Outcomes of left renal vein stenting in patients with nutcracker syndrome

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ABSTRACT

Background: Nutcracker syndrome (NCS) is a rare condition that can be manifested with hematuria, flank pain, pelvic varicosities, or chronic pelvic congestion related to left renal vein (LRV) compression. Open surgery, specifically LRV transposition, has been the mainstay of treatment, but in the past few years, LRV stenting has emerged as a less invasive alternative without sufficient evidence to support it. This study aimed to assess outcomes of renal vein stenting in the treatment of NCS.

Methods: A retrospective chart review of patients with NCS who underwent LRV stenting between 2010 and 2018 was performed. End points were perioperative adverse outcomes, symptom relief, and stent patency. Symptom resolution was classified as complete, partial, and none on the basis of the interpretation of medical records on clinical follow-up. Standard descriptive statistics and survival analysis were used.

Results: Eighteen patients (17 female; mean age, 38.1 ± 16.9 years) diagnosed with NCS and treated with LRV stenting were identified. Five of these had a prior LRV transposition that had failed within a mean of 7.0 ± 4.9 months, manifested by symptom recurrence (or no improvement) along with imaging evidence of persistently severe renal vein stenosis. Twelve patients had coexisting pelvic congestion syndrome treated with gonadal vein embolization. The most frequent sign and symptom were hematuria (10/18 patients) and flank pain (15/18 patients), respectively. All patients received self-expanding stents (mean diameter, 12.8 ± 1.6 mm), the smaller ones typically placed in the previously transposed LRVs. No perioperative complications occurred. Nine patients were discharged on the same day; the remaining patients stayed longer for pain control (mean hospital stay, 1.0 ± 1.3 days). At an average follow-up of 41.4 ± 26.6 months, 13 (72.2%) patients had symptoms resolved or improved (9 complete, 4 partial). Three of the five patients whose symptoms remained unchanged had previous LRV transposition surgery, and two of these three patients eventually required renal autotransplantation. Six of 10 patients who presented with hematuria had it resolved. Three patients underwent a stent reintervention at 5.8 months, 16.8 months, and 51.7 months because of symptom recurrence or stent restenosis. The two early ones required balloon venoplasty and the third one restenting. Two-year primary and primary assisted patency was 85.2% and 100%, respectively. No stent migration occurred.

Conclusions: Endovascular treatment with renal vein stenting is safe, providing encouraging results with good midterm patency rates and symptom relief. Minimally invasive approaches may have a potential role in the treatment of NCS. Larger series and longer follow-up are needed to better assess the comparative performance against LRV transposition. (J Vasc Surg: Venous and Lym Dis 2019;7:853-9.)

Keywords: Nutcracker syndrome; Left renal vein compression; Left renal vein transposition; Left renal vein stenting

Nutcracker syndrome (NCS) is a rare condition of left renal vein (LRV) compression that can be manifested with debilitating flank pain, hematuria, pelvic varicosities, or chronic pelvic congestion. Treatment of NCS is indicated when patients are symptomatic, and it should generally be guided by the severity of symptoms and the patient's age and implemented after all other possible diagnoses have been ruled out.[1-4] The aim of any NCS intervention is to reduce LRV hypertension, pelvic venous reflux, and eventually the associated symptoms.

Open surgery, specifically LRV transposition, has been the mainstay of treatment, but in the past few years, LRV stenting has emerged as a less invasive alternative without sufficient evidence to support it.[2,4-7] The proposed rationale, except for its minimally invasive nature, is that venous stenting in similar clinicoanatomic diseases, such as May-Thurner syndrome, is used as primary therapy with excellent outcomes.[8] Our study aimed to assess outcomes of LRV stenting in the treatment of NCS.

METHODS

The study protocol was reviewed and approved by the Institutional Review Board of the University of Pittsburgh.

