

CASE REPORT

Combined Nutcracker and Ehlers-Danlos Syndromes: A Case Report

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Introduction: Nutcracker syndrome refers to the clinical manifestations of left renal vein compression between the superior mesenteric artery and the abdominal aorta, causing urinary changes and low back pain.

Report: A 44 year old woman presented with low back and pelvic pain. Following the diagnosis of nutcracker syndrome, she underwent endovascular treatment with renal vein stent placement; however, the patient continued to complain of pain. Further examinations revealed left renal vein compression by the portal vein. The patient underwent a second procedure; however, improvement was temporary and her pain returned. Further investigation revealed previously undetected nephroptosis and hyperelasticity. A diagnosis of Ehlers–Danlos syndrome made, possibly explaining the mobility of viscera and unusual compression of the left renal vein by the portal vein.

Conclusion: Ehlers–Danlos syndrome can cause nutcracker syndrome and may give rise to visceral pain of mixed origin.

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INTRODUCTION

Nutcracker syndrome (NCS) refers to the clinical manifestations caused by the compression of the left renal vein (LRV) between the aorta and the superior mesenteric artery (SMA). Clinical manifestations include LRV to gonadal vein reflux and venous hypertension, causing left flank pain and haematuria. In some cases, the syndrome may also cause pelvic and ureteric varices, varicocele in men and pelvic congestion syndrome in women, with symptoms such as dysmenorrhoea, dyspareunia, post-coital ache, lower abdominal pain, dysuria, left ovarian vein insufficiency, and emotional disturbances. Nutcracker syndrome was observed in 72% of patients undergoing medical imaging; however, the exact incidence of symptomatic NCS is not known.¹

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of genetic connective tissue disorders² that are under-diagnosed,³ characterised in particular by skin

hyperextensibility,² vascular and visceral fragility,⁴ and joint hypermobility; the latter appears to be the dominant clinical manifestation, frequently associated with joint dislocation and chronic pain.⁵ According to the Villefranche criteria,⁶ there are six major subtypes of EDS based on clinical, genetic, and biochemical features.⁵ Hypermobility and vascular subtypes are the most common.⁶ Recurrent chronic pain is the most frequent neurological symptom in EDS, affecting the entire musculoskeletal system, the nervous system, and internal organs.³

A case of NCS and EDS occurring concomitantly in a female patient is reported, with overlapping symptoms and anatomical influences. No similar cases could be found in the literature. Because both diseases are currently under-diagnosed, this association might be more frequent than it appears to be.

CASE REPORT

A 44 year old Caucasian woman complained of very intense low back and pelvic pain episodes. She had two previous pregnancies with vaginal deliveries and a family history of acute myocardial infarction, stroke, and hypertension. A previous laparoscopy (Fig. 1A, B) revealed substantial pelvic and abdominal vascularisation on the left in the infundibulum and inferior vena cava, excluding the diagnosis of endometriosis.

On physical examination, the patient was 47 kg and her body mass index was below 18.5 kg/cm². Two imaging tests (Fig. 1C, D) demonstrated compression of the LRV between

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the SMA and the aorta, suggesting reflux to the left ovarian vein, which was significantly dilated, and explaining the pelvic varices secondary to renal vein compression visible on laparoscopy.

Because the diagnostic hypothesis was pelvic congestion secondary to NCS, the chosen approach was intravascular stent placement (Zilver Vena stent, 16 mm × 60 mm, Cook Medical, US) and balloon angioplasty (ATB Advance, 14 mm × 40 mm, Cook Medical, US) (Fig. 2A, B). Doppler ultrasound (Fig. 3B) and post-operative computed tomography (CT) angiography confirmed that the device was properly placed and the LRV compression was resolved (Fig. 3A, C). The patient reported improvement of symptoms. Nevertheless, one month later, she returned because of intense pain episodes, similar to the previous ones. Doppler ultrasound and magnetic resonance angiography (Fig. 4A) confirmed that the stent was correctly placed, and a patent LRV suggested that the NCS was resolved. Because the patient continued to complain of pain, a new ultrasound was performed, this time by a different operator, to examine the various painful sites. This examination revealed extrinsic compression of the LRV proximal to the vena cava, now by the portal vein (Fig. 4B).

