REVIEW ARTICLE

CURRENT CONCEPTS

Fibromuscular Dysplasia

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Fibromuscular dysplasia is a nonatherosclerotic, noninflammatory vascular disease that most commonly affects the renal and internal carotid arteries but has been described in almost every arterial bed in the body (Table 1).[1-12] Although the disease was first described by Leadbetter and Burkland in 1938,[13] the report by McCormack and coworkers two decades later of four cases of "fibromuscular hyperplasia" was the first accurate pathological description of this entity.[14] The clinical presentation may vary from an asymptomatic condition to a multisystem disease that mimics necrotizing vasculitis,[15] depending on the arterial segment involved, the degree of stenosis, and the type of fibromuscular dysplasia.

TYPES OF FIBROMUSCULAR DYSPLASIA

The pathological classification scheme for fibromuscular lesions of the renal arteries is based on the arterial layer — intima, media, or adventitia — in which the lesion predominates.[16] Macroaneurysms and dissections are complications of fibromuscular dysplasia and do not represent distinct histopathological categories.

Medial fibroplasia, which is characterized by its classic "string of beads" appearance, represents the most common dysplastic lesion.[4,16] Typically, the beading is larger than the normal caliber of the artery and is located in the middle-to-distal portion of the artery (Fig. 1).[17] Histologically, there is involvement of the media, whereas the intima, internal elastic lamina, and adventitia are preserved.[4,16] The lesion of perimedial fibroplasia is characterized by a homogeneous collar of elastic tissue at the junction of the media and the adventitia. The elastic elements of the media and intima appear normal. Perimedial fibroplasia is diagnosed when focal stenoses and, occasionally, multiple constrictions are observed, often with a robust collateral network. The "beads" are usually less numerous than in medial fibroplasia and are typically smaller in diameter than the normal caliber of the artery (Fig. 2).[18] Medial hyperplasia accounts for less than 1 percent of arterial stenoses and may be indistinguishable angiographically from intimal fibroplasia.[19]

Intimal fibroplasia occurs in less than 10 percent of patients with arterial fibrodysplasia.[4,16] Angiographically, it may appear as a focal, concentric stenosis (Fig. 3A and 3B); a long, smooth narrowing similar to that seen in large-artery vasculitides such as giant-cell arteritis or Takayasu's arteritis[17]; or a redundancy of the artery (Fig. 3C).

Adventitial (periarterial) hyperplasia is the rarest type of fibrodysplastic lesion.[4,16] Although there is currently limited angiographic information, sharply localized, tubular areas of stenosis have been observed.[18,19]

PATHOGENESIS

Although a variety of genetic, mechanical, and hormonal factors have been proposed, the cause of fibromuscular dysplasia remains unknown. Cigarette smoking and a history

of hypertension are associated with an increased risk of this condition. No association has been found between fibromuscular dysplasia and previous use of oral contraceptives or abnormalities of endogenous sex hormones.[21] Genetic factors may play a part in the development of fibromuscular dysplasia, since the disease is more common among the first-degree relatives of patients with fibromuscular dysplasia of the renal arteries[22,23] and among persons with the angiotensin-converting–enzyme allele ACE-I.[24]

DIFFERENTIAL DIAGNOSIS

It is usually not difficult to differentiate atherosclerosis from fibromuscular dysplasia. Atherosclerosis generally occurs at the origin or proximal portion of the artery in older patients with typical cardiovascular risk factors. In contrast, fibromuscular dysplasia occurs in the middle or distal arterial segments in younger patients with few cardiovascular risk factors.