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Study design. A retrospective chart review of consecutive patients with NCS who underwent LRV stenting between 2010 and 2018 was performed. Five of our LRV transposition patients who were then stented were included in our analysis. Patients who underwent LRV transposition alone were excluded from the analysis. Medical records were reviewed for patients' demographics, baseline characteristics and risk factors, venous imaging studies, indications, intraprocedural notes, periprocedural complications, and long-term outcomes.

End points were perioperative outcomes, symptom relief, and stent patency. Symptom resolution was classified as complete, partial, and none on the basis of the interpretation of the follow-up medical records.

Preprocedural protocol. All patients thought to have NCS have typically undergone computed tomography venography of the abdomen and pelvis and duplex ultrasound imaging of the LRV. Invasive venography was used in all patients, often with renocaval pressure gradient measurements and more recently intravascular ultrasound (IVUS) for confirmation of renal vein compression before stenting it. Invasive venography was accompanied by diagnostic IVUS in 11 (61%) patients, which confirmed renal vein stenosis or compression.

The decision to treat with primary or secondary (after a failed LRV transposition) stenting was based on the physician's preference after a thorough discussion with the patient. Stenting was typically performed in the same setting as diagnostic venography. Coexisting pelvic congestion was treated simultaneously or as a first-stage procedure, and on symptom persistence, LRV stenting followed. As a general rule, with predominantly pelvic congestion syndrome (PCS) symptoms, PCS is treated first; with predominantly NCS symptoms, NCS is treated first. We typically wait, and if there is no improvement within 6 to 12 months, further intervention is considered.

Technique. All interventions were performed by vascular surgeons in endovascular suites equipped with fixed imaging capability. Our technique has evolved over the years, but it can be summarized as follows. Under local anesthesia and moderate sedation, percutaneous access of the right common femoral vein is obtained and selective catheterization of the LRV is performed. Confirmation of the diagnosis can be made on venography (using Valsalva maneuver) by visualization of washout and well-developed collaterals as well as by renocaval pressure gradient measurements (≥3 mm Hg). In equivocal cases, IVUS can be invaluable not only to establish the diagnosis through pullback imaging but also to obtain measurements of the renal vein diameter for proper stent sizing. After heparinization, a stiff wire is directed into the renal vein branches (or into the left ovarian vein) to allow sufficient purchase for sheath delivery. After balloon predilation, a self-expanding stent, typically Wallstent (Boston Scientific, Natick, Mass) or Protégé EverFlex (Medtronic, Plymouth, Minn), 12 to 16 mm in diameter and 4 to 6 cm in length, is then deployed and postdilated.

All 18 patients underwent diagnostic venography generally with pressure gradient measurements, and 11 also underwent IVUS before stenting. In these 11 patients, completion IVUS was likewise used after stent placement and confirmed resolution of the stenosis. Fig 1 shows venography and IVUS images before and after stenting of the LRV after previously failed LRV transposition.

We gradually shifted from smaller to larger stents to prevent migration and future restenosis. Partial protrusion of the stent into the IVC does not seem to cause any complication and is generally advocated. Distal landing of the stent just beyond the first large branch of the LRV has been suggested to reduce the risk of migration.[3,9,10] However, the long-term implications of stent placement across the first large branch on renal function and symptom recurrence are not well known. Anecdotally, these large stents expanded inside smaller renal vein branches can disrupt them in the long term, so we have shifted away from distal branch landing. The deployed stent is postdilated to the desired diameter, and IVUS can again be used to confirm appropriate landing and lack of residual stenosis. Antiplatelet therapy is our preferred postoperative regimen, dual (aspirin 81 mg and clopidogrel 75 mg) for 1 to 3 months and baby aspirin (81 mg) indefinitely.

