Nutcracker syndrome accompanied by hypertension: a case report and literature review

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Abstract
Nutcracker syndrome (NCS) refers to characteristic clinical symptoms that develop secondary to the nutcracker phenomenon (NCP), defined as compression of the left renal vein between the superior mesenteric artery and the aorta. A 22-year-old Chinese man presented with a 2-year history of hypertension and left flank pain after activity; his blood pressure fluctuated within 130–150/90–100 mmHg without treatment. He had microscopic hematuria (2+) and increased plasma renin activity. The findings of both color Doppler ultrasound and computed tomography angiography were consistent with a diagnosis of NCS. The patient had no history of familial hypertension or special medications. Secondary hypertension-related examinations showed no significant abnormalities. After placement of an endovascular stent in the left renal vein, normal blood flow resumed and the collateral circulation was reduced. Both the hypertension and flank pain were alleviated within 3 days after the intervention and did not reappear during the following 11 months. NCP/NCS accompanied by hypertension is very rare. The possibility of NCP/NCS should be considered when secondary hypertension cannot be explained by other factors. The mechanism by which hypertension is caused by NCP/NCS is rather complex and deserves further investigation.

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Introduction

Both the nutcracker phenomenon (NCP) and nutcracker syndrome (NCS) refer to compression of the left renal vein (LRV) between the superior mesenteric artery (SMA) and the aorta. In patients with the NCP, anatomic findings suggestive of a nutcracker are present without clinical symptoms. NCS is used to describe patients with clinical symptoms associated with a nutcracker anatomy.1 The prevalence of NCS is not clearly defined but might have slight female predominance. The main clinical manifestations of NCS include left flank and/or abdominal pain, hematuria, varicocele formation, and ovarian vein outflow obstruction.2,3

Hypertension is not a classic sign of NCS, and only a few reports have described NCP/NCS accompanied by hypertension.4,5 We herein describe a young man with hypertension accompanied by NCS. After endovascular stent placement, his pain and hypertension were completely relieved without administration of antihypertensive drugs. We present the following case report in accordance with the CARE Guideline.6

Case report

A 22-year-old Chinese man with a 2-year history of hypertension and left flank pain after activity was admitted to the Department of Interventional Radiology, the First Hospital Affiliated to the University of Science and Technology of China. The patient’s hypertension and left flank pain had often occurred simultaneously throughout the last 2 years, with his blood pressure fluctuating within 130–150/90–100 mmHg without treatment. Seven months previously, he had developed severe headache and worsening left flank pain, and his blood pressure reached 200/105 mmHg. Amlodipine (5 mg twice daily) and spironolactone (40 mg twice daily) were administered to reduce his blood pressure, but treatment was ineffective. His blood pressure had recently fluctuated within 150–180/95–110 mmHg, and he was hospitalized for further investigation.

On admission, the patient was 182 cm tall and weighed 68 kg. Physical examination revealed slight throbbing pain over the left kidney area with a visual analog scale score of 4. No other obvious abnormalities were found.

Laboratory data revealed a normal 24-hour urine protein level at 135 mg (reference range, 0–150 mg/24 hours), microscopic hematuria (2+), and increased plasma renin activity (renin activity, aldosterone, angiotensin I, and angiotensin II) (Table 1). Color Doppler ultrasound examination (HD9 color Doppler ultrasound system; Philips, Amsterdam, Netherlands) revealed diffuse renal lesions, a broadened inner diameter of the LRV (approximately 12.7 mm), and an inner LRV diameter of 4.1 mm at the level of the SMA–aorta angle. These findings were consistent with a diagnosis of NCS (Figure 1). In addition, a computed tomography (CT) examination...
was performed using a GE Discovery CT750 (GE Healthcare, Chicago, IL, USA) with the following scanning parameters: tube voltage, 120 kV; tube current, 160–360 mA; scanning slice thickness, 5 mm; and reconstruction slice thickness, 1.25 mm. CT angiography (CTA) confirmed NCS (Figure 2). The patient had no history of familial hypertension or special medications. His thyroid function, cortisol concentration, prolactin concentration, and adrenocorticotropic hormone concentration were normal. Thin-section enhanced CT of the adrenals showed no adrenal enlargement or occupying lesions. Pituitary magnetic resonance imaging showed no abnormalities. Renal artery CTA showed no stenosis. None of the above secondary hypertension-related examinations showed significant abnormalities. These findings indicated the possibility that the hypertension might be associated with the observed abnormal LRV anatomy.