The Ehlers–Danlos syndrome (type IV) has been associated with medial fibroplasia.[25] This syndrome should be suspected in patients with multiple aneurysms in addition to the typical angiographic findings of fibromuscular dysplasia. There have been isolated reports of fibromuscular dysplasia associated with Alport's syndrome,[26] pheochromocytoma,[27,28] Marfan's syndrome,[29] and Takayasu's arteritis.[30,31]

At times, it may be difficult to distinguish fibromuscular dysplasia from vasculitis. Fibromuscular dysplasia is, by definition, a noninflammatory process and is therefore not associated with anemia, thrombocytopenia, or abnormalities of acute-phase reactants, except when it occurs during acute infarction. Large-vessel vasculitis may occur in the absence of changes in acute-phase reactants in up to 40 percent of cases.[32] When histologic proof or markers of inflammation are unavailable, it may be difficult to distinguish these entities, because their angiographic appearance may be similar, especially if the intimal fibroplasia is of the multivessel type. Although magnetic resonance angiography may show wall thickening in patients with giant-cell arteritis or Takayasu's arteritis,[33] it is not useful in patients with renal or intestinal fibromuscular dysplasia, because the resolution of magnetic resonance angiography is inadequate for the visualization of branch-vessel involvement. In some cases, intravascular ultrasonography may help to distinguish fibromuscular dysplasia from vasculitis.[34] Multiple-organ involvement in fibromuscular dysplasia is particularly troublesome, since ischemia may be associated with increased risks of complications and death.[35]

Table 1. Arterial Involvement in Fibromuscular Dysplasia.*

Arteries Involved	Frequency of Involvement (%)
Renal arteries	60–75
Bilateral	35
Extracranial cerebrovascular circulation (carotid or vertebral arteries)	25–30
Associated intracranial aneurysm	7–50
Multiple vascular beds	28
Other arterial beds (iliac, popliteal, splanchnic, hepatic, coronary, subclavian, brachial, aorta, superficial femoral, tibial, or peroneal)	Uncommon, exact frequency unknown

* Fibromuscular dysplasia may be a generalized process; in rare cases, it has also been identified in the venous system.

FIBROMUSCULAR DYSPLASIA OF THE RENAL ARTERIES

Renovascular fibromuscular dysplasia tends to affect women between 15 and 50 years of age. It is not uncommon, however, to encounter patients in whom it first presents after 60 years of age. In most cases, these persons have been asymptomatic for many years, and fibromuscular dysplasia is discovered incidentally during the investigation of another problem. According to recent reports, fibromuscular dysplasia accounts for less than 10 percent of cases of renovascular hypertension.[36]

The natural history of renal fibromuscular dysplasia has been described in several studies.[19,37-40] The progression of angiographic disease, defined by the occurrence of a new focal lesion, worsening arterial stenosis, or the enlargement of a mural aneurysm, occurs in up to 37 percent of patients with renal fibromuscular dysplasia.[19,40] It is often difficult to assess disease progression according to angiographic criteria, especially in patients with medial fibroplasia, in whom it is difficult to gauge the degree of stenosis (Fig. 1A).[38]

Monitoring for changes in the renal parenchyma may provide another means of assessing disease progression. Mounier-Vehier and colleagues used computed tomographic angiography to compare