The patient underwent a second surgical procedure for diagnostic purposes to confirm the potential compression. The procedure was performed under local anaesthesia and, as the catheter and guide wire passed through the renal vein, the patient reported low back pain. Following sedation, an intravascular ultrasound (Fig. 5A) was performed,

and measurement of intravascular LRV pressure before and after stent placement (Fig. 5B) showed pressure differences and extrinsic vein compression, suggestive of significant stenosis. Then, a second intravascular stent was placed (Zilver Vena stent, 16 mm × 60 mm, Cook Medical, US) using a telescoping technique.

The patient remained without pain for two weeks and was discharged from the hospital. Then, the pain returned. Doppler ultrasound (Fig. 6A), magnetic resonance imaging, and excretion urography revealed nephroptosis of the right kidney (Fig. 6B) that had been previously undetected (Fig. 3A). As the case was reassessed, the patient reported extreme joint mobility for the first time which, in association with the new image demonstrating nephroptosis, opened a new line of investigation. The patient scored 9 (maximum score) on the Beighton scale and met the criteria for EDS and hypermobility. She was referred to a team specializing in pain management with nerve block and to the genetics department, where the diagnosis of EDS was confirmed.

DISCUSSION

NCS is characterised by a set of signs and symptoms secondary to LRV compression and decreased angle between the SMA and aorta, reducing the LRV calibre by 50%.⁷ This event is believed to be associated with nephroptosis and/or little or absent retroperitoneal fat. LRV compression causes increased venous pressure, which originates from secondary collateral vessels, pelvic congestion, and pelvic venous plexus varices. They can cause haematuria associated with

