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IS THERE A FAMILY LINK IN THE NUTCRACKER SYNDROME: A SERIES OF 5 CASES AND REVIEW OF THE LITERATURE

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ABSTRACT

Nutcracker Syndrome is a rare disease. The aim of this study was to the aim of our study is to find out whether there is a family link with nutcracker syndrome and to identify the factors responsible. This is a retrospective, descriptive study conducted from January 2009 to September 2022 at the Vascular Surgery Department of the NORD Hospital in Marseille, using prospectively collected data on patients with NCS. Of the 133 patients diagnosed with NCS, five were first-degree relatives. The median age was 31.5 years [19; 44], and the mean body mass index (BMI) was 20.05 ± 1.95. All five patients underwent venous echo doppler and pelvic phlebography with pressure measurement, which demonstrated the presence of NCS associated with Cockett syndrome (CS). This study highlights the presence of NCS in several members of the same family with a low BMI, as well as the constant association with CS.

KEYWORDS: Nutcracker Syndrome; Left Renal Vein; Cockett Syndrome; Ptosis of the Left Kidney.

INTRODUCTION

Nutcracker syndrome (NCS) is considered as a rare disease, but its incidence is probably underestimated.[1]

It involves compression of the left renal vein (LRV) in the fork formed by the abdominal aorta posteriorly and the superior mesenteric artery (SMA) anteriorly, leading to stenosis of the aorto-mesenteric part of the LRV and dilatation of its distal part.[2]

More rarely, a retro aortic LRV is compressed between the aorta anteriorly and the spine posteriorly, which may be the cause of a posterior nut cracker. There have also been cases of nutcracker syndrome in circum-aortic LRV.[3]

Compression of the LRV leads to venous hypertension, which may be responsible for the formation of pelvic varices due to left gonadal vein (LGV) incontinence, left flank pain and/or hematuria.[4] Due to LGV incontinence, NCS may lead to pelvic congestion syndrome in women and left varicocele in men.

The management of NCS, ranging from surveillance to nephrectomy, remains controversial.[4]

The aim of this study is to describe the cases of familial NCS identified in our experience.

MATERIALS AND METHODS

This is a retrospective, descriptive study conducted from January 2009 to September 2022 at the Vascular Surgery Department of the NORD Hospital in Marseille, using prospectively collected data on patients with NCS.

Of 133 patients diagnosed with NCS, five were first-degree relatives.

All patients underwent a primary consultation to confirm the diagnosis of NCS. Investigations included vascular ultrasound, Contrast computed tomography, and pelvic phlebography with pressure measurements.

Data were collected from patient records, consultation notes and telephone calls.

Data collected for our study included age, sex, weight, height, body mass index, clinical symptoms, imaging results, type of treatment adopted, and association or not with Cockett syndrome (CS).

RESULTS

Two patients were members of the same family (mother and daughter) and 3 patients were members of different families (mother, daughter and son). The median age was 31.5 years [19; 44]. The mean weight of our patients was 54.6 ± 3.5 kg, the mean height was 165 ± 2.5 cm, and the mean BMI was 20.05 ± 1.95. All patients were symptomatic. (Fig 1).

	Age	Gender	Height (cm)	Weight (Kg)	BMI
Patient 1	47 years	Female	168	51	18,07
Patient 2	22 years	Female	165	55	20
Patient 3	16 years	Male	161 ,4	51,6	19,8
Patient 4	44 years	Female	165	55	20,20
Patient 5	19 years	Female	165	60	22,03

Figure 1: table that showed the demographic criteria of our study.

All of these patients were symptomatic. The symptoms were chronic low back pain. 4 patients complained of dysmenorrhea, 3 women reported dyspareunia and one patient described dysuria without macroscopic hematuria. (Fig. 2).

	Lumbar Pain	Pelvic Pain	Dysmenorrhea	Dyspareunia	Dysuria	Macroscopic hematuria	Vulvar varicose vein	Varicocele
Patient 1	Yes	Yes	Yes	No	No	No	Yes	No
Patient 2	Yes	Yes	Yes	Yes	No	No	No	No
Patient 3	No	No	No	No	No	No	No	Yes
Patient 4	No	Yes	Yes	Yes	No	No	No	No
Patient 5	No	Yes	Yes	Yes	Yes	No	No	No

Figure 2: table that showed the patient's symptoms.

