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Renal Nutcracker Syndrome: A Case Series and Systematic Review of an Uncommon and Underdiagnosed Condition

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Abstract

Renal Nutcracker syndrome (NCS) is a rare cause of chronic abdominal pain. We present a case series about nut-cracker syndrome including 38 cases. Left flank pain was the most common pre-senting symptom (79%). The most utilized imaging was computed tomography (CT) (94.7%). The most common position for nutcracker syndrome was anterior (87.3%). Nutcracker syndrome should be considered in females with unspecified chronic abdominal pain. It is well known to be caused by a compression of left renal vein. A high level of suspicion and accurate preoperative imaging including a CTA can aid in diagnosis. Minimally invasive surgical treatment is feasible.

Keywords: Vascular Surgery, Abdominal Pain, Hematuria, Renal Vein, Renal Nutcracker Syndrome.

Introduction

A constellation of symptoms secondary to left renal vein (LRV) compression was first described in the 1950s and coined "Nut-cracker syndrome" in 1972. Renal nutcracker syndrome (NCS) is a rare cause of chronic pain, hematuria, and urogenital issues. Compression of the LRV is most of-ten anterior, between the superior mesenteric artery (SMA) and abdominal aorta. NCS also oc-curs from posterior compression of the LRV between the aorta and vertebral column [1]. Patients typically present with chronic left flank, pelvic, or abdominal pain. Other symptoms include he-maturia, nausea, vomiting, weight loss, and pelvic congestion syndrome. Failure to diagnose NCS in the presence of these non-specific symptoms often leads to referrals to years of ineffective pain treatment, including referral to pain special-ists, opioids, and nerve stimulators.

This review examined case reports and case series of NCS over the past 10 years to highlight which symptoms are most com-mon, the diagnostic workup, and proper management of NCS.

Overall, we include 40 case reports and series in addition to our own series [2-41].

Methods

A literature search was conducted through PubMed, SCOPUS, and Cochrane Databases from October 2012 to October 2022 for all confirmed cases of Nutcracker Syndrome. Additionally, seven cases from our own institution were included. Informed consent was not obtained as there are no identifiable patient fac-tors in any of the records reviewed.

Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Selection Criteria

The PRISMA diagram (figure 1) describes the selection pro-cess. All case reports and case series involving patients with confirmed diagnosis of NCS were included for screening. Sys-tematic re-views, meta-analyses, and other types of papers were excluded with one exception. A systematic review that contained an individual case report was included, but only data from the case report was used in our review [33]. Reports of pediatric pa-tients (under age 18) were excluded, as were reports in languag-es other than English and those where NCS was not ultimately diagnosed. Reports with incomplete patient data were also ex-cluded. Most articles were excluded by screening abstracts but

several full text articles were also excluded for the above reasons after review. Seven cases from our own institution were included. Ultimately, 40 articles were included.

