

Case Series

Nutcracker Syndrome: A Single-Center Experience

Clara Pardinhas^a Carmén do Carmo^b Clara Gomes^b Luís Escada^a
Rui Alves^a

^aNephrology Department, Coimbra University Hospital Center, Coimbra, Portugal;

^bPediatrics Department, Coimbra University Hospital Center, Coimbra, Portugal

Keywords

Nutcracker syndrome · Diagnosis · Prognosis · Clinical evolution

Abstract

Nutcracker syndrome, whose prevalence and natural history are still poorly known, is a clinical syndrome caused by left renal vein compression between the superior mesenteric artery and the aorta. Long-term results and treatment outcomes are not well known. Our group aimed to characterize 7 patients diagnosed with nutcracker syndrome in childhood and to describe their clinical manifestations, diagnostic approaches, and mostly their clinical evolution, rate of complications, and treatment outcomes.

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Introduction

Nutcracker syndrome (NS), first described in 1950, whose prevalence and natural history are still poorly known [1], is a clinical syndrome caused by left renal vein (LRV) compression,

between the superior mesenteric artery (SMA) and the aorta (anterior NS) mostly, or between the aorta and the lumbar spine (posterior NS), which leads to venous hypertension and venostasis [1–3]. When significant compression occurs, hematuria (usually microscopic, less often macroscopic), orthostatic proteinuria, flank pain, or gonadal varices (varicocele or ovarian vein syndrome) can occur, and it can lead to chronic renal disease and renal vein thrombosis [1, 2]. NS can also be asymptomatic [4]. Limited data and a lack of universal diagnostic criteria make the diagnosis of NS challenging, as it requires a high index of suspicion [5]. NS is a diagnosis of exclusion, but in the presence of hematuria of unknown origin, it is important to consider it [2, 5]. The diagnosis is confirmed by imaging results, including Doppler ultrasound (DUS), which is recommended as a first-line study, computed tomography (CT), and magnetic resonance imaging (MRI) [3–5].

Long-term results in young patients and development of complications are not well known. It is vital that NS is recognized and treated, not only to prevent damage to the kidneys from chronic renal vein hypertension, but also to improve symptomatology [6, 7].

This study was conducted to contribute to existing data about NS. We aimed to characterize a group of 7 patients followed at the Nephrology Department, their clinical evolution since childhood to adult life, clinical manifestations, and diagnostic and therapeutic approaches and their outcomes.

Case Reports

We describe 7 patients diagnosed with NS with a mean of 4 years of follow-up at the Nephrology Department. All patients were diagnosed at pediatric age and the mean age at diagnosis was 14.42 years, with only 1 being female (85.7% male gender).

Regarding initial clinical manifestations, 3 patients (42.9%) presented with macroscopic hematuria, 3 (42.9%) with orthostatic proteinuria, and 1 patient (14.3%) with hematuria and orthostatic proteinuria. Two of the patients presenting with macroscopic hematuria had exercise-related symptoms and 1 simultaneously presented exercise-induced lumbar pain. Among patients presenting with proteinuria, this finding was identified in routine workup and was always in the orthostatic and non-nephrotic range. There was no clinical history of urinary tract infections in any patient, and subsequent complementary studies were negative: normal blood count and coagulation parameters, normal kidney function, negative inflammatory parameters, negative blood and urine culture, and negative infection serology tests. Antistreptolysin test (TASO) was negative. There was no complement consumption, and autoimmunity study was normal. Diagnosis was then established after exclusion of these other causes and confirmed by DUS or CT. DUS was performed in all patients, but in only 4 of them a CT scan was needed to improve diagnostic accuracy. They showed classic characteristics suggestive of NS, with compression of the LRV in the fork formed by the SMA and abdominal aorta and proximal dilatation (Fig. 1). They had also an increased velocity gradient between proximal and distal areas.

Regarding evolution, only 2 patients had recurrent symptoms after the age of 18 years. One patient maintained orthostatic proteinuria with no other associated symptoms, and

another maintained recurrent low back pain induced by physical exercise, without changes in the urinary sediment. No other symptoms or signs were reported on follow-up. No complications were reported in any of the patients, such as gonadal varices or renal thrombosis. None of the patients presented renal dysfunction in the course of disease progression. All patients were kept on active surveillance and no medical or surgical therapeutic measures were necessary.

Discussion

Left renal entrapment syndrome, also called NS, is the clinical manifestation caused by symptomatic unilateral renal venous hypertension due to compression of the LRV between the angle of the abdominal aorta and the SMA or between the aorta and the lumbar spine [1–4]. Frequently, it is associated with asthenic constitution and reduced retroperitoneal and mesenteric fat, or an abnormal route of the LRV and SMA [1]. Lesser known pathologic processes and conditions leading to LRV compression include pancreatic neoplasms, paraaortic lymphadenopathy, retroperitoneal tumors, overarching testicular artery, lordosis, and pregnancy [5]. NS can lead to chronic renal disease and renal vein thrombosis, and clinical evaluation is extremely important to assess its functional impact [1, 2]. While the syndrome apparently affects a higher proportion of female patients, its exact prevalence remains unknown [4, 5]. Reported cases involve patients with ages ranging from childhood to the seventh decade of life, with a greater prevalence among young adults (20–30 years) and middle-aged adults [6, 7].