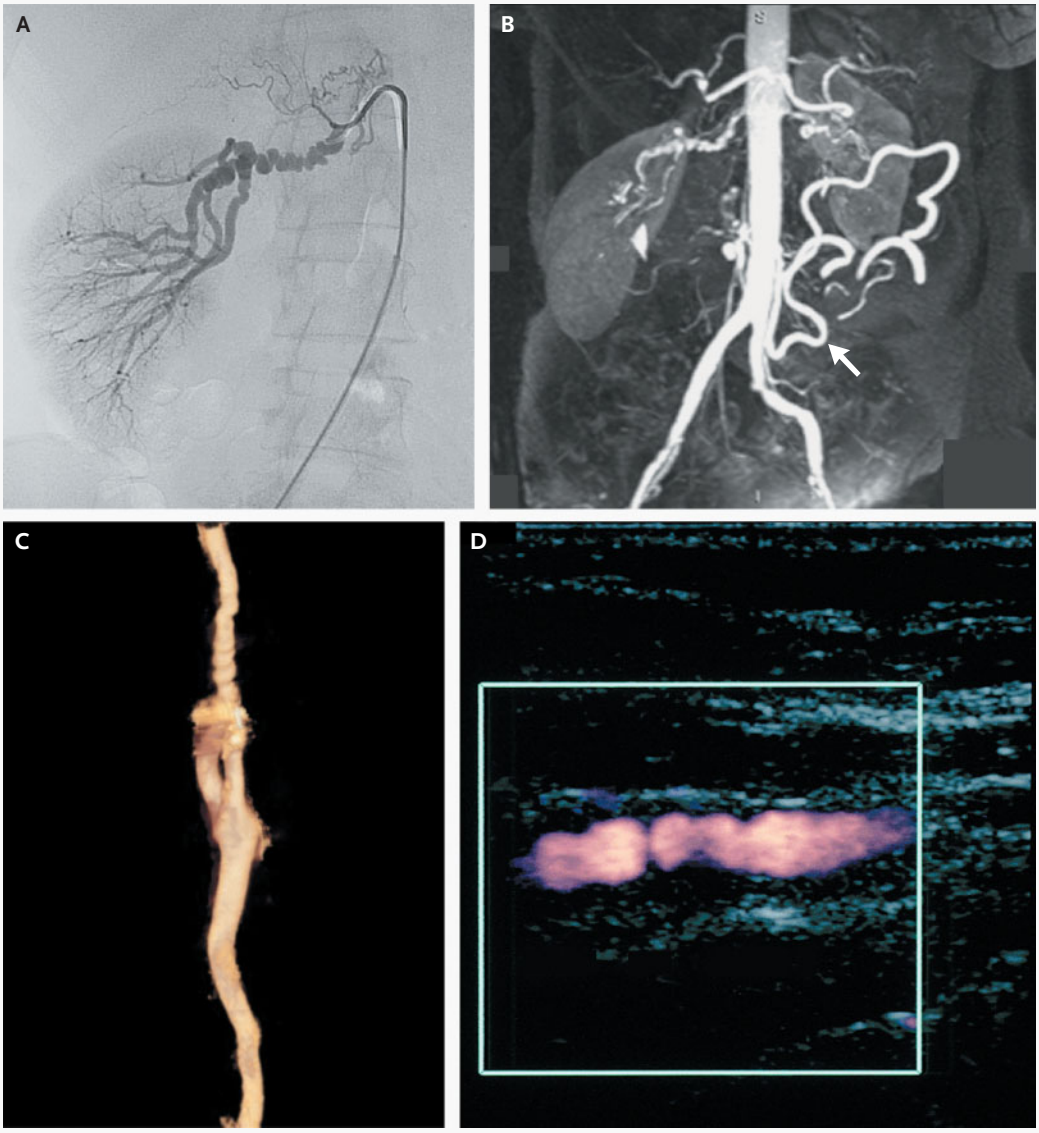

Figure 1. Imaging of Fibroplasia.

Panel A shows typical medial fibroplasia ("string of beads" appearance) on an angiogram of a right renal artery. Characteristically, the beads are larger than the normal caliber of the artery. Fibromuscular dysplasia is often located at the middle-to-distal portion of the renal artery. This 55-year-old woman presented with hypertension that was difficult to control. Panel B shows gadolinium-enhanced magnetic resonance angiography in the same patient, revealing bilateral medial fibroplasia of the renal arteries and a large marginal artery of Drummond (arrow), indicating that there is disease of the superior mesenteric artery. This patient had severe medial fibroplasia of the superior mesenteric artery (not shown). In Panel C, a 16-row-multidetector computed tomographic angiogram (a three-dimensional reconstructed image) of the internal carotid artery reveals beading typical of that seen in medial fibroplasia (courtesy of Corey Goldman, M.D., Ph.D., Ochsner Clinic, New Orleans). In Panel D, duplex ultrasonography (power imaging) of the carotid artery shows typical beading of medial fibroplasia in the internal carotid artery several centimeters distal to the carotid bifurcation.