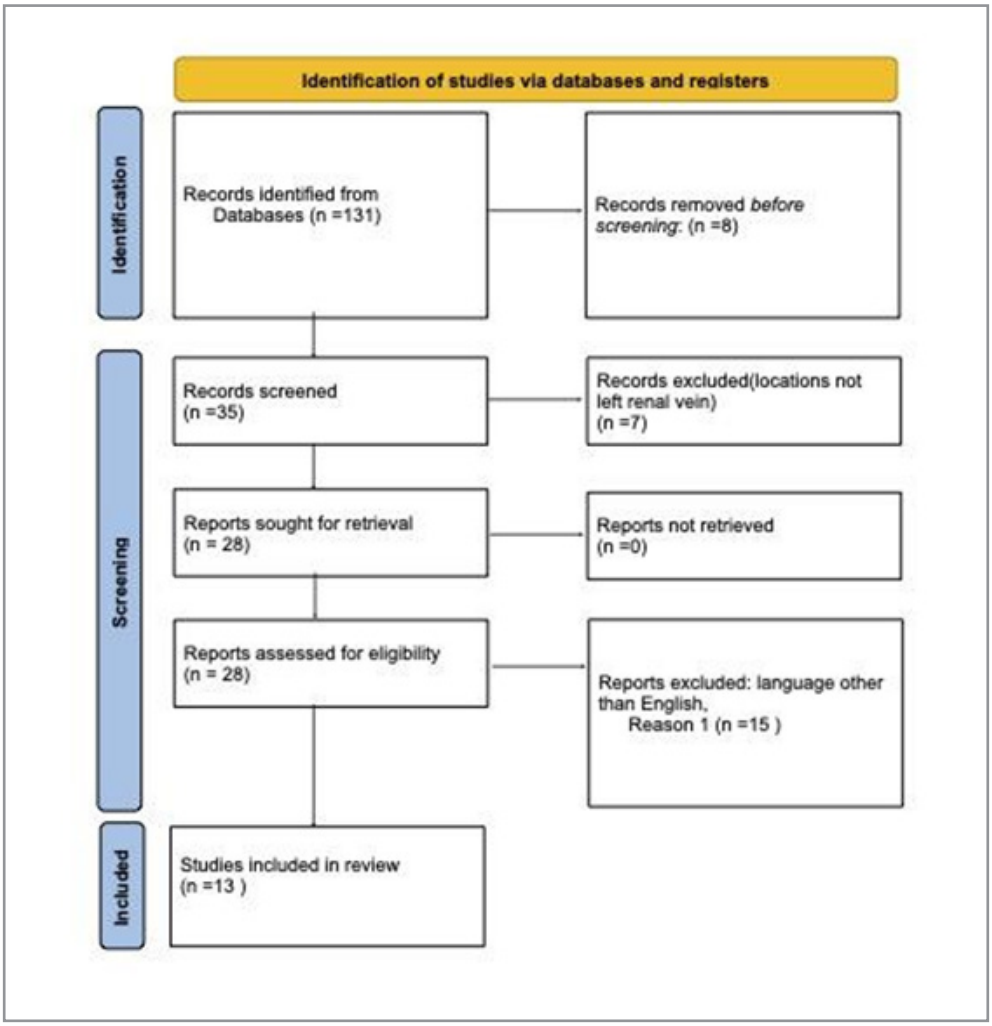

Figure 1: PRISMA flow diagram showing search algorithm used for systematic review.

Data Extraction

The following data was retrieved and appears in table 1: lead author, year of publication, country of origin, age, sex, presenting symptoms, diagnostic tests, location of the compression, presence of pelvic venous dilation, and type of treatment or procedure.

Statistical Analysis

Descriptive statistics were used to present the demographic, clinical, pathologic and treatment features of the pooled data from all the selected studies. This appears in the body of the paper below and in table 2.

Table 1: Reported cases of Nutcracker Syndrome. N/V: nausea/vomiting; NR: Not Reported; CIV: Common iliac vein; MTS: May Thurner Syndrome

Authors	Year	Age	Sex	Symptoms/Comorbidities	Hematuria	Workup/Imaging	Location (Anterior/Posterior)	Treatment
Copetti et al.	2017	31	F	Left flank pain	Yes	Renal Duplex	Anterior	No treatment reported
Miler	2017	26	F	Left flank pain, MTS	Yes	Renal duplex, CTA, IVUS	Anterior	Open gonadal vein transposition to left CIV
Taneja et al	2018	34	F	Left flank pain	No	Renal Duplex, CT Abdomen and Pelvis, IVUS.	Anterior	Endovascular Stent

Yu	2019	46	F	Left flank pain	Yes	CT Abdomen and pelvis	Anterior	Left renal vein transposition
Yu	2019	19	M	Left flank pain, Varicosities	Yes	CT Abdomen and pelvis	Anterior	Left renal vein transposition
Yu	2019	36	M	No flank pain, Anemia	Yes	CT Abdomen and pelvis	Anterior	Left renal vein transposition
Avgerinos	2019	21	F	Left flank pain	No	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	50	F	Left flank pain	No	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	25	F	Left flank pain, N/V	No	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	33	F	Left flank pain, Varicosities	No	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	50	F	Chronic pelvic pain	No	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	51	F	Left flank pain	No	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	30	F	chronic pelvic pain	No	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	39	F	Left flank pain, Varicosities	No	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	23	M	Left flank pain, Varicosities	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	24	F	Left flank pain	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	21	F	Left flank pain, Proteinuria	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	36	F	Chronic pelvic pain, Varicosities	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	55	F	Left flank pain	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	26	F	Left flank pain, Proteinuria	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	69	F	Left flank pain	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	19	F	Left flank pain, recurrent UTI	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	38	F	Left flank pain	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Avgerinos	2019	76	F	Left flank pain, Varicosities	Yes	CT Venography, IVUS.	NR	Endovascular Stent
Dahman	2019	10	F	Gross Hematuria	Yes	Renal Duplex and CTA	Anterior	Conservative
Dunphy	2019	39	F	General abdominal pain	Yes	CT Abdomen and pelvis	Anterior	Conservative
Kim	2019	18	M	NR	No	Renal Duplex and CT	Anterior	NR
Kim	2019	72	F	NR	No	Renal Duplex and CT	Anterior	NR
Kim	2019	49	F	NR	No	Renal Duplex and CT	Posterior	NR
Patel et al.	2019	38	F	Left flank pain, Gastroparesis	No	MRI Abdomen	Anterior	Open Renal Autotransplantation
Belczak	2020	42	F	Left flank pain	Yes	CT Venography, IVUS.	Anterior	Endovascular Stent

