Interventional Management of Nutcracker and Wilkie Syndromes

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Nutcracker and Wilkie syndromes are rare mesoaortic compression entities, and their association is even less common. Data on interventional treatment of these pathologies are still scarce, but results from limited case series are encouraging.

nutcracker Wilkie endovascular treatment left renal vein compression

1. Introduction

A reduced angulation of less than 22 degrees between the abdominal aorta and the superior mesenteric artery (SMA), with an aortomesenteric distance of less than 8 mm, is a very rare vascular alteration [1] which leads to a reduction in the aortomesenteric space and consequent compression of its structures, mainly of the left renal vein (nutcracker syndrome) and/or the duodenum (Wilkie syndrome) [2]. While each of these syndromes represent a rare finding, their association is even less frequent. Because the congenital form is not as common, several acquired etiologies have been described, including rapid weight loss, compression by adjacent lymphadenopathy or malignancy, severe lordosis, pregnancy, or intestinal malrotation [3]. Nutcracker and Wilkie syndromes share a common etiology, namely weight loss.

The precise epidemiology of nutcracker syndrome is unknown, partly because of an absence of definitive diagnostic criteria and partly because of the variability in symptomatic presentation. However, unexplained hematuria is a common symptom and nutcracker has been diagnosed by doppler ultrasound in 40% of patients with this clinical presentation [4]. There may be left flank pain, usually associated with hematuria and sometimes accompanied by albuminuria and pelvic congestion (characterized by symptoms such as dysmenorrhea, dyspareunia, lower abdominal pain, dysuria, pelvic, vulvar, gluteal, or femoral varices, and emotional disturbance). Compression of the left renal vein (LRV) can cause reflux from the left renal to the gonadal vein, leading to lower limb varices and varicoceles in men. Although it is primarily a vascular disease, manifestations are predominantly urologic or gynecologic, yet some patients are also treated by vascular surgeons when lower limb varices are the chief complaint. Interestingly, a recent study retrospectively analyzed the data from high-definition renal computed tomography (CT) in 324 normal asymptomatic patients and identified an aortomesenteric angle < 41° in 30.5% of patients, with a greater prevalence in women, but an LRV ratio ≥ 4.9 in just 0.7% of the cases [5]. This may explain that some acute angles do not lead to clinical manifestation or pathological diagnosis of the two syndromes and

remain only as an anatomical variant. This is sometimes called the nutcracker *phenomenon* and the term *syndrome* is reserved for patients with distinctive clinical symptoms associated with verifiable nutcracker morphologic features. The veins physiologically draining into the left renal vein include the left gonadal vein, left ureteral vein, left inferior phrenic vein, and left adrenal veins [6]. In nutcracker syndrome, these vessels are often engorged due to the decreased outflow of the left renal vein. These collaterals cause increased pressures in the gonadal vein, which causes increased pressures in the smaller and more fragile vesicular veins and pampiniform plexus, leading to varicocele development. Finally, because collaterals frequently fail to decompress the stenosed renal vein, hematuria results from blood transposition over fragile renal sinusoids into the collecting system [3]. Based on renal vein pressures, the patients' strong collaterals are likely decompressed sufficiently enough to avoid hematuria, and vice versa. The treatment must therefore be tailored from case to case.

The symptomatology in both syndromes is nonspecific and is common to many other abdominal pathologies [2]. In nutcracker syndrome, the hallmark clinical symptoms (hematuria, proteinuria, and flank/pelvic pain) occur only in the presence of hemodynamically significant LRV stenosis leading to venous hypertension [7]. Macroscopic or microscopic hematuria appears as a result of the rupture of intrarenal varices triggered by venous congestion [8], which also induces an immune cascade in the vessel wall and consequently causes a greater release of norepinephrine and angiotensin II upon standing, leading to orthostatic proteinuria [9]. The numerous communications of the LRV with the lumbar venous plexus, inferior vena cava, and the left gonadal vein may explain the pelvic pain seen in advanced cases, as these venous systems become dilated as a result of renal venous congestion [10].

On the other hand, the compression of the duodenum results in non-specific gastrointestinal symptoms, such as nausea, early satiety, abdominal pain and vomiting, all of which are aggravated by eating [7]. These manifestations promote weight loss, which triggers further subsequent mesenteric fat loss, further reducing the aortomesenteric angle, thus resulting in a pathological circle [11].

