Nonatherosclerotic Obstructive Vascular Diseases of the Mesenteric and Renal Arteries

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ABSTRACT

Nonatherosclerotic vascular diseases of the mesenteric and renal arteries are considered to occur less frequently than those caused by occlusive atherosclerotic disease. However, when present, they pose a significant diagnostic and therapeutic challenge. Such disorders include fibromuscular dysplasia, median arcuate ligament syndrome, the renal nutcracker syndrome, and some forms of acute and chronic mesenteric ischemia (embolic and thrombotic). This is a heterogeneous group of disorders with substantial differences in the pathogenesis and diagnostic approaches to these diseases. We provide an overview of the pathogenesis, clinical presentation, diagnosis, and current management of fibromuscular dysplasia, median arcuate ligament syndrome, and the renal nutcracker syndrome.

Introduction

Nonatherosclerotic vascular diseases of the mesenteric and renal arteries are functionally and anatomically distinct from those caused by occlusive atherosclerotic disease. Furthermore, there are substantial differences in the pathogenesis and diagnostic approaches to fibromuscular dysplasia (FMD), median arcuate ligament syndrome (MALS), and the renal nutcracker syndrome (NCS).

Although the pathogenesis of FMD remains unknown, several genetic, mechanical, and hormonal factors have been proposed.¹ Median arcuate ligament syndrome is caused by celiac artery compression by fibers of the median arcuate ligament or fibrotic celiac ganglion.² Renal NCS is the entrapment of the left renal vein, which is characterized by the compression of the vessel between the superior mesenteric artery and the abdominal aorta.³

The purpose of this review is to provide an overview of the pathogenesis, clinical presentation, diagnosis, and current management of FMD, MALS, and the renal NCS (Table 1).

Fibromuscular Dysplasia

Fibromuscular dysplasia is a nonatherosclerotic, noninflammatory vascular disease that most commonly affects the renal and carotid arteries, although it can affect any artery in the body.¹

In 1958, McCormack et al⁴ reported the pathological description of FMD in 4 patients with renovascular hypertension, 20 years after the original description of the disease. A decade later, in 1965, Hunt et al⁵ suggested the term dysplasia upon discovering that hyperplasia was not a mandatory component of the disease process.

Although the overall prevalence in the general population is unknown, results from the US Registry for Fibromuscular Dysplasia (hereinafter FMD Registry) revealed that 91% of the patients included were women, with a mean age of 52 ± 13 years.⁶ In the same report of 447 patients, FMD was identified in the renal artery in 294 patients, extracranial carotid arteries in 251 patients, and vertebral arteries in 82 patients.

Pathogenesis

In the early 1970s, Harrison et al⁷ proposed the first pathologic classification of renal arterial disease in renovascular hypertension. This histological scheme discriminates 3

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Table 1. Pathogenesis, Clinical Presentation, Diagnosis, and Current Management of FMD, MALS, and Renal NCS

	FMD	MALS	NCS
Epidemiology	Females > males, mean age 52 years	Females > males, 20–40 years	Females > males, 30–40 years
Etiology	HLA DR-w6 polymorphism	Inadequate caudal migration of the celiac artery and low insertion of the ligament	Angle between abdominal aorta and SMA <16 degrees
Angiography	Beaded aneurysmal appearance	Superior indentation of celiac axis (proximal to origin at abdominal aorta)	No specific characterization
Pathophysiology	Fibromuscular hyperplasia or fibroplasia Can affect any artery, but usually limited to renal and carotid artery	Proximal celiac trunk compression by median arcuate ligament Mechanism unclear: mesenteric ischemia, intermittent foregut ischemia, stimulation of celiac ganglion and plexus	Left renal vein entrapment caused by SMA and abdominal aorta Renal vein hypertension
Clinical presentation	Renovascular, hypertension, hypertension, headache, tinnitus	Postprandial abdominal pain, nausea, vomiting, diarrhea, malabsorption, weight loss	Hematuria albuminuria, left flank pain, varicocele, pelvic congestion syndrome
Evaluation and diagnosis	Renal duplex, captopril renal scintigraphy, renal MRA, CT angiography Digital subtraction angiography (gold standard)	Epigastric bruit on exam that increases on deep inspiration Abdominal color duplex (screening) Abdominal imaging (CT, CT angiography, MRI), gastric emptying study, gastroduodenoscopy Lateral aortic angiography (gold standard)	Duplex ultrasound (screening) Venography (gold standard)
Treatment	Balloon angioplasty and stenting Surgical reconstruction	Open surgical resection of MAL with removal of celiac ganglion Laparoscopic surgical decompression of celiac artery PTA Purely endovascular treatment not recommended (risk of stent compression or fracture)	Surveillance Surgical decompression Endovascular stents