Table 2: Statistical Analysis

Sex	n		Imaging Modality		
Female	58	79.5%	CT	29	39.7%
Male	15	20.5%	CTA	12	16.4%
Age			CTV	29	39.7%
Age range	18 to 77		CT in any form (CT, CTA, CTV)	68	93.2%
Median age	34		MRI/MRA	4	5.5%
Mean age	36		US	24	32.9%
n patients below age 40	54	74.0%	Treatment Modality	n	
Radiographic Findings	n		Medical management*	9	12.3%
Anterior LRV compression	41	56.2%	No treatment**	5	6.8%
Posterior LRV compression	3	4.1%	Endovascular stent	28	38.4%
Anterior and posterior LRV compression	1	1.4%	Robot-assisted Extravascular LRV stent	6	8.2%
Location of LRV compression not stated	27	37.0%	LRV transposition	11	15.1%
LRV Compression by dilated splenic vein	1	1.4%	Open LRV bypass (PTFE or vein graft)	2	2.7%
Pelvic venous dilatation	32	43.8%	Robotic laparoscopic LRV PTFE cuff	3	4.1%
Presenting Symptoms	n		Renal autotransplant or nephrectomy	2	2.7%
Hematuria	38	52.1%	Transposition of vein other than LRV	2	2.7%
Left flank pain	45	61.6%	Ligation/embolization other than LRV***	6	8.2%
Pelvic pain	27	37.0%	*Medical management includes pain control, anti-hypertensives, and nutritional support for weight gain. **This includes patients who were not treated for NCS but were treated for concomitant conditions like SMAS. ***2 of the 6 cases also were treated with endovascular stenting		
Abdominal pain	11	15.1%			
Nausea, vomiting, weight loss	9	12.3%			
Urogenital Symptoms	18	24.7%			
Concomitant conditions	n				
May-Thurner Syndrome (MTS)	8	11.0%			
Superior Mesenteric Artery Syndrome (SMAS)	10	13.7%			

Results

Forty studies and our own series were included in the review, for a total of 73 individual patient cases. The mean age at diagnosis was 36. The vast majority of patients were female (79.5%). Left flank pain was the most common presenting symptom (61.6%) with hematuria presenting as the second most common (52.1%). However, a significant proportion of patients presented with pelvic pain (37.0%), abdominal pain (15.1%), as well as nausea, vomiting, and weight loss (12.3%). Many patients also had urogenital symptoms (24.7%), such as dyspareunia, dysmenorrhea, testic-ular pain, UTI, urinary frequency, or uterine bleeding. Diagnosis was almost always made with computed tomography. Ultrasound generally served to augment the diagnosis. Treatment modali-ties were highly varied, although endovascular stenting was most commonly done (38.4%). Other options included left renal vein transposition, left renal vein bypass, PTFE cuff placement, renal auto transplantation, nephrectomy, and conservative management with pain control and nutri-tional support.

The seven patients treated at our institution appear in Table 1 as “present cases.” All seven com-plained of long-term severe left flank and abdominal pain. Other symptomatology included he-maturia of unknown etiology and pelvic congestion symptoms. These patients had been treated for non-specific pain. Many were on long term opioid therapy.

There were six females and one male. Age ranged from 19 to 58. Our initial workup consisted of CT venography, which showed LRV enlargement in all seven patients. IVUS was subsequently used in all seven patients and showed LRV diameter and degree of compression supportive of NCS.

One patient underwent endovascular intervention with stenting. One had gonadal vein transposi-tion. Three underwent robot-assisted laparoscopic LRV PTFE cuff placement. One had LRV by-pass with PTFE. One had LRV transposition (Figure 2). All patients reported reduced postopera-tive pain. Some had lingering mild discomfort but opioid pain medications were discontinued in all seven patients. They reported significant improvements in quality of life and symptoms at fol-low up visits.