Selective renal arteriography and venography (GE Innova 3100; GE Healthcare) were performed. The renal arteriography data were normal, but left renal venography indicated that the LRV was significantly narrowed before descending into the inferior vena cava, with clear regular compression; the anterior vein was significantly dilated (approximately 13 mm), and left-side varicoceles were seen (Figure 3(a)). The inferior vena cava pressure was 6 mmHg, and the LRV pressure was 15 mmHg. These findings confirmed a definitive diagnosis of NCS.

Considering that the patient had severe flank pain and that his hypertension might

|                      | Supine (before stent placement) | Supine (after stent placement) | Reference range          |
|----------------------|---------------------------------|---------------------------------|--------------------------|
| Renin activity (pg/mL/hour) | 2150                            | 850                             | 50–790                   |
| Aldosterone (pmol/L)    | 723.60                          | 406.20                          | 164.80–481.00            |
| Angiotensin I (nmol/L)  | 1.60                            | 0.44                            | 0.04–0.64                |
| Angiotensin II (pmol/L) | 60.20                           | 33.58                           | 13.33–52.25              |

Figure 1. Color Doppler ultrasonography showing compression of the LRV between the SMA and the abdominal AO. (a) Two-dimensional ultrasonography image. (b) Color doppler ultrasonography flow image. LRV, left renal vein; SMA, superior mesenteric artery; AO, aorta.
have been associated with this pain, an endovascular stent (14 × 60 mm; C. R. Bard, Murray Hill, NJ, USA) was placed into the stenosed part of the LRV. As a result, normal blood flow resumed and the collateral circulation was reduced (Figure 3 (b)). Follow-up renal venography revealed a 2-mmHg pressure gradient between the LRV and inferior vena cava. Finally, the patient’s blood pressure was reduced to 130–140/80–95 mmHg 1 day later without drugs, and his 3-day postoperative visual analog scale score for the left flank pain was reduced to 1 to 2. Aspirin (0.1 once daily; Bayer, Leverkusen, Germany) and clopidogrel (75 mg once daily; Sanofi, LRV, left renal vein; SMA, superior mesenteric artery; AO, aorta.

**Figure 2.** Contrast-enhanced computed tomography showing compression of the LRV between the SMA and the abdominal AO. (a) Axial scan image. (b) Sagittal reconstruction image. LRV, left renal vein; SMA, superior mesenteric artery; AO, aorta.

**Figure 3.** Imaging manifestations before and after endovascular stent placement. (a) Before stent placement, digital subtraction angiography reveals compression of the LRV and dilation of the distal renal vein. (b) After endovascular stent placement, the renal vein blood flow is accelerated and the intrarenal vein branches are underdeveloped. IVC, internal vena cava; LRV, left renal vein.
Paris, France) were administered as a blood thinner and decongestant, respectively. The hypertension and flank pain did not recur during the following 11 months. Because the patient declined to undergo a biopsy, a pathological examination could not be performed.