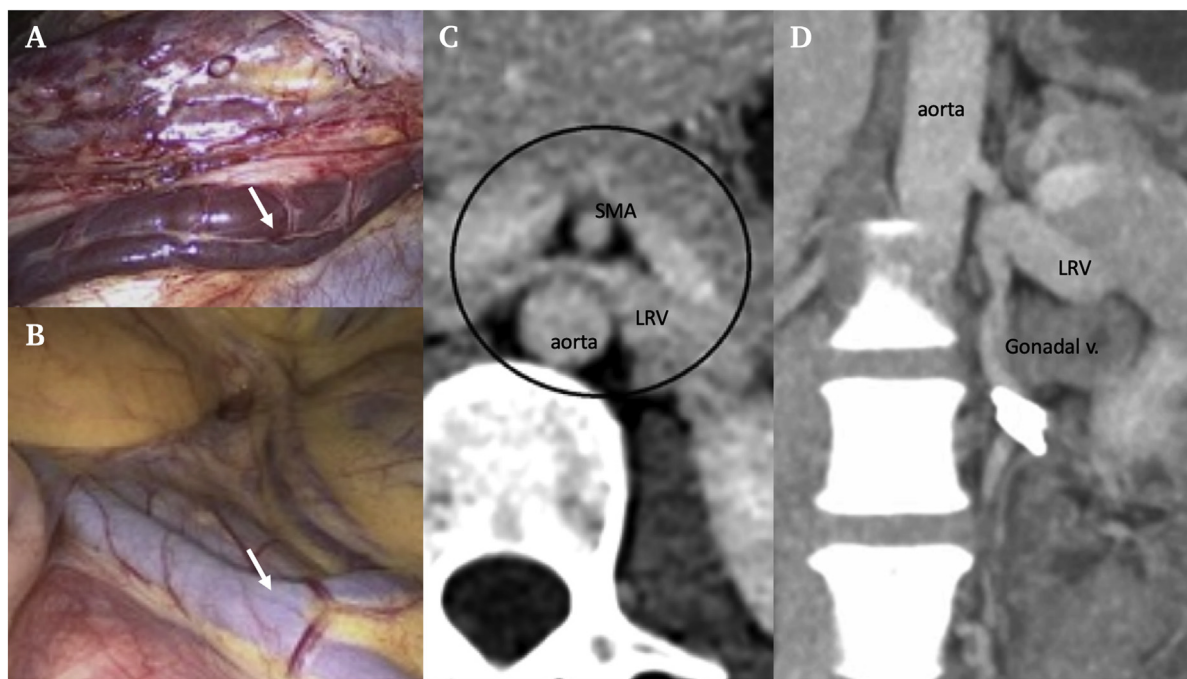


Figure 1. **A and B)** Laparoscopic images revealing substantial pelvic and abdominal vascularisation on the left, especially in the infundibulum and inferior vena cava, with engorged veins (white arrows) despite intra-abdominal hypertension caused by the pneumoperitoneum. **C)** Abdominal computed tomography scan, axial view, showing left renal vein compression by the superior mesenteric artery and aorta, with common “bird’s beak” sign (circled). **D)** Diagnostic computed tomography angiography with coronal reconstruction showing left renal vein and gonadal vein, both dilated.

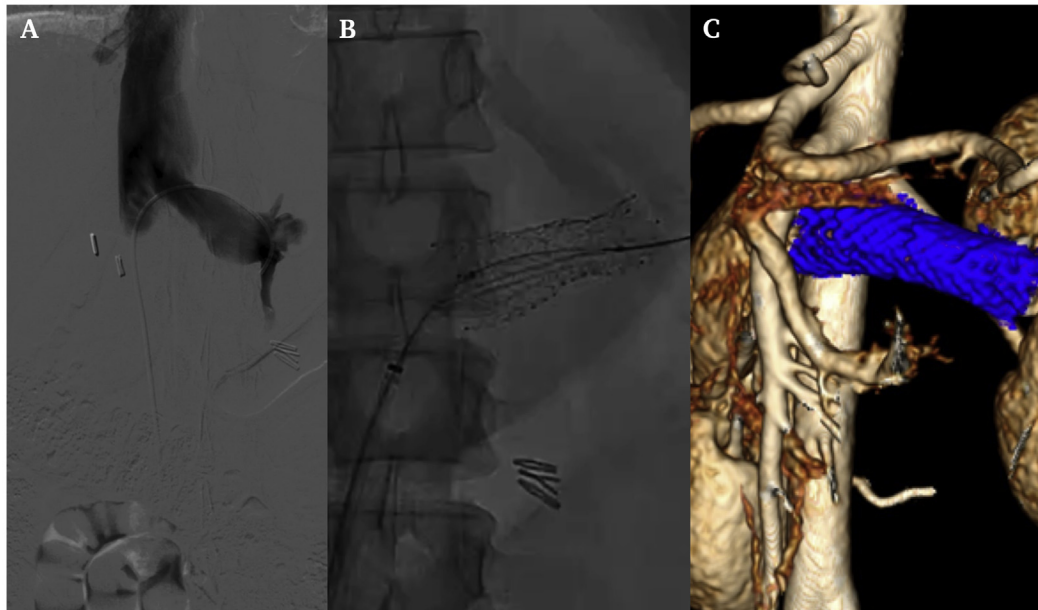


Figure 2. **A)** Intra-operative phlebography revealing competent gonadal veins and the compressed area of the left renal vein, which is dilated and has slow flow. **B)** Final venogram demonstrating stent placement. **C)** Three dimensional reconstruction of computed tomography angiogram after the surgical procedure revealing the intravascular stent properly placed in the left renal vein.

chronic left flank pain, abdominal and/or pelvic pain.⁷ Women aged 20–40 years are most frequently affected. The patient initially presented with anterior NCS and then with extrinsic compression by the portal vein, which is unusual and had not been described. Distinguishing the phenomenon from NCS is challenging because symptoms are non-specific and relatively common in other clinical conditions, including endometriosis. To determine a

diagnosis, a causal link must be established.⁷ Doppler ultrasound is the preferred method for initial investigation,⁷ followed by CT angiography,⁷ which has greater clinical applicability in treatment planning and pain investigation. All tests confirmed the diagnosis of NCS, and there was a clear symptomatic correlation. Phlebography and intravascular ultrasound, currently recommended during surgery,⁷ also confirmed the diagnosis.

