International Journal of Sciences

Research Article Volume 12 – September 2023 (09)

Complications of Endovascular Treatment in Patients with Nutcracker Syndrome: A Literature Review

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Abstract: Nutcracker Syndrome, a rare anatomical condition, consists of the compression of the Left Renal Vein as it passes at the Aortomesenteric level and results in nonspecific signs and symptoms. Its exact prevalence is unknown and can present at any age, with a peak prevalence between the second and third decade. Its diagnosis is of exclusion and is primarily through imaging tests, with Venography and pressure gradient measurement being the gold standard. Treatment varies according to clinical severity, ranging from conservative measures to surgical approach, either open or endovascular. The latter, despite being safer, can present various complications. In view of this, a literature review was conducted to analyze potential complications of endovascular treatment for Nutcracker Syndrome. A total of 21 articles correlating the complications of endovascular treatment for patients with this syndrome were found and included. Most studies presented restenosis, local fibromuscular hyperplasia, erosion, thrombus occlusion, and stent migration as the main and most common complications. Stent migration can lead to worse outcomes necessitating surgical reapproach. Nutcracker Syndrome, being rare, has few studies that follow the long-term outcomes of possible treatments. Among these, endovascular treatment is currently the most recommended as it is minimally invasive, but it is not failure-free, necessitating individualized stent choice and follow-up to reduce the incidence of various complications.

Keywords: Endovascular, Vascular, Nutcracker Syndrome, Complications, Treatment, Pelvic Congestion Syndrome

Introduction

The Nutcracker Phenomenon (NCP), a rare anatomical condition, was first described in 1937 as the situation where "[...] the left renal vein (LRV) is compressed between the aorta (AO) and the superior mesenteric artery (SMA) like a nut in a nutcracker". Subsequently, atypical anatomical variations of this condition were described, notably the posterior NCP that occurs in cases where the LRV is retroaortic and becomes compressed between the abdominal aorta and the spinal column.

The compressive process culminates in different levels of renal branch stenosis, causing conditions ranging from asymptomatic to a complex of symptoms, defining Nutcracker Syndrome (NCS) (WANG et al., 2012; ANANTHAN et al., 2017). The progressive increase in LRV pressure promotes the development of varices in the renal pelvis and ureter, leading to the most commonly found symptom, hematuria. Other possible symptoms include left flank pain, diffuse abdominal pain, chronic pelvic pain, varicocele, and chronic fatigue (WANG et al., 2012; ANANTHAN et al., 2017; VELASQUEZ et al., 2017; AGLE et al., 2019).

The exact prevalence of NCS is unknown, partly due to the lack of definitive diagnostic criteria and partly due to the variability in clinical presentation (AGLE et al., 2019). Patients can present at any age, from infancy to the seventh decade, with a peak prevalence in young people (second or third decade) and middle-aged adults (ANANTHAN et al., 2017). Initially, the prevalence of this condition was reported as higher in females, however, subsequent studies demonstrated that it is equally prevalent among both sexes (ANANTHAN et al., 2017; VELASQUEZ et al., 2017; AGLE et al., 2019).

The diagnosis requires a high index of suspicion, it is extremely rare and represents a diagnosis of exclusion. More common conditions, such as urinary tract infection, nephritis, kidney stones, endometriosis, and autoimmune diseases with abdominal lesions must be

Published at: http://www.ijsciences.com/pub/issue/2023-09/
DOI: 10.18483/ijSci.2718; Online ISSN: 2305-3925; Print ISSN: 2410-4477

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ruled out (VELASQUEZ et al., 2017). Confirmation is done through imaging tests, with Doppler ultrasound (US) being the most used method (VELASQUEZ et al., 2017; AGLE et al., 2019).

Treatment varies according to clinical severity, ranging from a conservative approach for young patients or those with mild symptoms, to endovascular surgical methods for those who did not improve after conservative therapy or who present severe symptoms (AGLE et al., 2019). The first surgical interventions for NCS took place in the 1970s, and since then a wide variety of techniques have been highlighted, with the first report of the use of vascular stents for the treatment of NCS dating back to the 1990s (AGLE et al., 2019; HULSBERG et al., 2016; MENARD et al., 2002).