2. Imaging Diagnosis

Normally the SMA emerges from the abdominal aorta at a 90-degree angle. The normal aortomesenteric angle is reported to be 28 to 65 degrees, and the normal aortomesenteric distance ranges from 10 to 34 mm [2]. The LRV is situated anterior to the aorta in the fork between the SMA and abdominal aorta. In anterior nutcracker syndrome, the SMA arises from the aorta at an acute angle, compressing the LRV and causing left renal venous hypertension and/or final part of duodenum (**Figure 1**). In posterior nutcracker syndrome, the LRV has a course posterior to the aorta and is compressed between it and the vertebral bones. In combined nutcracker syndrome, the anterior branch of the duplicated LRV is constricted between the aorta and the SMA, while the posterior is squeezed between the aorta and the vertebral bones.

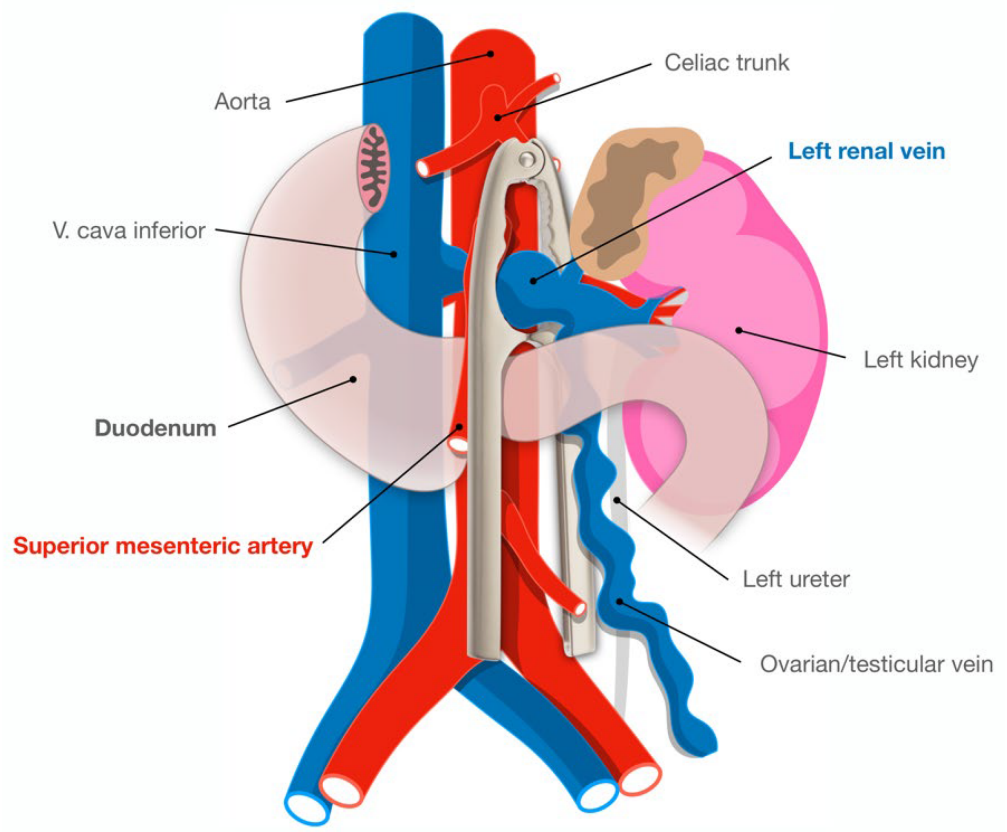

Figure 1. Illustration of the aortomesenteric angle in relation to the left renal vein and the terminal duodenum, tangling the two simulates the shape of a nutcracker (overlaid).

The “gold standard” for diagnosis remains phlebography, intravascular pressure measurement, and intravascular ultrasound through which the venous pressure gradient between the LRV, the inferior vena cava, and the renal vein diameter can be accurately identified [12]. But all of these dedicated invasive investigations are being conducted on the basis of a high suspicion or a provisional diagnosis, which is always firstly based on a non-invasive imaging work-up. In a patient with an unremarkable workup for the common causes of hematuria and/or flank pain, a multimodality approach of a Doppler ultrasound followed by either CT or magnetic resonance (MR) venography will often suggest the diagnosis of an abnormal mesoaortic angle.