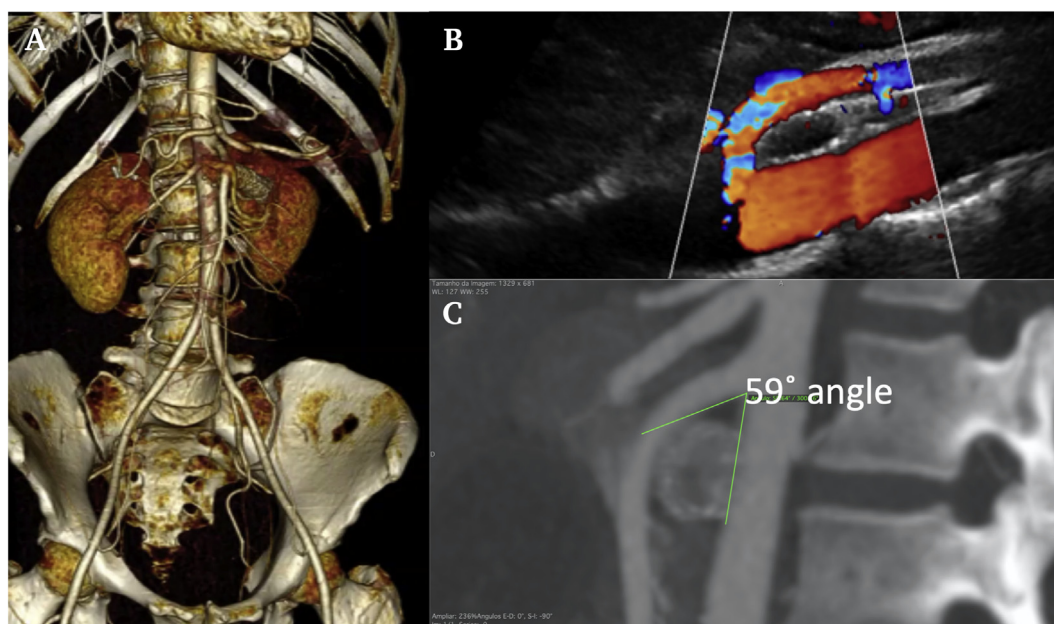


Figure 3. **A)** Three dimensional reconstruction of post-operative computed tomography angiogram revealing a properly placed stent and no significant nephroptosis on the right kidney. **B)** Doppler ultrasound after the first procedure revealing good venous flow in the left renal vein between the superior mesenteric artery and the aorta. **C)** Confirmation image, sagittal view, demonstrating an angle of 59° between the superior mesenteric artery and the aorta.