One woman had a vulvar varicose vein and the only man in our study had an associated varicocele.

Although none of the patients in our study reported the presence of current or previous macroscopic hematuria, 3 patients had microscopic hematuria on ECBU.

All our patients underwent vascular ultrasound, venous phleboscan and pelvic phlebography with pressure measurement which revealed the presence of NCS, which was associated with CS with a significant renal-cava pressure gradient in all five patients. (Fig. 3, 4, 5, 6)

	Doppler-ultrasound	CT	Phlebography	Associated Cockett's syndrome	Treatment
Patient 1	SNC +	SNC +	SNC +	Yes	Stenting LPIV
Patient 2	SNC +	SNC +	SNC +	Yes	Stenting LPIV
Patient 3	SNC +	SNC +	SNC +	Yes	Medical treatment
Patient 4	SNC +	SNC +	SNC +	Yes	Stenting LPIV +Reno-cave bypass
Patient 5	SNC +	SNC +	SNC +	Yes	Stenting LPIV

Figure 3: table that showed the imaging and management.

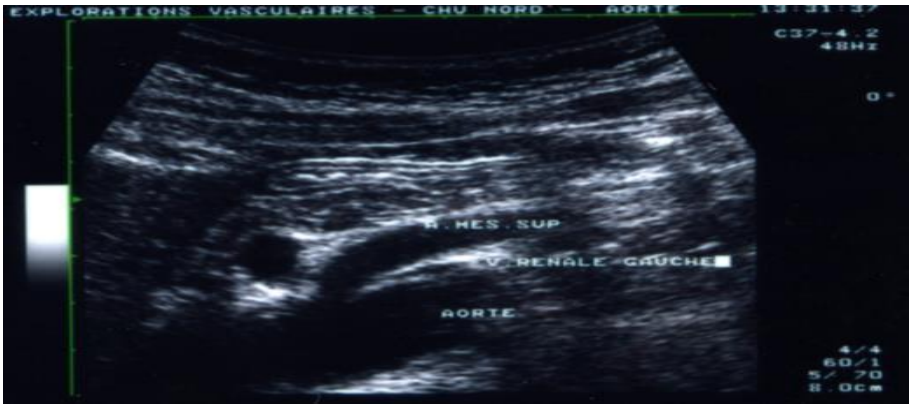

Figure 4: doppler ultrasound image of compression of the left renal vein in the aorto-mesenteric clamp.

The only man in our series was treated conservatively with analgesics and monitoring because he was only moderately symptomatic.