Ultrasonography can often reveal the compressed renal vein and allow for the measurement of the vein diameter and stenosis secondary to the compression. The long axis color Doppler view can exemplify the presence of a velocity gradient from the perihilar to mesoaortic region [12]. The presence of an increased flow through the collateral veins is further proof of renal venous hypertension. Although ultrasound can nicely display the stenosis and collaterals, studies have shown a poor correlation between the Doppler and the gold standard of the renocaval pullback invasive pressure measurements [13][14], which considering to be the basis of the variation in the collateral decompression of the renal vein. For this reason, a direct measurement of the pressure between the left renal vein and inferior vena cava remains valuable for securing a diagnosis of nutcracker syndrome, with a pressure difference greater than 5 mmHg considered significant [12].

CT and MR angiography tests allow for the highlighting of the mesenteric artery origin from the abdominal aorta and the compression and stenosis of the LRV. Coronal and sagittal reconstructions also allow for the depiction of the left gonadal vein and collateral circulation with the lumbar veins. With sagittal reconstruction, it is possible to evaluate the incriminated angle, which if it is less than 35 degrees, is compatible with the diagnosis of the compression of the LRV and further clinical and physiological assessment should define if the physician is facing a *syndrome* or just a nutcracker *phenomenon*. Finally, an LRV diameter ratio (hilar to aortomesenteric ratio) of more than 4.9 has a positive predictive value of 100% [14].

3. Surgical or Interventional Management

Patients with mild symptoms can be treated conservatively, with emphasis on weight gain that increases retroperitoneal adipose tissue, resulting in a change in the position of the left kidney with a decrease in tension on the LRV; this approach has been shown to relieve symptoms of nutcracker in 30% of patients [12]. This is highly encouraged in young individuals (those <18 years) as body growth releases the LRV from the arterial fork.

As per open surgical treatment, various techniques have been employed in an attempt to either decrease venous hypertension or alleviate the predominant symptoms of hematuria or pelvic congestion. The severity of symptoms, patient demographic, and the level of understanding of the available local expertise techniques can guide the clinician as to when and how to intervene. The first reported case of treated nutcracker was in 1974 [15]. Since then, a number of surgical approaches have been described. These include direct reimplantation of the left renal vein [16], SMA transposition [17], nephropexy [18], autotransplantation of the left kidney [19], isolated nephrectomy [20], and external stenting or “shielding” of the LRV [21]. Most of these approaches were developed to lower venous hypertension. Some techniques, such as left gonadal vein ligation, gonadocaval bypass, splenorenal venous bypass, and/or embolization and sclerosis of pelvic varices, are more directed to treat pelvic congestion symptoms [22]. The ligation of the collateral vessels, coil embolization of the gonadal veins, and ablation of the varices have been established together with renocaval pressure gradient relieving procedures in cases where pelvic congestion resulted from nutcracker syndrome [23].

Endovascular stenting of the left renal vein has recently been documented, with multiple studies demonstrating symptoms relief [24][25][26]. In fact, endovascular treatment could also solve the problem of duodenal compression (“2 in 1”), a great advantage over surgical reimplantation. The first stent was implanted in 1994 by Neste et al. [23] and since then, transcatheter treatment has gained popularity and notoriety due to its high success rate and few complications. The most relevant complication (for incidence and potentially damage) is stent migration, while in-stent restenosis and venous occlusion resulting from fibromuscular hyperplasia or thrombosis rarely occur. Thrombosis rather occurs before stenting, due to stasis in the dilated vein [27]. This detail is not negligible as the thrombus can embolize and cause acute pulmonary embolism [28]. There is no consensus on the post-interventional antithrombotic regimen but a “defensive” management would be 2–3 months of initial anticoagulation (until the stent endothelialization occurs) and prescribing aspirin long-term or dual antiplatelet therapy for at least 2 months [12][14]. The only limitation with endovascular stenting would be the lack of long-term data, although there is a signal of good long-term follow-up after 2–3 years [29]. The most pertinent reported cohorts of stented nutcracker