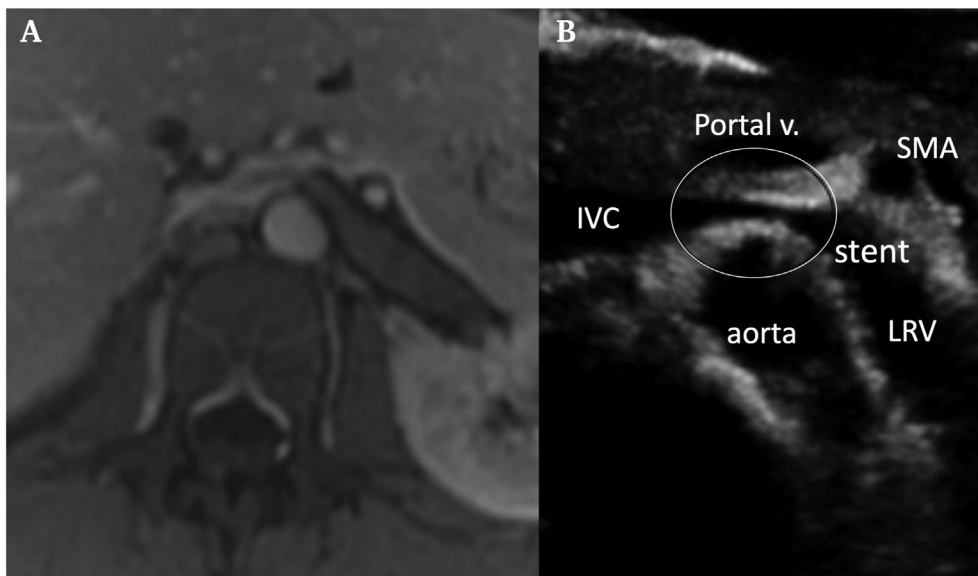


Figure 4. **A)** Magnetic resonance image, axial view, revealing decompression of the left renal vein between the superior mesenteric artery and the aorta. **B)** Left renal vein stenosis by the portal vein, proximal to the vena cava, ultrasound image revealing the area compressed by the portal vein (circled).

Though controversial, treatment depends on the severity of symptoms and may be conservative for patients with bearable symptoms. Surgery is indicated for those with severe haematuria associated with anaemia, functional renal failure, intense pelvic pain, or ineffective conservative treatment after 24 months clinical follow up. In the present case, surgery was indicated because of severe symptoms. Endovascular treatment has been proven effective, safe, and less invasive, with lower morbidity and mortality than other open surgical procedures.¹ Endovascular treatment consists of intravascular LRV stent placement; the device exerts radial force on the wall of the vein, opening it when

the SMA is pushed. Because no improvement was observed after the first procedure, other potential causes of pain were considered. An extensive investigation showed that unusual compression of the LRV by the portal vein was responsible for persistent NCS symptoms and led to the second procedure.

Even after LRV compression was corrected for a second time, the patient continued to complain of pain. A concomitant diagnostic investigation was then initiated, targeting other infrequent causes and guided by a visceral anatomical change and a new report of extreme joint mobility that led to the diagnosis of EDS. Pain is a common

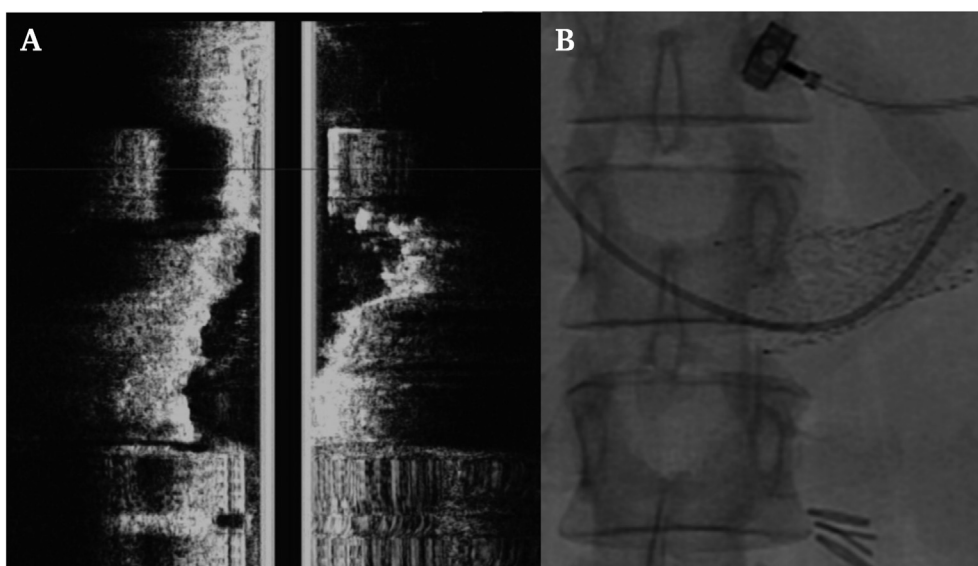


Figure 5. Intravascular ultrasound performed during the second procedure. **A)** Two dimensional reconstruction showing segment with extrinsic compression. **B)** Pressure gradient measurement.