Abbreviations: CT, computed tomography; FMD, fibromuscular dysplasia; HLA, human leukocyte antigen; MAL, median arcuate ligament; MALS, median arcuate ligament syndrome; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NCS, nutcracker syndrome; PTA, percutaneous transluminal angioplasty; SMA, superior mesenteric artery.

main subtypes based on the dominant arterial wall layer involved: intima, media, or adventitia. As a result, 3 main types of FMD have been classified: intimal, medial, and perimedial,⁸ with the medial subtype the most common, accounting for 85%. This type of FMD is characterized by a homogeneous collar of elastic tissue that presents as multiple stenoses interspersed with aneurysmal outpunching, with a preserved internal elastic lamina. The other 2 forms are far less common; for instance, intimal FMD accounts for 5% and perimedial 10% of renal artery FMD cases. Intimal FMD is characterized by irregularly arranged mesenchymal cells within a loose matrix of subendothelial connective tissue, and perimedial FMD is characterized by excessive tissue deposition at the junction of the media and adventitia. However, some data suggest that in some areas >60% of patients may have ≥ 1 layer involved.⁹

In contrast to these findings, in the FMD Registry,⁶ the medial subtype was by far the most common subtype (91.4%), followed by intimal (7.0%) and perimedial disease (0.7%). Of these, 3 patients (1%) had features of both medial and intimal disease.

The true etiology of FMD is poorly understood. Associations with environmental factors in individuals with genetic predisposition have been noted, the most common

of these being exposure to exogenous estrogens and mechanical stress to the renal arteries; however, this is still controversial.

Sang et al¹⁰ found no association between the occurrence of FMD and prior oral contraceptive use, endogenous sex-hormone abnormality, or an increase in renal mobility. However, their results suggested that cigarette smoking and genetic predisposition are of etiologic importance in FMD. In contrast, the FMD Registry reports exposure to either oral contraceptives or hormone-replacement therapy in 69.6% of women, with 13.5% of women receiving systemic hormone-replacement therapy at the time of enrollment in the registry.⁶

Bofinger et al¹¹ examined the relationship between smoking and severity of FMD in a small group of 50 subjects. Twenty-four out of the 50 subjects were smokers. At the time of diagnosis of FMD, smokers were younger than nonsmokers (38.7 years vs 48.9 years, $P < 0.01$), had a shorter median history of hypertension (1.5 years vs 8.5 years, $P < 0.05$), and had a higher prevalence of unilateral renal atrophy (67% vs 27%, $P < 0.01$). Therefore, they concluded that patients who smoke have a more severe arterial disease than those who do not. Interestingly, in the largest registry to date,⁶ only 37% of patients reported smoking.

Some evidence suggests that genetic factors may play a role in the development of FMD. Pannier-Moreau et al¹² in 1997 conducted a retrospective analysis of 104 patients and showed a prevalence of 11% for familial cases. HLA-DRw6¹⁰ and polymorphisms of the renin-angiotensin system are perhaps linked to FMD¹³; however, further studies need to confirm these findings.

Clinical Presentation

The hallmark of FMD is renovascular hypertension. The data provided by the FMD Registry⁶ revealed that hypertension (63%), headache (52%), and pulsatile tinnitus (28%) were the most common presenting symptoms. The progression of FMD, defined by the occurrence of a new focal lesion, worsening arterial stenosis, or the enlargement of a mural aneurysm, occurs in up to 37% of patients with FMD.¹⁴

In renovascular hypertension, the reduction of renal blood flow due to renal artery stenosis induces excessive activation of the renin-angiotensin-aldosterone (RAA) system and leads to hypertension. The sensing mechanism of the RAA system remains elusive. In patients and animal models of renovascular hypertension, expression of cyclooxygenase 2 (COX-2), a rate-limiting enzyme for prostanoid synthesis, has been reported to be increased in the kidneys.¹⁵ Fujino et al¹⁶ addressed this issue by investigating the role of PGI₂ in renovascular hypertension in mice lacking the PGI₂ receptor (IP $-/-$ mice). They found decreased susceptibility to renovascular hypertension in mice lacking the prostaglandin I₂ receptor, and therefore concluded that PGI₂ derived from COX-2 plays a critical role in regulating the release of renin and consequently renovascular hypertension in vivo.