Herein, we report 7 patients diagnosed with NS who showed presenting symptoms or signs on routine workup in the second decade of life (mean age at diagnosis of 14.42 years), and hematuria was the most common finding. Six were male, in contrast to reports by previous studies [4].

During compression of the LRV, an increased pressure gradient between the LRV and the inferior vena cava (IVC) causes increased pressure in the renal vasculature and rupture of small veins in the renal fornix [7]. NS has variable severity and symptomatic presentation that reflect the degree of LRV compression, renocaval hypertension, and development of collateral circulation [8]. A study identified a strong correlation between the degree of LRV compression on imaging and symptoms [8]. It is important to recognize that the pressure gradient between the LRV and the IVC is normally less than 1 mm Hg but can rise to 3 mm Hg or more if the LRV is compressed by the SMA [1–5]. When significant compression occurs, hematuria, orthostatic proteinuria, flank pain, and gonadal varices (varicocele or ovarian vein syndrome) can occur [1–5]. Hematuria, usually secondary to rupture of renal calices, varices may be the presenting symptom of NS which is usually microscopic. Macroscopic hematuria occurs in only one-fifth of cases and is usually intermittent. When it is triggered by exercise, it is highly suggestive of NS [1]. Cystoscopy performed during a period with hematuria shows that the blood comes only from the left ureter [2]. Another symptom commonly noted with NS is orthostatic proteinuria, probably caused by increased pressure in the LRV and changes in renal hemodynamics on standing, altering the release of angiotensin II and norepinephrine [3].

In a review study, symptoms and signs at the time of presentation include abdominal and left flank pain (43.4–65.2%), macroscopic hematuria (39.1–69.5%), microscopic hematuria (8.6–21.7%), proteinuria (4.3–26.1%), and varicocele (8.7–21.7%) [5].

In this report, 42.9% ($n = 3$) presented with macroscopic hematuria, 42.9% ($n = 3$) with proteinuria, and 14.3% ($n = 1$) with hematuria and orthostatic proteinuria simultaneously. One patient maintained recurrent lumbar pain during exercise and another maintained orthostatic proteinuria. There was no reported varicocele or pelvic dysfunction. All of our patients did a complementary study that was negative. Blood count and coagulation time, renal function, inflammatory parameters, blood and urine cultures, infection serology, C3 and C4, TASO, and autoimmunity study (ANCA, ANA, antiphospholipid antibodies, anti- β 2-glycoprotein antibodies, anti-SSA, and anti-SSB) were normal.

DUS is recommended as a first-line study. It has been reported that DUS has a sensitivity and specificity of 69–90% and 89–100%, respectively, in identifying LRV compression [5]. A ratio of peak systolic velocity of the aortomesenteric segment to the hilar portion of >4.2 – 5.0 is considered one of the diagnostic criteria of NS [3, 5]. Where DUS is not diagnostic, axial imaging may be required. Both CT and MRI can demonstrate compression of the LRV in the fork formed by the SMA and abdominal aorta, gonadal vein distension, and pelvic congestion [3]. Furthermore, findings such as an LRV hilar diameter to aortomesenteric diameter ratio of >4.9 , the “beak sign,” and an SMA branching angle of $<35^\circ$ from the aortic origin can also be useful for the diagnosis of NS [3, 5]. The current evidence in the literature reports that the presence of a “beak sign” or narrowing in the LRV between the SMA and aorta with a proximal LRV dilation has a sensitivity of 91.7% and a specificity of 88.9% for substantiating a NS diagnosis [8]. If the diagnosis of NS remains unclear, it can be confirmed by phlebography and measurement of the venous pressure gradient between the LRV and the IVC, or by intravascular ultrasound [3]. A patient with NS usually demonstrates a pressure gradient of >1 – 3 mm Hg with phlebography [3, 5].

In our group of patients, the diagnosis was confirmed on imaging results, including DUS and CT findings. A reduction of the LRV caliber at the inter-aortomesenteric region and reduction of the aortomesenteric angle in all our patients were identified, and just 1 patient had signs of perirenal venous collateralization (Table 1).

Treatment is controversial [5]. In cases presenting with mild hematuria or mild tolerable symptoms, conservative management is recommended, especially for young patients (under the age of 18 years) [6]. Younger patients can have spontaneous resolution of symptomatology with body growth and increased body mass index [1]. However, surgery may be considered for gross hematuria (especially if recurrent), for severe symptoms including flank or abdominal pain, autonomic dysfunction, impairment of renal function including persistent orthostatic proteinuria, varicocele formation, and for ineffective conservative measures after 24 months in patients aged less than 18 years and after 6 months in adults [3, 8]. Surgical options include renocaval reimplantation, resection of fibrous tissue, and placement of a wedge at the aortomesenteric angle, LRV or SMA transposition, auto-transplantation of the kidney, and laparoscopic splenorenal vein ligation, and in extreme cases nephrectomy [7, 6]. Percutaneous endovascular stenting of the LRV is another option that has shown long-term resolution of

symptoms [6]. Management depends on NS severity, and long-term results in young patients and the development of complications are not known [6, 9].