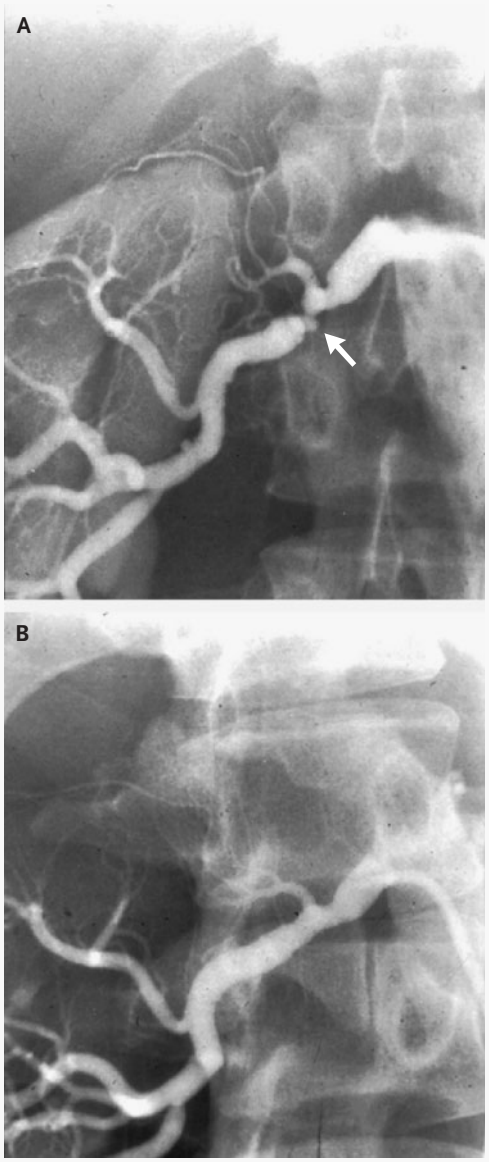

Figure 2. Perimedial Fibroplasia of the Renal Artery (Panel A) and a Near-Normal Renal Artery after Percutaneous Balloon Angioplasty (Panel B).

Careful observation shows that the beads (arrow) in perimedial fibroplasia are less numerous and smaller than those in medial fibroplasia. There is usually a robust collateral circulation in patients with perimedial fibroplasia. (Images courtesy of Anthony W. Stanson, M.D., Mayo Clinic, Rochester, Minnesota.)

the mean cortical thickness and renal length in 20 patients who had essential hypertension with those in 20 patients who had hypertension and unilateral renal-artery fibromuscular dysplasia.[41] As compared with the patients with essential hypertension, the patients with unilateral renal fibromuscular dysplasia had significantly decreased mean cortical thickness and reduced renal length. In the unaffected contralateral kidney, the cortical thickness was also markedly decreased, although the renal length was preserved. Although the loss of renal mass occurs in up to 63 percent of patients with renal-artery fibromuscular dysplasia, renal failure is rare in these patients.[38]

IMAGING

Various imaging methods have been used to detect renal-artery stenosis. Duplex imaging of the renal arteries can accurately detect elevated blood-flow velocities in the proximal portion of these arteries, as well as in the middle-to-distal portion.[42,43] Since atherosclerosis rarely occurs in the distal portion of the renal arteries, elevations of velocity in those segments are most often due to fibromuscular dysplasia. Consequently, it is important to scan patients not only by means of an anterior approach, but also with an oblique or flank approach, in order to visualize the distal portions of the renal arteries adequately.[34,43] Duplex ultrasonography of the renal arteries serves two other important functions: by measuring the resistive index in the cortical blood vessels, one can predict with a high degree of accuracy the likelihood of a favorable response to revascularization. (The resistive index=[1−(end-diastolic velocity ÷ peak systolic velocity)] × 100.) In a study by Radermacher et al.,[44] subjects were more likely to have an improvement in blood pressure and renal function when the resistive index was less than 80 than when it was 80 or higher. However, the resistive index has not been tested in patients with renal-artery stenosis secondary to fibromuscular dysplasia. In addition, duplex ultrasonography is an excellent means by which to assess restenosis after percutaneous intervention.[45,46]

Although 16-row, multidetector computed tomographic (CT) scanners may play an increasing part in the diagnosis and follow-up of renal-artery fibromuscular dysplasia, there are no good data comparing CT angiography with catheter-based angiography at present.[47,48] Similarly, the role of magnetic resonance angiography in the evaluation of renal-artery fibromuscular dysplasia remains uncertain. Even with better equipment and the use of gadolinium contrast medium, the spatial resolution of magnetic resonance angiography (approximately 1 mm) remains inferior to that of catheter angiography (200 to 300 μm).[49] The combination of de-