Discussion

El-Sadr and Mina\(^7\) first described LRV compression between the SMA and aorta in 1950. In 1972, De Schepper\(^8\) coined the terms “nutcracker phenomenon/nutcracker syndrome” (NCP/NCS) to describe this condition, which has gradually attracted clinical attention. NCS is generally divided into two types: anterior and posterior. Most cases of NCS are anterior NCS, which is caused by compression of the normally situated LRV by the abdominal aorta and the SMA. Posterior NCS results in narrowing of the LRV in its retroaortic position, where it is compressed between the aorta and the vertebral column.\(^9\) Compared with anterior NCS, the incidence of posterior NCS is much lower, ranging from 0.1% to 3.2%.\(^10\) The main clinical manifestations of NCS include abdominal/pelvic pain, flank pain, hematuria, and varicocele or ovarian vein syndrome.\(^11,12\) Similar to previous reports, our patient had two typical symptoms of NCS: left flank pain and microscopic hematuria. These symptoms might have been induced by pelvic congestion and venous renal hypertension resulting from poor blood flow in the LRV.

In the clinical setting, renal vein angiography is considered the gold standard for the diagnosis of NCP/NCS. The compression status is reflected by pressure measurement, by which LRV compression can be diagnosed with a >3-mmHg pressure gradient at the level of compression.\(^13\) CTA, magnetic resonance angiography, and color Doppler ultrasound can also be used for diagnosis. In the present case, the manifestations on CTA and color Doppler ultrasound included a compression phenomenon of the LRV with a pressure gradient of 9 cm H\(_2\)O (6.76 mmHg) (reference range, <3 mmHg) by renal vein angiography, and the clinical features of left flank pain and varicocele formation helped to confirm the diagnosis of NCS.

Interestingly, in addition to the common clinical manifestations of NCS, our patient displayed an unusual manifestation: continuous hypertension. He had no family history of hypertension. Blood, urine, and imaging examinations revealed no factors that could cause secondary hypertension, including renal parenchymal disease, hypercortisolism, or tumors of the adrenal cortex or medulla. Therefore, his hypertension could not be explained by common associated factors. Considering the compression of the LRV, we assume that the hypertension was likely related to NCS.

NCP/NCS accompanied by hypertension is rarely reported. Hosotani et al.\(^14\) reported a case of NCS accompanied by hypertension in a young Japanese woman. After the patient had undergone endovascular stent placement, her blood pressure returned to normal. In this patient, increased plasma renin activity and aldosterone levels were detected in the peripheral blood despite the absence of renal artery stenosis or a renin-producing tumor. Based on these findings, the authors attributed the renin-dependent hypertension in this woman to the NCS. Another recent case report described a young Korean woman with secondary hypertension associated with the NCP; the authors also considered that the hypertension was renin-dependent.\(^5\) In the three other known cases of NCP/NCS accompanied by hypertension, there was no significant increase in hormone levels; the blood pressure was well controlled after treatment with medication, and the authors suggested
that the two ailments may be coincidental.\textsuperscript{4,15,16}

Similar to the above-mentioned case reported by Hosotani et al.,\textsuperscript{14} our patient’s blood renin activity, aldosterone concentration, and angiotensin I/II concentrations were significantly increased before stent placement, after which the hormone levels returned to normal, as did the blood pressure. These findings indicate that the hypertension may have been associated with the LRV compression. Studies have revealed complications of high pressure in the renal vein, including elevated renal interstitial pressure, myogenic and neural reflexes, baroreceptor stimulation, activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, and endothelin release.\textsuperscript{17} Hypertension might occur in patients with NCS through the following mechanisms. First, the reflowing blood is blocked by pressure in the renal vein, and the high pressure in the glomeruli reduces the ability of the kidney to excrete sodium, causing sodium retention; the increased circulating blood volume causes high blood pressure.\textsuperscript{18} Second, high blood pressure in the renal vein leads to renal ischemia and hypoxia, to which the capillary network of the renal medulla is very sensitive. The capillary network of the renal medulla is the key structure in the mechanism of stress diuresis; capillary network damage results in decreased or suppressed stress diuresis, leading to increased blood volume. In addition, chemoreceptors and mechanoreceptors of the kidney itself may sense the hemodynamic and metabolic changes in the glomerulus and produce excitatory signals, which generate norepinephrine after passing to the hypothalamus, elevating the blood pressure.\textsuperscript{19}

Our patient recovered from his hypertension, left flank pain, and varicocele formation after stent placement, indicating that the diagnosis of hypertension was associated with NCS.