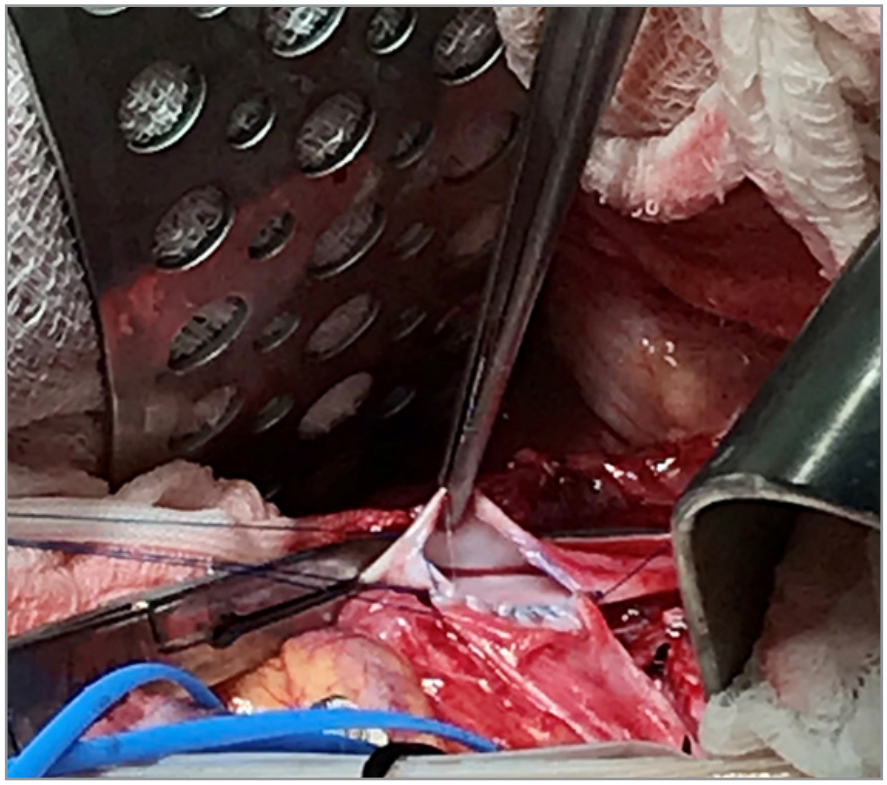

Figure 2: Renal Vein Transposition

Systematic Review

Forty articles met our selection criteria, as described in Figure 1. Of these, four were case series [7, 35, 36, 41]. The remaining 36 articles were individual case reports [2-6, 8-34, 37-40]. From these forty articles, 66 individual cases were reported. Our seven clinical cases were included for a total of 73 cases (Table 1).

The majority of the patients were young females complaining of left flank pain and/or hematuria. Age at diagnosis ranged from 18 to 77. Mean age was 36 and median was 34. Eight-two percent of patients were below age 50. The majority of patients (79.5%) were female. The most common presenting symptom was left flank pain (61.6%), followed by hematuria (52.1%), which included both gross and microscopic hematuria. About a third of patients (37.0%) complained of pelvic pain. Notably, 24.7 percent experienced urogenital symptoms such as pelvic congestion syn-drome, dyspareunia, dysmenorrhea, urinary frequency, dysuria, or testicular and scrotal pain. A handful of patients (12.3%) had concomitant superior mesenteric artery syndrome (SMAS) and 11.0 percent had concomitant May-Thurner syndrome (MTS).

LRV location was mostly anterior. Only three patients had posterior NCS--one of our clinical cases and two case reports [12, 15]. Location was not described in 37 percent of cases. Forty-one patients had anterior compression, which is 56.2 percent of the total and 89.1 percent of cases that reported location. One case described a patient with an anterior and posterior LRV, both of which were compressed [11]. Another report described compression of the LRV by a dilated splenic vein, in a patient with splenomegaly [27]. Imaging revealed enlarged gonadal veins, ad-nexal varices, or varicocele in 42.5 percent of cases.

Some form of computed tomography (CT) was used in the vast majority of cases (93.2%). This includes CT abdomen pelvis, CT angiogram (CTA), and CT venogram (CTV). Of the five cases that did not use CT, four used MRI. One case used Doppler ultrasound alone to diagnose NCS. In 21 cases (28.8%), ultrasound was used in combination with one of the forms of CT. Angi-ography, venography, and intravascular ultrasound (IVUS) were also used but generally as part of an intervention rather than primary diagnosis. Exploratory laparotomy or diagnostic laparosco-py was also seen in three cases when a diagnosis other than NCS was suspected.