syndrome patients are summarized in **Table 1**; at first sight, variability can be observed in the study population and follow-up. In one of the largest available registries to present, Chen et al. [25] retrospectively evaluated 61 patients with nutcracker syndrome treated by an endovascular approach and at long-term follow-up (66 months), there were only 2 patients without a significant improvement in the symptoms of hematuria, proteinuria, and flank pain, while the rest of the patients experienced clinical improvement at various periods of time (most of them after 6 months). Based on these observations, the researchers recommended this approach as the primary option for nutcracker syndrome. The stenting techniques were mostly “borrowed” from the percutaneous experience in superior vena cava syndromes or May–Thurner syndrome (chronic compression of the left iliac vein against lumbar vertebrae by the overlying right common iliac artery) [30]. Due to the risk of migration, an oversized auto-expandable stent should always be preferred; they have more radial force and prevent recoil compared to dedicated venous stents. There is only a single published study that has implanted a specifically designed venous stent (Zilver Vena; Cook Medical, Bloomington, Ind) with relatively good outcomes, but in a small cohort (20 patients) with a short follow-up (10–122 days) [31]. Notably, a recent study from the University of Pittsburgh, USA used IVUS in 61% of their cases and had no stent migration, which highlights the importance of accurate stent sizing [32]. Interestingly, a group from China managed to build customized stents for patients with nutcracker syndrome by 3D printing; for the first step, they printed the entire kidney model based on CT images exported in DICOM format, then, through surgical planning, they finally printed out the stents using titanic alloy powder [33]. The only downside to this innovative idea is that the stent needs to be implanted surgically, as it is already expanded [33]. With time and more intensive imaging screening, it is likely that the prevalence of these syndromes will increase, which will inevitably refine researchers' experience with these percutaneous techniques. The principle is the same as in coronary interventions: multidisciplinary teams, intraprocedural imaging, and proof of ischemia are encouraged [34].

Table 1. Studies of left renal vein stenting for patients with nutcracker syndrome; age and follow-up are mean values.

Study	Year	Cohort (Patients)	Age (Years)	Stent Type	Outcomes	Reintervention/Complications	Follow-Up (Months)
Chen et al. [35]	2005	3	10	Optimed (self-expandable)	100% stent patency at follow-up, resolution of hematuria	None	36
Hartung et al. [36]	2005	5	34	WALLSTENT	Symptoms resolution in all	2 patients presented stent migration after 3–4 months and recurrence of symptoms due to re-compression of the vein	14
Basile et al. [37]	2007	3	19	Luminexx (self-expandable)	100% stent patency at follow-up, resolution of hematuria	None	14–18

Study	Year	Cohort (Patients)	Age (Years)	Stent Type	Outcomes	Reintervention/Complications	Follow-Up (Months)
Chen et al. [25]	2011	61	26	WALLSTENT, SMART, Palmaz	Improvement of symptoms in 59/61 patients; 100% stent patency after 6 years, including the re-stented patients	2 stent migrations and reinterventions	66
Baldi et al. [38]	2011	2	50	SMART control	100% resolution of symptoms	None	12–24
Wang et al. [39]	2012	30	18	SMART control	100% stent patency at follow-up, resolution of hematuria	2 stent migrations (uneventful at follow-up)	36
Li et al. [40]	2013	3	16	Protégé	100% stent patency at follow-up, resolution of hematuria	None	6–60
Wu et al. [41]	2016	75	27	WALLSTENT, SMART control	3/5 patients who had stent migration developed symptoms again	5 stent migrations, from which 3 required open surgery	6–126
Policha et al. [42]	2016	3	33	WALLSTENT	100% stent patency at follow-up, resolution of hematuria	2 uneventful stent migrations	20
Avgerinos et al. [43]	2019	18	38	WALLSTENT, Protégé, SMART control, ev3, Zilver	72% symptoms resolution, 85% primary and 100% primary-assisted patency at 2	1 re-stenting, 2 balloon post-dilatations, 2 renal auto transplantations	41

References

Study	Year	Cohort (Patients)	Age (Years)	Stent Type	Outcomes	Reintervention/Complications	Follow-Up (Months)
					years follow-up		
Cronan et al. [44]	2021	10	16	Zilver, Venovo	70% symptoms resolution,	2 re-stenting with WALLSTENT for restenosis	3–37

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