In this context, the placement of an endovascular stent has been described as an alternative treatment option and is usually preferable to open surgery due to the higher possibility of complications in these cases (MACEDO et al., 2018). However, possible associated complications are highlighted, especially with the type and size of the device, balloon dilatation, and the surgeon's lack of knowledge who performed the procedure (MENARD et al., 2002; MACEDO et al., 2018). The main complications include incorrect stent placement, migration or partial displacement of the device (to the inferior vena cava or the LRV hilum region). Also noteworthy are stent embolization, in-stent restenosis, and thrombosis resulting in venous occlusion (HULSBERG et al., 2016; MENARD et al., 2002; MACEDO et al., 2018).

The stent migration rate described in all reported cases is 7.3% (MACEDO et al., 2018), hence, there is a need for more concrete evidence and theoretical knowledge about NCS.

Methodology

This is a literature review, conducted by consulting articles published in English, Spanish, and Portuguese on database platforms (Lilacs and Medline).

Studies published between 2010 and 2020 were included that contained the keywords: "Nutcracker Syndrome", "complications", "treatment", "endovascular", "stent" and their corresponding terms in English.

Articles that could not be fully viewed, published before 2010, and restricted to posterior Nutcracker Syndrome were excluded.

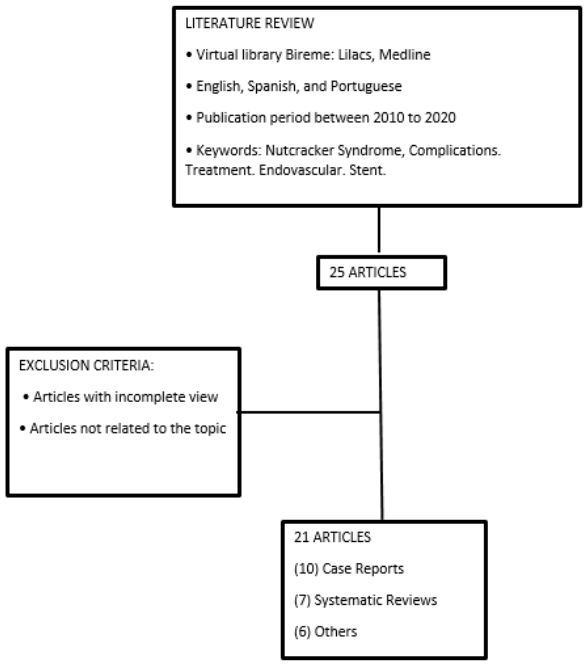

Figure 1 - Flowchart of the methodology employed

Review:

Nutcracker Syndrome is a rare vascular anomaly with significant clinical implications. It arises from the compression of the LRV by the SMA as it passes between it and the abdominal aorta, due to the reduced angle between both arteries (Figure 2). Such condition has as predisposing factors left nephroptosis with secondary compression of the LRV over the aorta, excessive fibrous tissue in the aorto-mesenteric angle, lumbar hyperlordosis and reduction of perirenal fat volume (GAUDIANO et al., 2015), in addition to being associated with a low body mass index (HANSRAJ et al., 2017).

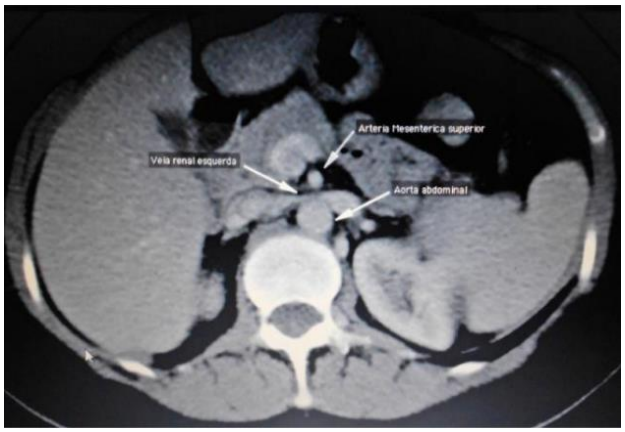

Figure 2 - Angiotomography showing the compression of the left renal vein by the superior mesenteric artery.
Source: http://www.scielo.br/pdf/jvb/v12n3/1677-5449-jvb-12-03-00247.pdf

The condition can be presented at any age, with peaks in young patients (due to the restriction of the angle between the aorta and the SMA due to the rapid development of the vertebral bodies and height gain

during puberty) and middle-aged adults, with equal prevalence between sexes (AGLE et al., 2019).