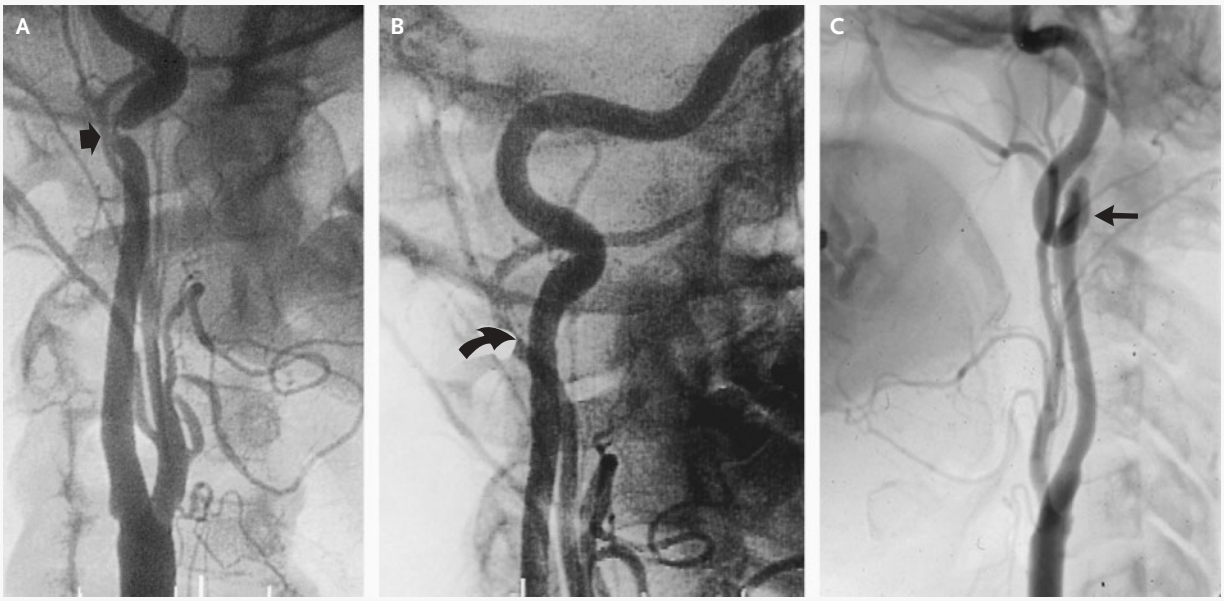

Figure 3. Carotid Arteriography in a Patient with Transient Ischemic Attacks.

The arteriogram in Panel A was obtained at presentation; it shows a severe concentric stenosis in the distal internal carotid artery (arrow) in a 36-year-old female patient with a right hemispheric transient ischemic attack (left hemiparesis). This angiographic appearance is typical of intimal fibroplasia. After percutaneous balloon angioplasty, the internal carotid artery had a normal appearance on angiography (Panel B, arrow). Several months later, this patient had several left hemispheric transient ischemic attacks (aphasia and right-sided weakness). The left carotid arteriogram (Panel C) shows a severe redundancy (arrow) and a kink (not demonstrated in this view) in the distal internal carotid artery. This lesion was resected with an end-to-end anastomosis. The pathological features were typical of intimal fibromuscular dysplasia. The patient was asymptomatic from the cerebrovascular standpoint after this operation. (Panels A and B reprinted with permission from Begelman and Olin[17]; Panel C reprinted with permission from Begelman and Olin.[20])

creased spatial resolution and the movement of the patient may result in an appearance of beading when none exists. Despite improvements in noninvasive imaging methods, catheter-based angiography remains the most accurate method for diagnosing fibromuscular dysplasia.