Follow-up. Patients were followed up at 1 month, 3 months, 6 months, and 12 months and annually thereafter for clinical evaluation and duplex ultrasound imaging to assess LRV patency.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** Renal vein stenting in 18 patients diagnosed with nutcracker syndrome, in five after failed left renal vein transposition, resulted in good midterm outcomes without any major complications. Partial or complete symptom relief occurred in 13 (72.2%) patients. Three patients underwent stent reintervention because of symptom recurrence or stent restenosis. Two-year primary and primary assisted patency was 85.2% and 100%, respectively. No stent migration occurred.
- **Take Home Message:** Endovascular treatment with renal vein stenting is safe, providing encouraging results with good midterm patency rates and symptom relief, and may have a potential role in the treatment of nutcracker syndrome.

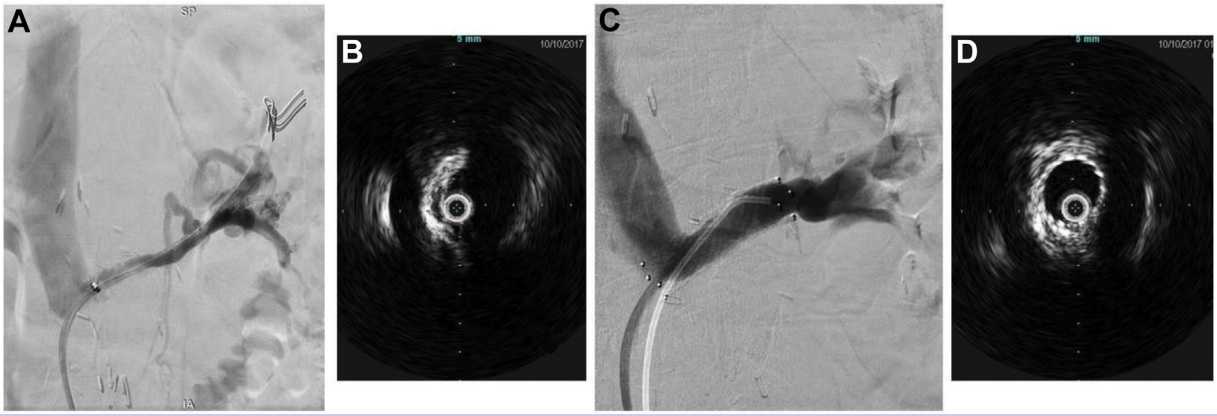

Fig 1. A 27-year-old woman with prior left renal vein (LRV) transposition and symptom recurrence. **A,** Prestenting venogram of the LRV. **B,** Prestenting intravascular ultrasound (IVUS) image showing tight stenosis at the midrenal vein (tethered by the underlying aorta). **C,** Venogram after stenting with a 14- × 60-mm Wallstent. **D,** IVUS after stenting and balloon venoplasty showing the widely patent stent in the LRV.

Statistical analysis. Descriptive characteristics are reported as mean ± standard deviation or as number of cases and percentages. Kaplan-Meier analysis was used to describe the proportion of those whose LRV remained patent with follow-up. Results were considered statistically significant when *P* value was <.05. Data were analyzed using Statistical Package for the Social Sciences, version 17 (SPSS Inc, Chicago, Ill).

RESULTS

Eighteen patients (17 female; mean age, 38.1 ± 16.9 years) diagnosed with NCS and treated with LRV stenting were identified. The mean body mass index was 21.2 ± 4.0 kg/m^2 (range, 16.3-31.9 kg/m^2). Symptom duration had varied between a few months and several years. In general, female patients were first assessed by their gynecologists or urologists or by gastroenterologists if atypical gastrointestinal symptoms were predominant, although more recently, there has been better disease awareness and a trend toward faster referrals to vascular surgeons.

