity and 91% specificity for NCS with a “compression ratio” of 2.25, which was described as adequate to raise suspicion for the disease, in the context of symptoms (39). Predictably, higher compression ratios were associated with more symptoms.

MRI is particularly beneficial in children and adolescents owing to the absence of radiation while retaining the ability to evaluate adjacent abnormal vascular structures, such as an enlarged gonadal vein (40). Vein diameter ratios and “beak sign” can be evaluated in similar fashion as CT (Figure 6). A comparison of various MRI sequences determined that True Fast Imaging with Steady-State Free Precession (T2-TRUFI) has particularly good image quality for evaluating the LRV (41). High signal intensity in the LRV on fast-spin-echo T2-weighted sequence due to venous hypertension and stagnation may be particularly useful for diagnosis and evaluating response to therapy (42).

A comparison of DUS (LRV systolic velocity ratios) to CT (vein diameter ratios) demonstrates higher sensitivity and specificity of DUS findings (sensitivity of 80% vs. 69%; specificity of 94% vs. 89%, respectively) (34,36). However, invasive testing is frequently pursued for definitive diagnosis, as therapy could require invasive surgery. Venography with direct pressure measurements (Figure 7) (17), with or without intravascular ultrasound (IVUS), is considered the “gold standard” for diagnosis. However, even studies evaluating these methods utilized cystoscopy to confirm isolated left-sided hematuria (2). An elevated pressure gradient between the LRV and the IVC (≥3 mmHg) is the standard reference point by which venous
hypertension is diagnosed (43). However, it should be noted that some patients may be symptomatic with “compensated” NCS, where compensatory flow through collaterals is large enough that only a borderline renocaval pressure gradient exists (2).

**Therapy**

**Conservative management**

Conservative management is sufficient in many cases of NCS, most notably in the pediatric population. It is well-
established that the majority of pediatric patients with NCS will have spontaneous resolution, an effect possibly related to increased retroperitoneal and/or mesenteric adipose during growth and the accumulation of fibrous tissue at the SMA origin. The most widely accepted therapy for the pediatric population is angiotensin converting enzyme inhibitors (ACEIs) to minimize orthostatic proteinuria and treat concomitant hypertension, with or without aspirin, to maximize renal perfusion (3,44,45).

Surgical treatment

Renal vein transposition is the standard of care for patients with non-remitting symptoms and is the most common invasive intervention for anterior NCS, with excellent immediate and long-term symptom control. The great saphenous vein may be harvested for use as an extension graft or patch onto the LRV if the vein has been damaged by chronic compression. Although a relatively low-risk procedure, reported complications include paralytic ileus, small bowel adhesion, and LRV restenosis (46). Minimally invasive approaches with laparoscopic or robot assisted-laparoscopic techniques reduced recovery times and are increasingly becoming standard practice (47,48). Nevertheless, re-intervention rates have been reported to be up to 68%, mostly for re-stenosis of the LRV (49).

Left kidney auto-transplantation is also relatively common, though more invasive, as it involves relocating the kidney to the iliac fossa (10,50). This is considered a more thorough approach as it obviates the issue of renal ptosis (51,52). However, the procedure involves a protracted period of renal ischemia, a more extensive dissection, and a total of three anastomoses (artery, vein, and ureter) with consequent possible complications (i.e., stenosis) at any of these sites (16). Nevertheless, auto-transplantation remains a valid option for many patients. In particular, it is utilized in patients who suffer recurrent NCS, or lack of symptoms relief, following LRV transposition (32).

Laparoscopic placement of an extravascular stent (external to the LRV) is a newer means of treating NCS via laparoscopic approach without the need to mobilize or clamp the LRV (Figure 8) (53). A case series of 13 patients reported symptom resolution in 10 and improvement in 2, with one case of stent migration (54). More recently, a 15-patient cohort that underwent 3D-printed titanium extravascular stent placement were asymptomatic and without restenosis or migration at 24 months (55).