There is little description in the medical literature regarding this syndrome, first described in 1950 (PALACIOS; MARTÍNEZ; HERNÁNDEZ, 2018; GAUDIANO et al., 2015; CHEN et al., 2019), due to the infrequency of its diagnosis, both due to its low incidence and the difficulty in suspecting it in front of its signs and symptoms common in other differential diagnoses such as renal colic, glomerulonephritis, endometriosis, primary varicocele, malformation of the renal pelvis and pelvic venous incompetence (ALCOCER-GAMBA et al., 2012; ERBEN et al., 2015; ANDRADE; LAVANDEIRA, 2017; AGLE et al., 2019).

It presents a clinical picture composed of abdominal pain and left flank pain, macroscopic hematuria, microscopic hematuria, proteinuria, and varicocele. (VELASQUEZ et al., 2018; SHI; SHI; LI; CHEN; TANG; HUANG, 2019; PALACIOS; MARTÍNEZ; HERNÁNDEZ, 2018; CHEN et al., 2019; POLICHA et al., 2016).

Despite the findings in the literature not being very voluminous, there is evidence of cases of asymptomatic carriers of the syndrome. Therefore, more frequent conditions such as urinary tract infection, nephritis, kidney stones, endometriosis and autoimmune diseases with abdominal pain should initially be ruled out from a well-described clinical history, physical examination and additional tests such as hematuria, urine culture and urine cytology in order to exclude malignant or infectious causes. A characteristic of the syndrome is non-dysmorphic hematuria, that is, of non-glomerular origin, due to the rupture of dilated pelvic and paraurethral veins (GONZÁLEZ; VILLALBA; LÓPEZ, 2019).

Currently, ultrasound with renal vein Doppler is the most used initial evaluation exam and according to the literature, it has a sensitivity of 69-90% and a specificity of 89%-100% (VELASQUEZ et al., 2018; ERBEN et al., 2015; GONZÁLEZ; VILLALBA; LÓPEZ, 2019; POLICHA et al., 2016), in identifying the vascular alteration of this syndrome. Ultrasound allows real-time evaluation of flow speeds and peak within the lumen of the LRV, and also allows visualization of the compressive process of the SMA on the LRV. As a diagnostic criterion, it is defined that the ratio between the peak systolic speed of the aorto-mesenteric segment and the hilar portion should be greater than 4.2 to 5.0 (VELASQUEZ et al., 2018; QUEVEDO; ARAIN; RAFEH, 2014). The disadvantages of this method are the variability with the patient's postural change, small sampling area, and examiner's ability dependence.

Other methods such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) can be used to demonstrate other changes such as dilation of the gonadal vein and pelvic congestion (VELASQUEZ et al., 2018), collateral circulation in the renal hilum, early opacification of the left gonadal vein (inferring reflux), and reduction of the aortomesenteric angle (< 10º) (MACEDO et al., 2018), "beak sign" or beak sign (described as an abrupt narrowing of the aortomesenteric angle) (HANSRAJ et al., 2017) and branching angle of the SMA less than 35º-45º (VELASQUEZ et al., 2018; MACEDO et al., 2018) in relation to its origin in the aorta (Figure 3), which are useful in diagnosing NCS. (VELASQUEZ et al., 2018).

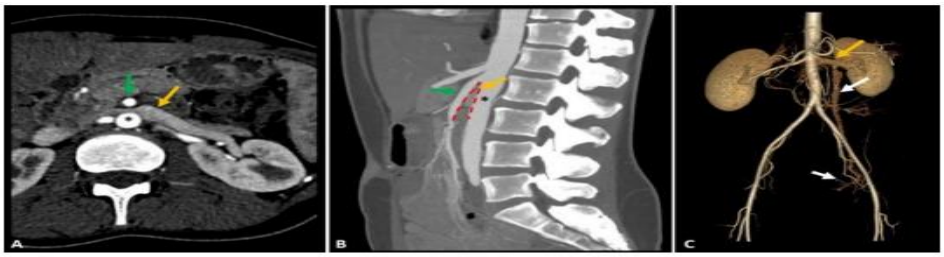

Figure 3 - Narrowing of the LRV (yellow arrow) between the aorta (black asterisk), SMA (green arrow) with an aortomesenteric angle (red dotted line) of 20 ° and distension of the LGE (white arrow).
Source: https://epos.myesr.org/

Venography with renal vein pressure gradient measurement is the gold standard method (HANSRAJ et al., 2017; MACEDO et al., 2018), but because it is an invasive procedure, it is left as a late option for diagnosis. It allows the calculation of parameters such as the presence of collateral vessels and increased pressure gradient, which is classified as normal (less than 1mmHg), borderline (1-3mmHg) and hypertension (greater than 3mmHg), between the left renal vein and the inferior vena cava (ANDRADE; LAVANDEIRA, 2017), the surface area of the stenosis, the percentage of narrowing, and the degree of post-stenosis dilation (HANSRAJ et al., 2017). High pressure gradients, with widening of the left renal vein, are associated with the development of subcapsular and retroperitoneal collateral circulation.