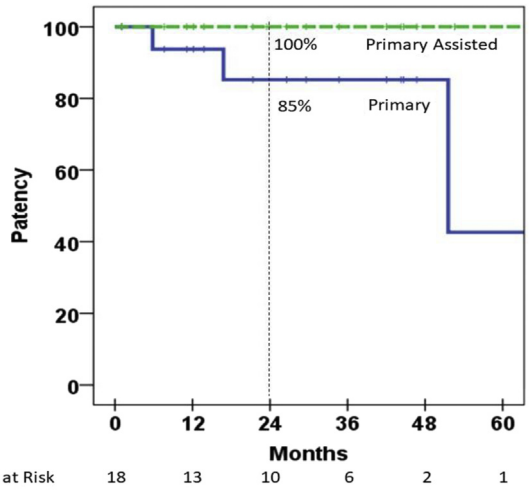

Fig 2. Primary and primary assisted patency of left renal vein (LRV) stenting.

The most frequent sign and symptom were hematuria (10/18 patients) and flank pain (15/18 patients), respectively. Other commonly reported symptoms included chronic pelvic pain with associated dyspareunia or dysmenorrhea (n = 12) and atypical gastrointestinal pain or symptoms with decreased appetite or weight loss (n = 8). Seven patients had evidence of pelvic varicosities on imaging, generally with complaints of bothersome varices in the lower abdomen or proximal-medial thigh or genital region. On physical examination, these varices were often visible and sometimes even painful on palpation. Five patients had prior LRV transposition surgery, but it had failed within a mean of 7.0 ± 4.9 months. Failure was defined as symptom recurrence (or no improvement) along with imaging evidence of severe renal vein stenosis.

Twelve patients had coexisting PCS treated with gonadal vein embolization, six in the same setting and six as staged procedures. All patients received self-expanding stents (mean diameter, 12.8 ± 1.6 mm), with the smaller ones typically placed early in our experience or in previously transposed LRVs. No perioperative complications occurred. Nine patients were discharged on the same day; the remaining patients stayed longer for pain control (mean hospital stay, 1.0 ± 1.3 days).

At an average follow-up of 41.4 ± 26.6 months, 13 (72.2%) patients had symptoms resolved or improved (9 complete, 4 partial). Three of the five remaining patients whose symptoms remained unchanged had a history of previous LRV transposition surgery, and two of these three patients eventually required renal autotransplantation because of debilitating symptoms despite patent stents. After renal autotransplantation, symptoms partially improved in one patient but remained severe

Table. Summary of procedural details and outcomes of patients

Patient No.	Sex/age, years	Clinical manifestation	Prior LRV transposition	Stent size, mm	Stent type
1	M/23	Hematuria, flank pain, varicocele, ureteral colic, weight loss	Yes	14 × 40	Protégé EverFlex
2	F/21	Flank pain, chronic pelvic pain, weight loss	No	12 × 40	Self-expanding
3	F/50	Flank pain, chronic pelvic pain, pelvic varicosities	No	12 × 40	Protégé EverFlex
4	F/25	Flank pain, chronic pelvic pain, nausea/vomiting	Yes	14 × 40	Protégé EverFlex
5	F/33	Flank pain, pelvic varicosities, abdominal pain	No	10 × 40 and 10 × 30	SMART
6	F/24	Hematuria, flank pain, ureteral colic, chronic pelvic pain, nausea	No	12 × 30	Protégé EverFlex
7	F/21	Hematuria, flank pain, proteinuria	Yes	12 × 30	Protégé EverFlex
8	F/50	Chronic pelvic pain	No	12 × 40 and 12 × 40	SMART
9	F/36	Hematuria, chronic pelvic pain, pelvic varicosities, weight loss	No	12 × 30	Protégé EverFlex
10	F/55	Hematuria, flank pain, chronic pelvic pain, lower limb varices	No	12 × 30	Protégé EverFlex
11	F/26	Hematuria, flank pain, dysuria, chronic pelvic pain, proteinuria	Yes	14 × 60	Wallstent
12	F/51	Flank pain	No	12 × 40	SMART
13	F/39	Flank pain, pelvic varicosities, weight loss	Yes	10 × 40	Zilver
14	F/69	Hematuria, flank pain, chronic pelvic pain	No	14 × 40 and 14 × 40	ev3, SMART
15	F/30	Chronic pelvic pain, pelvic varicosities	No	14 × 60	Wallstent
16	F/19	Hematuria, flank pain, chronic pelvic pain, frequent UTI	No	14 × 60	Wallstent
17	F/38	Hematuria, flank pain, chronic pelvic pain	No	16 × 40	Wallstent
18	F/76	Hematuria, flank pain, chronic pelvic pain, lower limb varices	No	14 × 40	Protégé EverFlex