Our patients were kept on active surveillance, and since there were no severe symptoms or complications, no medical or surgical treatment was initiated. Although we describe the clinical evolution of a small number of patients, we want to draw attention to the fact that NS is still an underdiagnosed entity that can lead to iatrogenic diagnostic or therapeutic measures.

Conclusion

NS is not always an easy diagnosis to reach given the broad spectrum of symptoms and clinical signs that may arise, the absence of a systematic diagnostic approach, and some lack of knowledge about the natural course of the disease. Given the absence of reliable diagnostic criteria and treatment, every effort should be made to collect data that could lead to a new understanding about this disease. It is, therefore, evident that there is a need to improve underlying theoretical knowledge of NS, which is the objective of this report and review.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. We uphold that this article has not been published elsewhere and is not under consideration by another journal. Patients have given their written informed consent for publication of this case report and any accompanying images. All authors have approved the manuscript and agree with its submission.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Research idea and study design: C.P., L.E., C.C.; data acquisition: C.P., C.C., C.G.; data analysis/interpretation: C.P., C.C., C.G.; statistical analysis: L.E.; supervision or mentorship: R.A.

C.P., C.C., C.G., L.E., and R.A. take responsibility that this study has been reported honestly, accurately, and transparently and accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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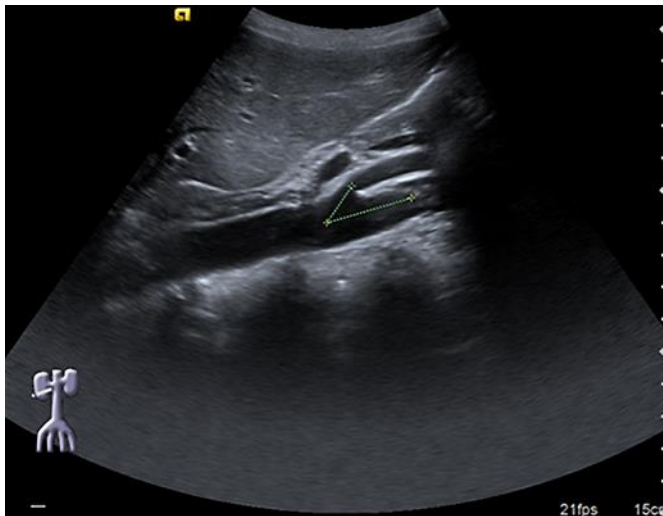


Fig. 1. Kidney ultrasound: reduction of aortomesenteric angle with LRV compression.

Table 1. Summary of clinical characteristics

Case	Age at Diagnosis, years	Presenting Symptoms	Exercise-related symptoms	DUS findings	CT findings	Treatment	Evolution	Follow-up
1	17	Macroscopic hematuria	Yes	Reduction of LRV caliber at the inter-aortomesenteric region 2 mm; no increased velocity gradient (2.9)	Reduction of LRV caliber distally and dilatation at proximal region (11 mm) Reduction of aortomesenteric angle 11°	Conservative	No recurrent symptoms	2 years
2	15	Asymptomatic; non-nephrotic orthostatic proteinuria	No	Reduction of LRV caliber at the inter-aortomesenteric region 1.8 mm	Reduction of aortomesenteric angle and presence of perirenal venous collateralization	Conservative	No recurrent symptoms	4 years
3	17	Macroscopic hematuria and lumbar pain	Yes	Reduction of LRV caliber at the inter-aortomesenteric region 1.6 mm	Reduction of LRV caliber at the inter-aortomesenteric region Reduction of aortomesenteric angle 26° Increased caliber of inferior vena cava and common iliac vein	Conservative	Lumbar pain with exercise	2 years
4	9	Palpebral edema, orthostatic non-nephrotic proteinuria	No	Increased velocity gradient at the aortomesenteric region	Reduction of aortomesenteric angle 9° Reduction of LRV caliber at the inter-aortomesenteric region 3 mm	Conservative	Orthostatic non-nephrotic proteinuria	9 years
5	15	Macroscopic hematuria and non-nephrotic proteinuria	No	Reduction of LRV caliber at the inter-aortomesenteric region (3 mm) Reduction of aortomesenteric angle (39°)		Conservative	No recurrent symptoms	5 years
6	16	Macroscopic hematuria	No	Reduction of LRV caliber at the inter-aortomesenteric region (2 mm) Reduction of aortomesenteric angle (30°)		Conservative	No recurrent symptoms	3 years
7	15	Asymptomatic; non-nephrotic orthostatic proteinuria	No	Reduction of LRV caliber at the inter-aortomesenteric region (2 mm) Increased velocity gradient between proximal and distal portions		Conservative	No recurrent symptoms	3 years