Evaluation

The evaluation and diagnosis of FMD is usually done by means of noninvasive tests. The most common of these is duplex imaging of the renal arteries, which can accurately detect an increase in blood-flow velocities in segmental portions of the renal arteries. Apart from providing direct visualization of the diseased segment, elevations of velocity in those segments are often a clue toward diagnosing FMD,¹ because atherosclerosis rarely occurs in the distal portion of the renal arteries. The role of other diagnostic tests, such as captopril renal scintigraphy, magnetic resonance (MR) angiography, and computed tomography (CT) angiography, is less well defined.¹⁷ Computed tomography angiography is a more specific test (92%) than MR angiography (84%), but both tests have poor sensitivities (64% and 62%, respectively).¹⁸

The gold standard for diagnosing FMD is digital subtraction angiography, which reveals a characteristic beaded, aneurysmal appearance (Figure 1). Because this is an invasive test, it is usually reserved for those who are likely to require revascularization.

Treatment

Scenarios in which treatment should be strongly considered include recent onset of hypertension, where the goal is to

Figure 1. Illustration of fibromuscular dysplasia with artistic schematic of typical “beads on string” angiographic appearance.

cure hypertension; hypertension despite a comprehensive antihypertensive regimen; intolerance to antihypertensive medicines; persistent hypertension due to noncompliance; and ischemic nephropathy as a result of lost renal volume.¹ In the FMD Registry, the most frequent indications for therapy were hypertension, aneurysm, and dissection.⁶

The preferred treatment is balloon angioplasty, with bailout stent placement if necessary. Most of the current recommendations for invasive treatment of FMD come from data on atherosclerotic renovascular disease. The first renal artery balloon angioplasties were performed by Felix Mahler in the late 1970s.¹⁹ To date, 2 randomized studies in atherosclerotic renovascular disease have demonstrated the superiority of stenting over conventional balloon angioplasty in terms of acute treatment success and technical durability in atherosclerotic renal artery stenosis.^{20,21} Whether these data may be extrapolated to FMD patients remains unknown. Surgical reconstruction is reserved for patients with complex FMD that extends to segmental arteries and those with microaneurysms.²²

Median Arcuate Ligament Syndrome

Median arcuate ligament syndrome is a rare disorder resulting from compression of the origin of the celiac trunk by the median arcuate ligament (MAL), the fibrous edge of the right and left diaphragmatic crura that crosses anterior to the aorta at the level of the celiac artery. Usually, the MAL crosses the aorta at the level of L1; therefore, it is located above the origin of the celiac trunk. However, in 10% to 24% of the general population, inadequate caudal migration of the artery during embryogenesis or low insertion of the ligament produces compression of the proximal part of the celiac trunk²³ (Figure 2).

Pathogenesis

Despite numerous theories since the early 1960s, the pathophysiology of MALS remains unclear. One theory

Figure 2. Illustration of median arcuate ligament syndrome with artistic schematic of the relationship of the MAL and the celiac trunk. (A) Anterior view demonstrating compression of the proximal part of the celiac trunk by the MAL. (B) Lateral view demonstrating compression of the proximal part of the celiac trunk by the MAL. (C) Normal anatomy. Abbreviations: MAL, median arcuate ligament.

attributes the symptoms of MALS to mesenteric ischemia secondary to decreased blood flow.²⁴ However, it is unlikely that mesenteric ischemia alone is the cause of symptomatic MALS and that intermittent foregut ischemia may play a role.

In a landmark paper, Reilly et al demonstrated that 70% of asymptomatic patients had a patent celiac artery, compared with 75% of symptomatic patients who had an occluded celiac artery.²⁵ Thus, the concept of compressive obstruction as the lone cause of symptoms in MALS seems less likely. It is possible that collateral blood supply through the superior mesenteric artery to the celiac artery causes postprandial “steal” of blood, and this is the cause of postprandial abdominal pain, making the transient ischemic theory more plausible. However, Tribble et al²⁶ proposed that symptoms may be caused by compression and stimulation of the celiac ganglion and plexus. Thus, symptoms such as abdominal pain, nausea, and vomiting may be the direct result of sympathetic pain-fiber stimulation or the indirect result of splanchnic vasoconstriction.