LRV, Left renal vein; *UTI*, urinary tract infection.
[a]Indicates time to last ultrasound follow-up. Whenever a reintervention was done, the follow-up reported indicates the timing of the reintervention.

in the other. As for the two remaining patients whose symptoms were unchanged after stenting, one was later diagnosed with endometriosis and the other remained undiagnosed.

Of the 10 patients who had hematuria on presentation, six had it resolved after LRV stenting. Five of the eight patients who complained of atypical gastrointestinal pain or other symptoms had them resolved on follow-up; in the remaining three patients, these symptoms persisted.

Three patients underwent a stent reintervention at 5.8 months, 16.8 months, and 51.6 months because of symptom recurrence or stent restenosis. The two early ones required balloon venoplasty and the third one restenting. Two-year primary and primary assisted patency was 85.2% and 100%, respectively (Fig 2). No stent migration occurred. Procedural details and outcomes for all patients are summarized in the Table.

DISCUSSION

Endovascular treatment of NCS is an appealing alternative to open surgery. However, there is paucity of evidence and lack of long-term follow-up, making it difficult to recommend it as a definite best treatment option for patients with NCS. Our study demonstrated safety and midterm efficacy of LRV stenting both as a primary treatment option and secondary to recurrent compression after LRV transposition.

Table. Continued.

Predilation/postdilation balloon diameter, mm	Symptom relief	Reinterventions	Follow-up, months[a]	Outcome
12/12	No	Renal autotransplantation	12.1	Symptoms persisted; cause unknown
8/12	Complete	None	46.7	Symptom and restenosis free
—/12	Complete	None	29.6	Symptom and restenosis free
6/10	Complete	None	65.1	Symptom and restenosis free
—/10	No	None	44.7	Symptoms persisted; cause unknown
8/12	Complete	None	2.57	Symptom and restenosis free
—/12	Partial	Restenting	51.6	Partial symptom relief; restenosis free at 52.5 months
—/12	Complete	None	44.3	Symptom and restenosis free
—/12	Complete	None	7.6	Symptom and restenosis free
—/12	Complete	None	1.1	Symptom and restenosis free
10/14	No	None	13.8	Symptoms persisted; diagnosed with endometriosis
8/12	Complete	None	42.0	Symptom and restenosis free
6/8	No	Balloon venoplasty, then renal autotransplantation	16.8/23.5	Partial symptom relief after autotransplantation at 26.1 months; diagnosed with loin pain-hematuria syndrome
10/14	Partial	None	11.3	Partial symptom relief; restenosis free
—/12	Complete	None	21.4	Symptom and restenosis free
—/12	No	None	26.6	Symptom worsened and persisted after pregnancy; diagnosed with endometriosis
—/16	Complete	Balloon venoplasty	5.8	Symptom and restenosis free at 74.7 months
—/14	Complete	None	3.0	Symptom and restenosis free

Renal vein transposition is undisputedly the current standard of care and is the most commonly used interventional management of patients for the treatment of NCS, with immediate success rates (symptom resolution) of roughly 90%.[5-7] Although generally low risk, it remains a maximally invasive procedure, making it particularly unfavorable to the targeted, typically young female patient. Reported complications include renal vein thrombosis, lower extremity deep venous thrombosis, retroperitoneal hematoma requiring surgical re-exploration, prolonged paralytic ileus, and longer term mechanical ileus.[5,6] Even if these complications are rare, symptom recurrence and need for intervention are not that rare. In the Mayo series of 36 patients, freedom from reintervention due to LRV (or ovarian vein) stenosis or occlusion after open surgery was 76% and 68% at 12 and 24 months, respectively.[5] Many of these reinterventions included LRV stenting.