The dissipation of the high pressure gradient is achieved through collateral circulation, but the fragility of the formed venous wall can predispose to

rupture of the septum between the small veins and the collecting system, causing hematuria and abdominal and left flank pain (ALCOCER-GAMBA et al., 2012). In addition, the method is useful for planning stent placement, as it allows measurement of the diameter of the left renal vein (VELASQUEZ et al., 2018).

According to bibliographic data (Figure 4), the findings most related to the diagnostic confirmation of the syndrome are: The existence of a venous gradient between the left renal vein and the inferior vena cava (IVC) ≥ 3 mmHg TAK; An increase of five times in the maximum flow speed in the left renal vein when passing by the superior mesenteric artery compared to the renal hilum; AngioCT or AngioMRI with an angle between the aorta and the superior mesenteric artery less than 35°- 45° (MACEDO et al., 2018). The decision about the best imaging method to be used in the diagnosis should relate to the characteristics of each patient such as urgency of the diagnosis, exposure to radiation, cost and accessibility of the examination, other non-vascular abdominal diagnostic suspicions, among others.

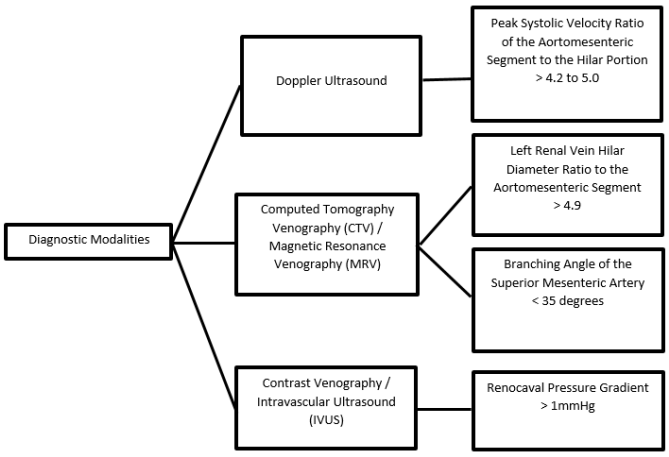

Figure 4 - Diagnostic Modalities for Nutcracker Syndrome
Source: Adapted by the authors from VELASQUEZ et al., 2018

The management of Nutcracker Syndrome (NCS) depends on the severity of symptoms and can range from conservative and observational for patients with mild and tolerable symptoms, especially in young individuals, as spontaneous resolution can occur with growth and weight gain, leading to increased retroperitoneal fat and a change in the position of the left kidney and an increase in the aortomesenteric angle. It is recommended to maintain non-surgical treatment for at least 2 years for this patient group, as 75% of patients under 18 years old will experience complete resolution of hematuria (YILDIZ et al., 2014; POLICHA et al., 2016; GONZÁLEZ; VILLALBA; LÓPEZ, 2019).

Similarly, asymptomatic patients with incidental findings of left renal vein compression or those with mild symptoms should initially be managed conservatively for at least 24 months, as up to one-third of patients may experience symptom resolution (YILDIZ et al., 2014; HANSRAJ et al., 2017; ERBEN et al., 2015; PALACIOS; MARTÍNEZ; HERNÁNDEZ, 2018; AGLE et al., 2019).

Among the different surgical techniques mentioned, distal transposition of the left renal vein (LRV) to the inferior vena cava (IVC) has been performed more frequently and has shown to be safe and effective, despite intraoperative complications such as those resulting from left renal artery clamping during the procedure, which can lead to renal ischemic injury (YU et al., 2019), as well as postoperative complications such as paralytic ileus or retroperitoneal hematoma. The second most commonly performed open surgical technique is reimplantation of the proximal end of the left gonadal vein (LGV) into the IVC to improve renal venous flow and orthotopic kidney transplantation (CHEN et al., 2019; VELASQUEZ et al., 2018).

Endovascular stenting (Figure 5) or external stenting are recently applied treatment options with increasing frequency in recent years as a minimally invasive alternative, showing favorable outcomes and lower morbidity. However, their long-term efficacy and safety need to be established, even though recent studies on the subject have demonstrated promising results (YILDIZ et al., 2014; ALCOCER-GAMBA et al., 2012; TIAN et al., 2015; LI et al., 2014).