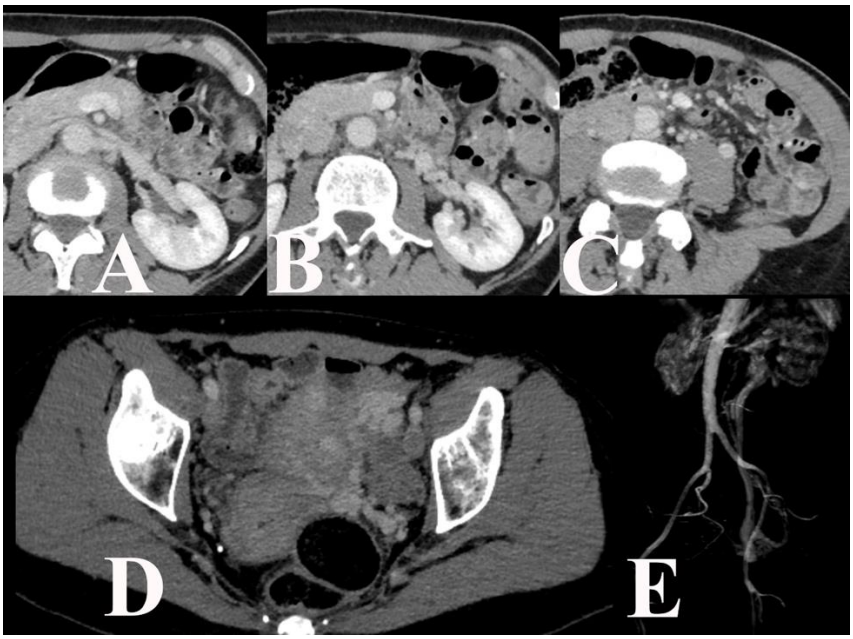

Figure 5: Nutcracker syndrome: CT: A: compression of the LRV in the aorto-mesenteric clamp; B: hilar collateral circulation; C: incontinence of the LRV; D: pelvic varices; E: tight aorto-mesenteric angle with compression of the LRV.

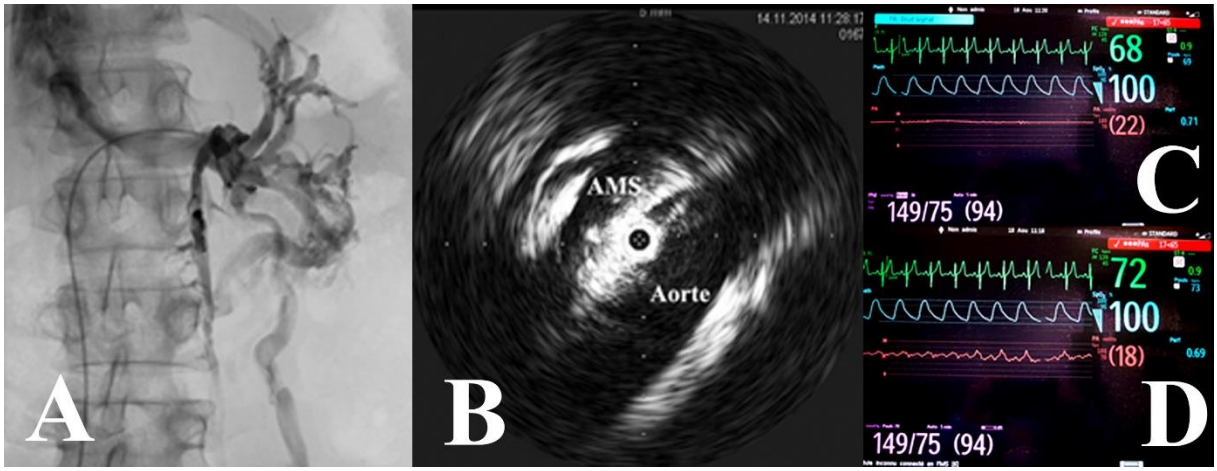

Figure 6: Preoperative invasive exploration by phlebography.

A: selective phlebography of the LRV showing compression of the LRV in the aorto-mesenteric clamp with collateral circulation and incontinence of the LRV;
B: IUVS showing compression of the LRV in the aorto-mesenteric clamp;
C: Pressure measurement in the LRV (red line): the pressure curve does not fluctuate and the pressure is 22 mm Hg;
D: Measurement in the IICV: the curve fluctuates according to cardiac activity and the pressure is 18 mm HG, i.e. a gradient of 4 mm Hg.

All four women underwent angioplasty and stenting of the left iliac vein as initial treatment for CS, with good clinical outcomes and a 100% primary patency rate. One of the four women in our study had a recurrence of symptoms four years after treatment for CS, which led to renal-cava bypass surgery with a good clinical and radiological outcome. (Fig.7)