In conclusion, NCP/NCS accompanied by hypertension is very rare. The possibility of NCP/NCS should be considered when secondary hypertension cannot be explained by other factors. The mechanism by which hypertension is caused by NCP/NCS is rather complex and deserves further investigation.

**Research ethics and patient consent**

Written informed consent was obtained from the patient for publication of this report and any accompanying images. Ethics approval was not required because we treated the patient according to an established regimen with no complications. The patient’s medical records were obtained during routine clinical treatment; this caused him no physical or mental pain and did not affect his privacy or health.

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The authors declare that there is no conflict of interest.

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References

1. Kim SH. Doppler US and CT diagnosis of nutcracker syndrome. *Korean J Radiol* 2019; 20: 1627–1637.
2. He Y, Wu Z, Chen S, et al. Nutcracker syndrome – how well do we know it? *Urology* 2014; 83: 12–17.
3. Lin TH, Lin CC and Tsai JD. Superior mesenteric artery syndrome and nutcracker syndrome. *Pediatr Neonatol* 2020; 27: 351–352.
4. Mazarakis A, Almpanis G, Tragotsalou N, et al. Is hypertension a manifestation of the nutcracker phenomenon/syndrome? Case report and brief review of the literature. *Hippokratia* 2012; 16: 187–189.
5. Park SJ, Kim SM, Won JH, et al. A case of secondary hypertension associated with the nutcracker phenomenon. *Korean Circ J* 2014; 44: 434–436.
6. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol* 2017; 89: 218–235.
7. El-Sadr AR, Mina E. Anatomical and surgical aspects in the operative management of varicocele. *Urol Cutaneous Rev* 1950; 54: 257–262.
8. De Schepper A. “Nutcracker” phenomenon of the renal vein and venous pathology of the left kidney. *J Belge Radiol* 1972; 55: 507–511.
9. Orczyk K, Wysiadecki G, Majos A, et al. What each clinical anatomist has to know about left renal vein entrapment syndrome (nutcracker syndrome): a review of the most important findings. *Biomed Res Int* 2017; 2017: 1746570.
10. Praveen M, Suseelamma D and Saritha S. Multiple renal vascular variations. *Open Access Sci Rep* 2012; 1: 334.
11. Orczyk K, Labetowicz P, Lodzinski S, et al. The nutcracker syndrome – morphology and clinical aspects of the important vascular variations: a systematic study of 112 cases. *Int Angiol* 2016; 35: 71–77.
12. Gulleroglu K, Gulleroglu B and Baskin E. Nutcracker syndrome. *World J Nephrol* 2014; 3: 277–281.
13. Ananthan K, Onida S and Davies AH. Nutcracker syndrome: an update on current diagnostic criteria and management guidelines. *Eur J Vasc Endovasc Surg* 2017; 53: 886–894.
14. Hosotani Y, Kiyomoto H, Fujioka H, et al. The nutcracker phenomenon accompanied by renin-dependent hypertension. *Am J Med* 2003; 114: 617–618.
15. Narkhede NA, Deokar AB, Mehta KP, et al. Nutcracker syndrome with hypertension as an unusual initial presentation. *Indian J Nephrol* 2017; 27: 472–474.
16. Azhar AB, Zeb NT, Shah S, et al. Nutcracker syndrome with hypertension: a case report. *Cureus* 2019; 11: e4781.
17. Ross EA. Congestive renal failure: the pathophysiology and treatment of renal venous hypertension. *J Card Fail* 2012; 18: 930–938.
18. Burnett JC Jr, Haas JA and Knox FG. Segmental analysis of sodium reabsorption during renal vein constriction. *Am J Physiol* 1982; 243: F19–F22.
19. Abildgaard U, Amtorp O, Agerskov K, et al. Renal vascular adjustments to partial renal venous obstruction in dog kidney. *Circ Res* 1987; 61: 194–202.