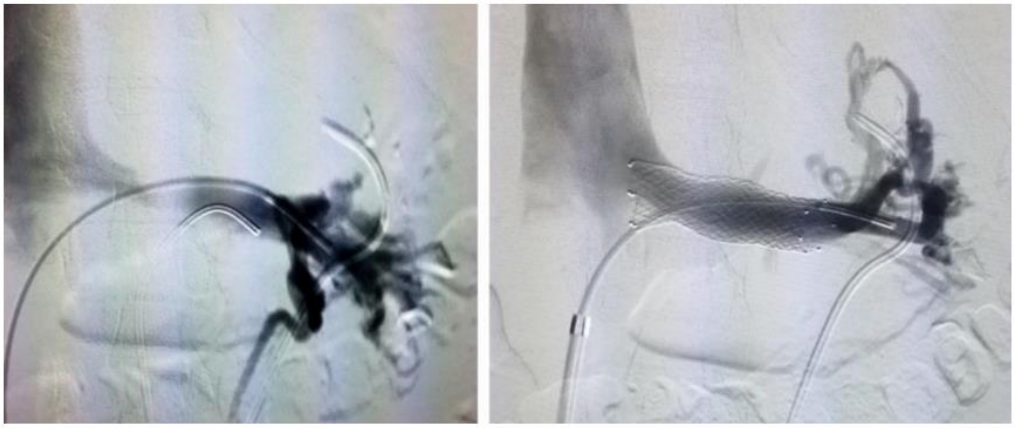

Figure 5 - Positioning of the stent in the left renal vein.
Source: http://www.institutoendovascular.com.br/blog/sindrome-quebra nozesnuctcracker-syndrome/

The endovascular VRE stent for the treatment of NCS (Figure 6) was first described by Neste et al. in 1996 (POLICHA et al., 2016) and has become an increasingly popular intervention method among specialists for NCS treatment. This trend is attributed to the advantages of shorter periods of renal congestion, reduced possibility of complications, and absence of extensive dissection required in surgical approaches (MACEDO et al., 2018).

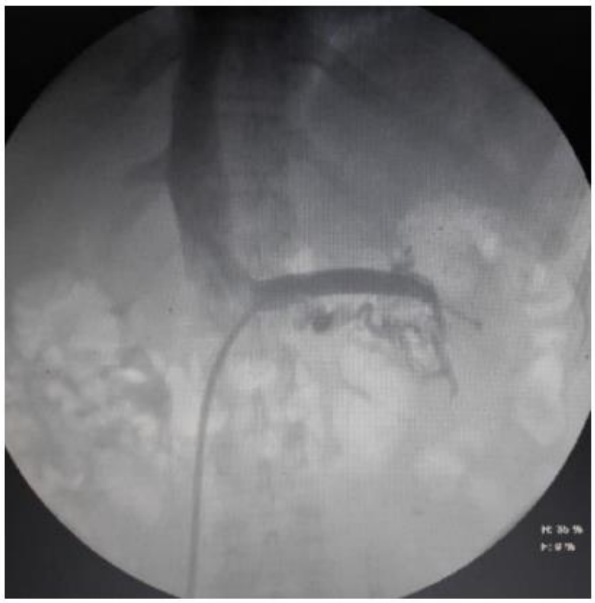

Figure 6 - Post-procedure venography
Source: http://www.scielo.br/pdf/jvb/v12n3/1677-5449-jvb-12-03-00247.pdf

The VRE (Venous Nutcracker Syndrome) presents anatomical challenges for endovascular procedures, such as a large diameter and reduced length. Consequently, there is a limited availability of properly designed self-expanding stents for this anatomy (RANA; ODERICH; BJARNASON, 2013). To ensure proper stent positioning, it must have high radial force to eliminate the stenosis, good conformability to adapt to the vessel's epithelium, and minimal length retraction (MACEDO et al., 2018; HANSRAJ et al., 2017; QUEVEDO; ARAIN; RAFEH, 2014).

For a higher chance of success in the procedure, obtaining accurate measurements of the VRE's diameter is recommended to facilitate stent size selection. Intravascular ultrasound is used as a method for this determination (POLICHA et al., 2016). There are also recommendations for performing the Valsalva maneuver during intravascular ultrasound to obtain individual anatomical parameters, as the VRE diameter increases by 50% to 58% during the maneuver (WU et al., 2016).