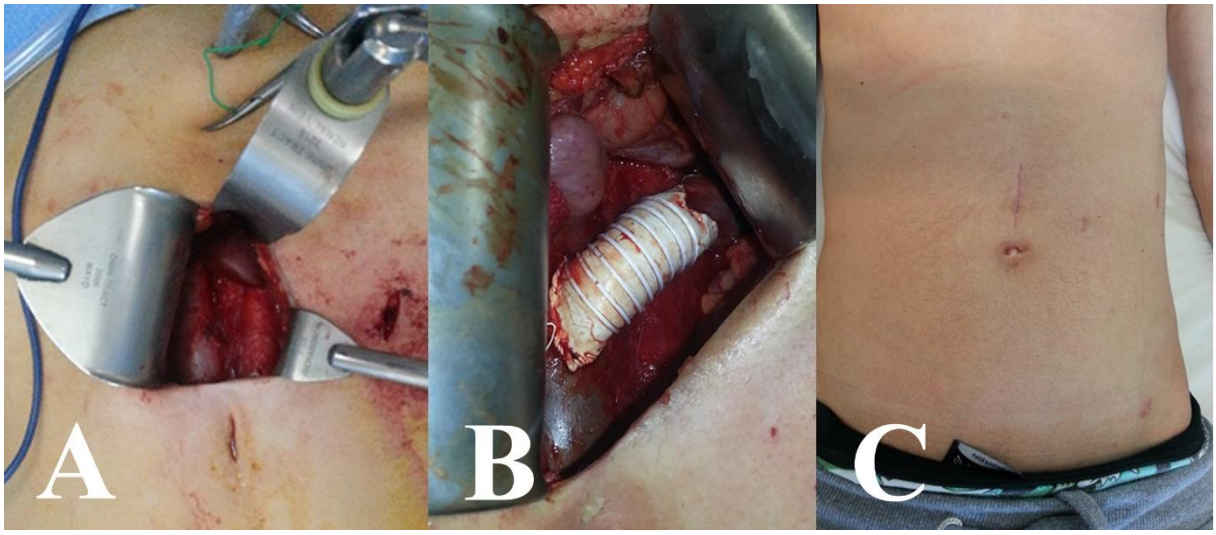

Figure 7: Reno-cava bypass using a coelio-assisted approach.

A: intraoperative view after laparoscopic dissection followed by mini laparotomy;
B: reno-cava bypass using a 14 mm PTFE-reinforced prosthesis;
C: postoperative result.

DISCUSSION

NCS is an anatomical variant characterized by extrinsic compression of the LRV and consequent impaired flow to the inferior vena cava (IVC) with dilatation of the hilar region and narrowing of the preaortic region of the LRV.

The prevalence of NCS is not well known, but it is regularly described in adolescents and young adults due to the narrowing of the angle between the aorta and the SMA as a result of rapid growth and maturation of the vertebral bodies. In children, it may resolve spontaneously due to an increase in retroperitoneal fat.[5] A higher prevalence in females; low body mass index has been shown to correlate positively with NCS, as thin subjects are mainly exposed to alterations of the aorto-mesenteric angle (AMA).[6] the vast majority of patients were from Turkey and Asia.[1]

In addition to anatomical variations, a low body mass index is considered to be a risk factor for LRV compression due to two different proposed mechanisms, both related to the scarcity of retroperitoneal adipose tissue: it may reduce the AMA and cause dorsal migration of the kidney and renal pelvis (posterior renal ptosis).[6]

Hartung et al. showed that in patients with symptomatic NCS, the angle of the AMC (aorto-mesenteric clamp) and the distance between the aorta and the SMA correlated with the amount of visceral fat.

They found that the length of the LRV was significantly greater in the NCS group than in the control group. The dilation of the proximal part of the LRV in relation to the smallest diameter was also greater in the NCS group. This excess length was mainly in the proximal, pre stenotic portion of the LRV, an element that would again favor a renal ptosis mechanism causing stretching of the LRV.[7]

This work also looked at the distribution of fat, and in particular visceral fat, as a cause that could partly explain the left renal ptosis. This showed that there was no difference in the amount of peri- and para-renal fat between the two groups, but there was a significant difference in the amount of visceral fat.[8] In addition, affected patients have a significantly different distribution with less fat in the posteroinferior part of the left kidney.