In posterior NCS, because the LRV sits in a retro-aortic space and is compressed between the abdominal aorta and the spine, open surgical transposition of the LRV to an ante-aortic course is preferred. Less common options include transposition of the SMA (which carries a risk of mesenteric ischemia), nephropexy with excision of renal varicosities, transposition of the left gonadal vein to the IVC or left common iliac vein, and finally nephrectomy, which is only performed as a last resort in cases where hematuria persists after multiple other attempted procedures (56,57).

Endovascular treatment

Due to a more minimally invasive nature, endovascular interventions have been applied to the treatment of NCS (Figure 9). Although no dedicated stent system has been developed solely for use in the renal vein, devices already...
on the market have been shown to be effective, including SMART Control (Cordis, Santa Clara CA, USA) and Wallstent (Boston Scientific, Marlborough MA, USA) (46,52,56). Though infrequent, endovascular stenting of posterior NCS has also been reported (58). It has been suggested that concomitant use of IVUS allows for more accurate sizing of stents (59). Benefits of this approach include rapid recovery time and symptom resolution. As with any intravascular stent, thrombosis is possible (though rare), and prevention requires anticoagulation and antiplatelet therapy for up to 3 months to allow for stent endothelialization (60). A study of 75 patients undergoing

![Figure 8](image1.png)

**Figure 8** Sagittal (A) and axial (B) CTA following laparoscopic exovascular stent (arrows) placement in a patient with previously diagnosed NCS. CTA, computed tomography angiography; NCS, nutcracker syndrome.

![Figure 9](image2.png)

**Figure 9** Axial (A), sagittal (B), and 3D-reconstruction (C) CTA following endovascular stent (arrows) deployment in a patient with previously diagnosed NCS. CTA, computed tomography angiography; NCS, nutcracker syndrome.
LRV stenting with mean 55 months follow-up identified a 6.7% rate of stent migration, either to the IVC [2], the right heart [2] or retrograde to the renal hilum [1], without significant variances in stent sizing or position to explain cause of migration (61). In a recent review of 18 cases of LRV stenting, primary patency was 85.2% at 2 years, however of five cases performed for stenosis after LRV transposition, three remained symptomatic despite stenting, suggesting limited utility as a salvage therapy (62).

**Conclusions**

NCS is a diagnostic consideration in patients with unexplained hematuria, proteinuria, and pelvic or flank pain. Diagnosis relies on determining the anatomic and physiologic degree of LRV compression between the aorta and SMA. DUS, CT, and MRI can suggest the diagnosis with an LRV hilar-to-AM ratio of >4–5:1. DUS has additional value for determining peak velocity ratios in the same locations. However, venography with IVUS or pressure measurements is frequently required for confirmation. Conservative therapy is often appropriate, especially in children and adolescents, with ACEIs the primary medical therapy for proteinuria. Endovascular, laparoscopic, and open surgical treatments have been utilized successfully for persistent cases. Due to the rarity of the condition, there are no clinical studies comparing treatments, however endovascular and extravascular stenting are promising minimally invasive interventions. Further appraisal of these treatments awaits larger and longer-term studies.

**Acknowledgments**

_Funding:_ None.

**Footnote**

_Provenance and Peer Review:_ This article was commissioned by the editorial office, *Cardiovascular Diagnosis and Therapy* for the series “Compressive Vascular Syndromes”. The article has undergone external peer review.

_Conflicts of Interest:_ All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cdt-20-160). The series “Compressive Vascular Syndromes” was commissioned by the editorial office without any funding or sponsorship. Drs. MKK and SK served as the unpaid Guest Editors of the series. Dr. SK serves as an unpaid editorial board member of *Cardiovascular Diagnosis and Therapy* from May 2019 to Apr 2021. Dr. SK reports personal fees from Medtronic, personal fees from Dova Pharmaceuticals, personal fees from Koo Foundation, Taiwan, personal fees from GE healthcare, personal fees from Springer, personal fees from Elsevier, other from Althea Health Inc, CA, personal fees from Boston Scientific, personal fees from Penumbra, grants from BD, grants from NIH, outside the submitted work. The authors have no other conflicts of interest to declare.

_Ethical Statement:_ The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

_Open Access Statement:_ This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

**References**