However, despite some studies highlighting the relevance of obtaining precise preoperative characteristics of the VRE, there is discussion regarding standardizing a baseline stent size based on population studies with Western and Eastern patients. In Western patients, a preference is given to a 16mm diameter by 60mm length stent, while in Eastern patients, a 14mm diameter by 60mm length stent is recommended. This difference is due to smaller anatomical proportions in the latter population. Moreover, it is recommended that the stent be approximately 20% larger than the venous diameter at the renal hilum to prevent migration (POLICHA et al., 2016; WU et al., 2016; MACEDO et al., 2018), a key factor to avoid migration. Additionally, it was concluded that the risk of migration is proportional to a larger anteroposterior diameter of the stenotic portion of the VRE (WU et al., 2016).

There are controversies regarding the use of balloon dilation. Some authors suggest using it only in cases where the stenosis persists even after stent insertion (MACEDO et al., 2018), while others prefer to use it whenever possible for better stent positioning (POLICHA et al., 2016).

Regarding venoplasty, it is not recommended before stent placement due to the mechanism of the syndrome being related to mechanical compression rather than

primary VRE stenosis. However, if there is difficulty in passing through the stenosis, selective venoplasty can be considered (POLICHA et al., 2016).

There is no standardization on anticoagulants or antiplatelet medications to improve stent patency (POLICHA et al., 2016; HANSRAJ et al., 2017). However, it is known that the use of these medications is necessary for 2 to 3 months, the time required for complete stent endothelialization (MACEDO et al., 2018; HANSRAJ et al., 2017; AGLE et al., 2019).

The mentioned recommendations are important to avoid complications. Continuous follow-up is essential for the early detection and treatment of possible complications (WU et al., 2016), including restenosis, local fibromuscular hyperplasia, erosion, and VRE thrombosis or occlusion, as well as stent migration, which can occur not only in the early stages after placement (PALACIOS; MARTÍNEZ; HERNÁNDEZ, 2018; RANA; ODERICH; BJARNASON, 2013; HANSRAJ et al., 2017; QUEVEDO; ARAIN; RAFEH, 2014; LI et al., 2014).

The most common causes of recurrence of signs and symptoms are thrombosis and restenosis, which can be treated with endovascular thrombolysis, angioplasty, and stent (HANSRAJ et al., 2017). Among such complications, stent migration is the most severe. The most frequent anatomical sites for stent impaction after migration are the pulmonary artery, right atrium, right ventricle, and proximal inferior vena cava (VCI). There are reports of severe complications such as myocardial perforation, pulmonary infarction, acute tricuspid insufficiency, and acute myocardial infarction. Although most patients are asymptomatic at the time of migration diagnosis (RANA; ODERICH; BJARNASON, 2013), there have been reports in the literature of chest pain, flank pain, and gross hematuria (WU et al., 2016).

Regarding stent migration, the management choice should include determining the precise location and anatomy of the dislodged stent, the type of stent, the need to intervene at the affected site, and more severe complications that may require more specific interventions. Percutaneous endovascular removal is the preferred technique for resolving stent migration as it has lower potential for morbidity compared to open removal (MACEDO et al., 2018; TIAN et al., 2015). Extravascular stenting is an alternative option recommended after endovascular stent migration in the left renal vein (TIAN et al., 2015).

The placement of endovascular VRE stents seems to offer equally good short-term results. However, for a characteristically young population of patients in the long term, it has not yet been determined. Improvements in venous stent technology are expected and will likely result in the endovascular treatment of most NCS cases in the future (POLICHA et al., 2016).

Conclusion: In conclusion, Nutcracker Syndrome is a rare condition, and its diagnosis is infrequent due to both its low incidence and the difficulty in suspecting it because of nonspecific clinical findings. Among the various possible treatments, the endovascular approach has become an attractive alternative due to its minimally invasive nature. However, it is not without failures, with the main ones being stent migration to the hilum of the VRE and the right atrium, and incorrect stent placement. Other less reported complications include stent embolization, thrombosis, intra-stent and vessel restenosis resulting in venous occlusion.

Another notable characteristic is the scarcity of long-term follow-up studies. Therefore, given the complications presented, individualized stent choice and follow-up are essential for reducing the incidence of complications. Additionally, it is concluded that there is a need for the development of a dedicated venous stent for NCS treatment and an improvement in theoretical knowledge related to the subject.

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