An AMA $< 35^{\circ}$ is consistent with the anatomical condition underlying LRV incarceration and may be associated with abnormal flow from the LRV to the IVC, with a significant increase in the pressure gradient between the LRV and the IVC.[8]

Other causes of LRV compression include pancreatic neoplasms, para-aortic lymphadenopathy, retroperitoneal tumors, aortic aneurysms or fibro lymphatic tissue between the MSA and the aorta, but the term NCS should not be used in relation to LRV compression from these causes.[9]

Hematuria is the most common sign, the mechanism of which can be explained by the increase in venous pressure in the LRV and the LGV, which can lead to rupture of the septa between the venules and the collecting system in the renal parenchyma.[6]

Pelvic symptoms are associated with incontinence of the LGV, which acts as a bypass due to hyper pressure of the LRV. In men they manifest as varicocele. In women, NCS manifests clinically as a pelvic congestion syndrome, which may include dysmenorrhea, dysuria,

dyspareunia and pelvic pain. Varicose veins of the vulva, buttocks and lower limbs may also be present.[6]

The screening test of choice is vascular ultrasound. Renal vein stenosis >80% with elevated peak systolic velocities is the most common criterion for the diagnosis of NCS. In addition to assessing LRV compression, it is important to assess for signs of disease in the pelvic venous territory. This can be done routinely by measuring LGV diameter and direction of flow (reverse) and the presence of pelvic varices and collateral vessels arising from the LRV.[10]

Contrast computed tomography (CT) with arterial, portal and venous phases or magnetic resonance imaging (MRI) with angiographic sequences may be used. Axial sections can be used to identify Beck's sign, which is a stenosis of the LRV between the aorta and the SMA; if this angle is <32◦ and the ratio of the LRV diameter at the hilar level to the LRV diameter at the aorta-mesenteric clamp is greater than 4.9, which has a positive predictive value of 100%, the diagnosis of NCS is maintained.[11] Thanks to sagittal reconstruction, we can assess the aorto-mesenteric angle, which usually varies from 38◦ to 65◦; an AAM of less than 35◦ is compatible with the diagnosis of compression of the LRV and therefore with NCS.[12, 13]

Phlebography with direct pressure measurements, with or without intravascular ultrasound (IVUS), is considered the gold standard for the diagnosis of NCS. It allows the assessment of compression of the LRV, in addition to the presence of collateral vessels and other venous compressive pathologies, and provides an objective measure of the pressure gradient. An elevated pressure gradient > 2 to 3 mm Hg is often used to define hypertension in the LRV and generally indicates the absence of decompressing collateral vessels. The presence of compression of the LRV with a normal renal-cava pressure gradient often indicates decompression by collateral vessels, such as an incompetent left gonadal vein, and should prompt further investigation to assess the presence of pelvic and extra pelvic varices.[6]

Conservative treatment is recommended for patients with mild hematuria under the age of 18, and any intervention should be followed by at least six months of conservative follow-up; it has been reported that in most patients with mild symptoms, there can be complete spontaneous resolution of symptoms. There is no consensus on the recommended pharmacological treatment for NCS patients.[4]

Numerous surgical approaches can be used, including medial nephropexy, reno-cava bypass, left renal vein transposition, SMA transposition, gonadal-cava bypass and left renal auto transplantation.[14], with endovascular treatment now coming to the fore.[15]

To date, there have been no large-scale studies of NCS. It is therefore difficult to reach a consensus on its diagnosis and treatment, especially when there is a family history of NCS. Our work is the first and only to date to investigate this association.

Our series includes five patients with a first-degree family link. The demographics of our study are consistent with those described in the literature, with a predominance of females and a low BMI. We found that all our patients had a low BMI, suggesting that there is a hereditary factor and that there are other family members with NCS who are not symptomatic because their BMI is not low.

Several studies have shown that a low BMI can be associated with renal ptosis, and therefore biological and genetic research should be pursued in the families of patients with symptomatic NCS to prove the existence of a genetic factor responsible for this renal ptosis.

Another peculiarity of our study is the presence of an associated CS in all our patients, which raises a number of questions, in particular the involvement of this factor in the pathogenesis of NCS.

CONCLUSION

Despite the limited number of patients, our study shows that several family members have NCS and that it is always associated with CS.

This new finding may lead to a better understanding of the pathophysiology of NCS and also to screening within the same family for this sometimes-disabling functional pathology. A larger study with a more comprehensive genetic study may confirm these results.

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