The use of stenting in the management of NCS has rapidly expanded during the past 10 years, and mainly Asian centers with extensive experience with both open and endovascular management advocate it as a primary option.[3,9-11] In the two large retrospective series from China, symptom relief was achieved in 59 of 61 and 30 of 30 patients, with no significant restenosis at a median 66 months and 36 months of follow-up, respectively.[9,10] The largest published Western series comes from France and is one of the earliest ones reported in

the literature; Hartung et al[12] described five patients who underwent successful LRV stenting, but during an average 14 months of follow-up, only two patients were symptom or intervention free. Multiple recent smaller series or cases reports typically refer to excellent results, but their value cannot be appreciated.[4,13-15]

Renal vein stenting is not without risks, however, and reported complications related to stent migration can be devastating, the most significant of which is stent migration to the vena cava and the heart.[16,17] Wu et al,[11] in their updated series of 75 patients, reported a 7% migration rate attributed to inappropriate diameter or sizing and therefore concluded that stent migration may not be as rare a complication. Still, in all these large Asian series, balloon predilation or postdilation was not done routinely, which may have added to the migration risk.[7,9-11] We have been regularly ballooning before and after stenting and have not yet experienced any case of stent migration. Long-term stent patency is another point of controversy, although experience from the iliac vein stenting[8] and permanent vena cava filter[18] literature is promising. The vascular surgery community has long acknowledged the efficacy of stenting in nonthrombotic compressive iliac vein lesions, and the pathologic process of NCS may be no different.[2,8]

Our experience of 18 patients has been overall positive, with no adverse events and three stent-related endovascular reinterventions within a reasonable midterm follow-up. Symptoms improved or resolved in 72%. Specifically, hematuria fully resolved in 60%. Persistence of hematuria has also been reported in patients who underwent surgery and has been attributed to the chronic LRV hypertension and renal parenchymal vascular alterations.[6,19] Our experience mirrors a contemporary mature deep venous practice that has incorporated the evolving knowledge in the field. In today's practice, stents are typically 14 to 16 mm in diameter and 6 cm in length but can be smaller for restenosis after LRV transposition. To avoid subjective estimates, IVUS incorporation improves accuracy of LRV diameter measurement and lesion localization. Whereas others have suggested anticoagulation for 3 months, our dual antiplatelet protocol for 1 to 3 months did not seem to compromise outcomes. It may be reasonable to consider lifelong aspirin.

Limitations of our study are inherent in its retrospective nature, the small sample, and the lack of long-term follow-up. Selection of patients was arbitrary based on the physician's preference, and the technique has not been standardized yet. It represents, though, the contemporary practice of a tertiary Western center and balances the large experience shared by our Asian colleagues. Moreover, the study group was heterogeneous. A substantial portion of the female patients were also treated with gonadal vein embolization because of coexisting PCS, which makes the independent assessment of renal vein stenting outcomes more difficult.

CONCLUSIONS

Although surgery continues to be the "gold standard" for patients with NCS, the endovascular minimally invasive option is gaining ground with encouraging results and should be presented to patients as a viable alternative, acknowledging the uncertain long-term outcomes and associated risks. There is little doubt that endovascular treatment may be the best alternative in patients with restenosis or persistent compression after LRV transposition. Larger series and longer follow-up are needed.

AUTHOR CONTRIBUTIONS

Conception and design: EA, MS, EH, MM, RC
Analysis and interpretation: EA, ZS
Data collection: ZS, RH, KS
Writing the article: EA, ZS, RH, RC
Critical revision of the article: EA, KS, MS, EH, MM, RC
Final approval of the article: EA, ZS, RH, KS, MS, EH, MM, RC
Statistical analysis: ZS
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Overall responsibility: EA

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