Clinical Presentation

Median arcuate ligament syndrome typically affects women between 20 and 40 years of age and usually presents

with postprandial abdominal pain, nausea, vomiting, and diarrhea. In extreme cases, it can induce intestinal malabsorption and weight loss.

On physical exam it may be possible to hear an epigastric bruit that varies with inspiration. As the lungs are expanding on deep inspiration, the celiac trunk moves in a caudal direction with respect to the MAL. As a result, compression decreases during inspiration and increases during expiration.²⁷

Evaluation

Most patients will have multiple previous evaluations for more common causes of postprandial abdominal pain, nausea, vomiting, and diarrhea. Therefore, the diagnosis is often one of exclusion. In young women with abdominal complaints, a full workup with CT scan, gastric-emptying studies, magnetic resonance imaging (MRI), and gastroduodenoscopy should be performed. If these diagnostic studies and procedures fail to find any other pathology, a diagnosis of MALS should be considered.²⁸

Scholbach et al²⁹ studied a total of 3449 children ages 0 to 18 years with abdominal color duplex sonographic examinations. Celiac artery flow velocity was measured at the branching-off from the aorta during inspiration, expiration, and in between. Diagnosis of MALS was made if a >2-fold acceleration of peak systolic flow in the celiac artery compared with the abdominal aorta or a peak systolic velocity (PSV) >200 cm/s was measured in the mid position and if a variation of flow velocity occurred during respiration. They found 59 patients (81% female) fulfilling color Doppler sonographic criteria of MALS (prevalence of 1.7%), slightly higher than expected in the general population. Duplex abdominal ultrasound may therefore be used as initial screening, with further imaging to confirm the diagnosis. The gold standard is lateral aortic angiography,³⁰ which typically shows superior indentation of the celiac axis approximately 5 mm from its origin at the abdominal aorta. The narrowing is variable within the breathing cycle, being accentuated on expiration and relieved on inspiration.

Computed tomography angiography, especially if combined with 3-dimensional reconstructions, can demonstrate all characteristic aspects seen on conventional angiography.³⁰ In addition, CT angiography offers information about the relationship of the celiac artery with the diaphragm and allows visualization of the compressed artery from various angles.³¹

Treatment

The traditional management of MALS has been open surgical resection of the MAL with removal of the celiac ganglion. In addition, several reports have shown that laparoscopic surgery is a potentially useful tool in the treatment of MALS.^{32–34} The operation should divide the fibrous bands of the MAL, including the celiac ganglion fibers around the celiac artery, leaving the celiac trunk completely free circumferentially.²⁸

In a recent series of 15 patients with laparoscopic surgical decompression of the celiac artery, there were no operative deaths, although 4 patients converted to open decompression, all for intraoperative bleeding.³⁴ Relative

contraindications to laparoscopic celiac artery decompression include inability to tolerate pneumoperitoneum, multiple previous abdominal operations, previous aortic or mesenteric reconstruction or bypass, and patients who have undergone surgical decompression of the celiac artery.³³

Percutaneous transluminal angioplasty (PTCA) was first performed in 1980 by Saddekni et al for recurrent stenosis after open surgery.³⁵ As demonstrated in the Johns Hopkins Hospital's series,³⁴ percutaneous revascularization with intraoperative angioplasty or postoperative stenting has been successful, although the utility of combining laparoscopic celiac artery decompression with percutaneous revascularization should be measured against open decompression with surgical revascularization. However, purely endovascular treatment of MALS is not recommended, and the use of stents without previous MAL division may be complicated by stent compression or fracture.³⁶

Renal Nutcracker Syndrome

The renal NCS is characterized by left renal vein entrapment between the superior mesenteric artery (SMA) and the abdominal aorta (Figure 3). This condition was first described by El Sadr and Mina in 1950 when describing the operative management of varicoceles.³⁷ The actual compression of the renal vein was demonstrated angiographically by Chait et al³ in 1971.

Pathogenesis

The angle between the abdominal aorta and the SMA is usually >35 degrees and commonly >90 degrees. In contrast, patients with NCS have frequently been noted to have an angle of <16 degrees.³⁸ Currently, 2 types of NCS are classified, anterior and posterior NCS.