Treatment modality was variable, although endovascular stenting was most common, appearing in 38.4% of cases. Other endovascular therapies included embolization of a left ovarian vein and a left second lumbar vein respectively in two cases. Two of the LRV stent cases also included embolization of the left ovarian vein. Medical management, including anti-hypertensives, pain medication, and nutritional support were found in only 12.3 percent of cases. There were a wide variety of non-endovascular procedures done. The most common was LRV transposition, done in 15.1 percent. Four of these were noted to have been done with a retroperitoneal approach.

There were six cases (8.2%) in which robot-assisted laparoscopic extravascular LRV stenting was performed. Other surgical options included robot-assisted laparoscopic LRV PTFE cuff place-ment (3 cases), LRV bypass with femoral vein graft (1 case) or PTFE (1 case), gonadal vein transposition (2 cases), varicocele ligation, gonadal vein ligation, renal auto transplant, splenec-tomy, and nephrectomy. Five cases

did not provide information on treatment, symptoms resolved spontaneously, or treatment of another condition (i.e. SMAS) resulted in relief of symptoms.

Discussion

NCS is an uncommon condition that presents in varied ways. However, this review demonstrates that commonalities exist among NCS patients, which should raise suspicion among clinicians. The majority of patients were young, female, and present with left flank pain and/or hematuria, which is likely due to the rupture of thin-walled varices formed from renal hypertension into the collec-tion system [1]. Features of pelvic congestion, such as dyspareunia, dysmenorrhea, scrotal or tes-ticular pain, or urinary issues, might also evince NCS. Even refractory headaches can be related to LRV compression. Any of these symptoms in this patient population should raise suspicion of NCS in the absence of a more obvious diagnosis.

Additionally, a normal to low BMI also appears to be associated with NCS. Not enough reports in this review included BMI information for us to include this data, but anecdotally, most reports of NCS occur in normal or underweight patients. A decreased aortomesenteric angle--or the an-gle between the SMA and aorta, risks compression of the LRV as it does to the duodenum in SMAS. [17, 43]. This is more likely to be found in underweight patients, who have decreased retroperitoneal and mesenteric fat.

There are multiple imaging modalities that can be used to diagnose NCS. While the gold stand-ard is retrograde venography, this invasive procedure is not always necessary. It is established that a pressure gradient between the LRV and inferior vena cava less than 1 mm Hg is normal, whereas greater than 3 mm Hg evinces nutcracker phenomenon and NCS with symptoms [17, 44]. It has been suggested that this pressure gradient can be estimated fairly accurately from Doppler ultrasound, by measuring differences in flow velocities [44]

Additionally, the size of the LRV can similarly be measured with Doppler ultrasound, to demon-strate a stenosis [13, 37, 44]. CT imaging can also show a decreased aortomesenteric angle, which when less than 38 to 45 degrees is considered abnormal [43, 44]. CT imaging can also show LRV compression. CT venography is preferable but not necessary in many of the studies we reviewed, which used CT of the abdomen pelvis or CT angiography to arrive at an NCS diagnosis. Overall, when NCS is suspected, invasive procedures are not necessary to arrive at a diagnosis. Relatively low risk procedures such as Doppler ultrasound and CT are available and should be used.

Regarding treatment, endovascular stenting was predominant. Some therapies aim at alleviating specific symptoms without disturbing the renal vein, such as gonadal vein transposition for pelvic congestion syndrome or lumbar vein embolization for headaches. Unfortunately, there was also not enough information in the reports regarding post-treatment course to determine if any of the treatment modalities are effective in the long term, and which would be preferable.

More research is needed to determine the best methods of treatment. Future studies might direct-ly compare the long-term effectiveness of conservative modalities, such as nutritional support, with endovascular or surgical options. There is still significant variation in treatment modalities. It may be that these should be adjusted to individual cases.

Our study was deficient in several ways. As stated, we did not include statistics on BMI. We also were unable to include information on outcomes of therapy, as most records did not state this. This study is retrospective in nature. Overall this was a small study population. It also in-cluded numerous institutions in different countries, which likely have different standards of practice. We did not include pediatric patients in this review [45, 46].

Conclusion

Diagnosis of NCS remains challenging. Most patients remain symptomatic without adequate workup and are treated for non-specific chronic pain. NCS should be in the differential for pa-tients who are below 40, female, and present with the constellation of symptoms outlined above. Diagnosis can be made with ultrasound or CT alone, without the need for angiography. Prompt referral to a vascular specialist is desirable as there are many treatment options for these patients. Increasing awareness is paramount as NCS is often overlooked and misdiagnosed. Treatment modalities range from minimally invasive to open surgery. A multi-institution or collaborative registry would be better to delineate strategies for diagnosis and management of NCS.

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