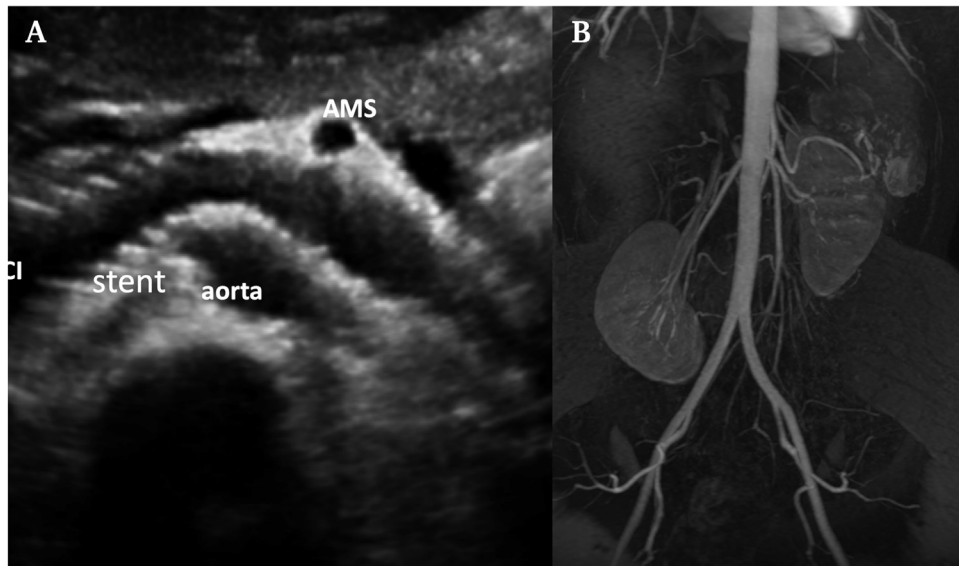


Figure 6. A) Ultrasound image after the second procedure showing proper stent coverage, preventing left renal vein compression by the portal vein. B) Nephroptosis of the right kidney, previously undetected on imaging.

feature in several EDS subtypes and it significantly affects quality of life.⁸ In the present case, the pain had mixed origins. Classical, hypermobile, and vascular EDS subtypes show the strongest associations between intense pain and functional impairment.⁸ Generalised chronic muscle pain is a diagnostic criterion.³ Venous malformations associated with superficial elastic changes have been described previously,² reinforcing the need to investigate possible associated causes for the symptoms. In EDS, pain responses are influenced by the adaptation strategy that each patient develops to handle symptoms.⁸

The present report highlights non-surgical resolution of symptoms and persistent complaints of chronic pain, even after proper treatment for an unusual form of NCS. The diagnosis of EDS was clinical, based on two major criteria (smooth, velvety skin and generalised joint hypermobility) and one minor criterion (chronic limb pain).³ The clinical diagnosis of EDS is challenging because of complex patient profiles.⁸ Although EDS affects 1 in 5000 people, it remains underdiagnosed.³

Chronic memory pain is persistent in nature and often has a direct anatomical relationship to the initial pain event. The central nervous structures of pain processing freeze the memory of the initial pain impression,⁹ possibly explaining the process of pain chronification in this patient.

The patient had signs and symptoms consistent with both NCS and EDS, potential causes of the chronic pain, possibly acting together and magnifying the symptoms. The authors believe that, due to hyperelasticity and altered collagen, mobility of the viscera occurred, allowing unusual compression of the LRV by the portal vein that in turn led to the reappearance of intense pain, a characteristic symptom of NCS. Visceroptosis can cause kinking of thin walled abdominal structures such as blood vessels, nerves and ducts, as explained by Reinstein et al.¹⁰ Even after the

second intravascular procedure, improvement of symptoms was only partial and temporary, leading to the belief that chronic pain in this patient may be explained also by EDS itself and pain imprinting.

CONCLUSION

The unusual association between NCS and EDS makes the resolution of renal vein compression more complex; thus, therapeutic planning should include the possibility of internal mobility of the viscera. Furthermore, pain may be of mixed origin, and its primary cause should be investigated. The authors suggest using the simple questionnaire for hypermobility¹¹ for patients diagnosed with NCS, and if detected, Beighton scores should be used to assess the degree of joint hypermobility.

ETHICAL APPROVAL

The study was approved by the Ethics Committee and conducted in accordance with the provisions of the Declaration of Helsinki.

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DECLARATIONS OF COMPETING INTEREST

None.

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