In anterior NCS, the SMA branches from the aorta at an acute angle (<90 degrees) with initial steep caudal descent, causing compression of the left renal vein in the narrow slit between the aorta and the SMA, resulting in renal venous hypertension.³⁹ Posterior NCS occurs as a result of a retroaortic course of the left renal vein, which causes compression of the left renal vein between the aorta and the vertebral column and leads to left renal venous hypertension.⁴⁰

The pathophysiology of NCS is not completely understood. It is believed that renal venous hypertension leads to development of valveless collaterals, which increase venous capacitance. These thin-walled venous sinuses have been histologically observed to communicate with the adjacent renal calyces, predisposing to the passage of red cells responsible for associated hematuria.⁴¹ It is also unclear why similar symptoms are not present in patients who undergo left renal vein ligation during aortic aneurysm repair or in whom the left renal vein is stretched taut over an aortic aneurysm.⁴¹

Clinical Presentation

Renal NCS usually presents with hematuria, albuminuria, or left flank pain in young women in their third or fourth decade.⁴² A less common presentation is a symptom complex termed "pelvic congestion syndrome,"

Figure 3. Illustration of renal nutcracker syndrome with artistic schematic demonstrating left renal vein entrapment between the SMA and the abdominal aorta. Abbreviations: SMA, superior mesenteric artery.

characterized by emotional disturbances, dysmenorrhea, dyspareunia, postcoital ache, lower abdominal pain, dysuria, and varices of pelvic, vulvar, gluteal, or thigh vessels.

Men may additionally have varicoceles.^{43,44} Systemic manifestations including headache, abdominal pain, fainting, and tachycardia mimicking clinical symptoms of an orthostatic disturbance have also been reported in adolescents.⁴⁵

Diagnosis

The diagnosis of NCS is often challenging. In 2003, Ali-El-Dein et al⁴⁶ proposed sequential diagnostic tests for confirmation of classical cases of NCS, including laboratory and imaging studies directed toward the many causes of hematuria with flank pain. In practice, duplex ultrasound should be the initial diagnostic test, followed by CT angiography.⁴⁷ Duplex ultrasound should be directed to image the obstruction as well as measure the ratio of PSV at the point of renal vein compression to the renal vein at the hilum. In the largest series published,⁴⁸ the mean PSV ratio was 7.3. A PSV ratio of 4.7 allows NCS to be diagnosed with 100% sensitivity and 90% specificity.⁴⁹ The gold standard for the diagnosis of NCS is venography, which allows both renocaval pressure-gradient determination and contrast mapping of the perihilar, gonadal, and pelvic collateral network. It can thus guide further decisions on which patients require intervention.⁴¹

Treatment

There are 3 accepted modes of treatment of NCS: conservative treatment (surveillance), surgical decompression, and percutaneous endovascular therapy. General conservative management is reserved for those with mild symptoms and young patients, because these frequently improve with conservative management.⁴¹ For example, Tanaka et al⁵⁰ reported a case of a 14-year-old boy who presented with gross hematuria associated with mild proteinuria. They showed spontaneous remission of persistent severe hematuria at 7 years of observation/conservative management, suggesting that a proportion of pubertal patients with NCS can be treated conservatively for a relatively long time.

The most common surgical approach to NCS has focused on decompression of the venous hypertensive state by direct manipulation of the left renal vein or dilated gonadal vein. Gonadocaval bypass using an H-graft fashioned out of either saphenous vein or Dacron prosthetic grafts has been successfully performed.⁴⁴ Left vein transposition through transperitoneal exposure involves division of the left renal vein at its junction with the inferior vena cava. A large series from the Mayo Clinic demonstrated the procedure's safety and efficacy for resolution of severe flank pain and hematuria.⁴⁸

The largest stenting experience to date is from China,⁴² in which 15 patients with NCS were treated percutaneously, compared with 5 treated surgically. Transposition of the SMA was performed in 3 cases, transposition of the left renal vein in 2, and stent implantation in the left renal vein in 15. Follow-up was made from 6 months to 6 years after the operation. All stented patients were asymptomatic, though 2 manifested persistent microscopic hematuria following exercise.

Although endovascular stenting may be a simpler, more attractive option, its future role in the management of NCS remains to be established. It is also known that stents in the venous system can cause fibromuscular hyperplasia, which may result in venous occlusion.⁴⁵

Conclusion

Fibromuscular dysplasia, MALS, and NCS are a heterogeneous group of intra-abdominal, nonatherosclerotic vascular diseases with varied clinical presentations. Current research efforts strive toward understanding the pathophysiology of these disorders, as well as assessing possible therapeutic approaches. Unfortunately, the low prevalence of these disorders makes large studies difficult to conduct. With increased recognition and formation of international registries, future research efforts may be better facilitated.

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