Although captopril renography was once the noninvasive diagnostic method of choice for patients with renal-artery stenosis, it has now been relegated to use in secondary screening, since the quality of other noninvasive imaging methods is so high. The sensitivity and specificity of captopril renography decrease in the presence of azotemia, bilateral disease, or disease in a solitary functioning kidney.[50,51]

THERAPY

Pharmacologic therapy for hypertension in patients with renal-artery fibromuscular dysplasia should follow the guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[52] Revascularization should be considered in certain types of patients: those with a recent onset of hypertension in whom the goal is to cure the hypertension; those in whom blood-pressure control has proved difficult to achieve despite the use of a comprehensive antihypertensive regimen; those with an intolerance to antihypertensive medications; those whose blood pressure has been difficult to control because of noncompliance; and those who have lost renal volume because of ischemic nephropathy.

Before the advent of percutaneous transluminal angioplasty, surgical revascularization was the primary therapeutic alternative for patients with refractory hypertension.[3,53-56] Overall, the technical success rates ranged from 89 to 97 percent. Hypertension was cured in 33 to 63 percent of patients, improved in 24 to 57 percent, and failed to improve in 3 to 33 percent. A longer duration of hypertension, concomitant atherosclerotic disease, and complex branch-vessel repair all adversely affect the results of surgical revascularization.[54,56]

Although there is a paucity of prospective data demonstrating the superiority of percutaneous transluminal angioplasty over surgical revascularization, the percutaneous approach has emerged as the mainstay of treatment for patients with fibromuscular dysplasia who meet the criteria for intervention. Percutaneous transluminal angioplasty is less costly than surgical revascularization, is less invasive, can be performed on an outpatient basis, and is associated with lower morbidity; moreover, if it is unsuccessful, surgical therapy may still be used (Table 2).[3,55,57-68] Important advances in the designs of guidewires, catheters, and balloons, as well as improvement in the relevant skills of clinicians, have made it possible to perform angioplasty for even the most complex renal-artery lesions, and it is equally effective in the main renal artery and in branch-artery stenoses.[69] Although stents have been used extensively for the treatment of atherosclerotic renal-artery stenosis, the use of stents for fibromuscular dysplasia has been reserved as a "bailout" procedure in cases in which there are suboptimal results with balloon angioplasty or in which renal-artery dissection occurs.[64,66] Adjunctive intravascular ultrasonography may be useful in determining whether an intervention has been technically successful.[34] Complications of percutaneous intervention occur in up to 14 percent of patients and most commonly involve minor access-related problems. Rarely, renal-artery perforation, dissection, or segmental renal infarction occurs.[57,59,60]

Successful angioplasty often results in a substantial and rapid reduction of both the systolic and the diastolic blood pressure. Improved blood-pressure control correlates with a marked reduction in plasma renin activity and angiotensin II levels.[67] Correlates of successful outcome include an age of less than 50 years, the absence of associated coronary or carotid stenoses, and a duration of hypertension of less than eight years.[66] The rate of restenosis after balloon angioplasty has ranged from 7 to 27 percent over follow-up periods of six months to two years.[61,63,70,71] In rare cases, fibrodysplastic stenosis may coexist with an aneurysm.[72] This condition may be treated percutaneously with the use of a covered stent graft or may be repaired surgically.[73]

Patients who are treated with endovascular or surgical revascularization should undergo duplex ultrasonographic imaging periodically to detect progression of disease, restenosis, or loss of kidney volume.[43,71,74] Imaging should be performed soon after revascularization to assess the adequacy of the intervention,[46] again after 6 months and after 12 months, and yearly thereafter, or whenever there is a recurrence or worsening of hypertension.

CEREBROVASCULAR FIBROMUSCULAR DYSPLASIA

Cerebrovascular fibromuscular dysplasia may be asymptomatic or associated with a variety of nonspecific symptoms, including headache, tinnitus,

Table 2. Results of Percutaneous Transluminal Angioplasty of the Renal Arteries in Patients with Fibromuscular Renovascular Disease and Hypertension.*

Study	Year	No. of Patients	Technical Success Rate	Effect on Blood Pressure			Months of Follow-up	Complication Rate
				Cured	Improved	Unimproved		
			%	%			*mean (range)*	%
Sos et al.[57]	1983	31	87	59	34	7	16 (4–40)	6
Baert et al.[58]	1990	22	83	58	21	21	26 (6–72)	NR
Tegtmeyer et al.[59]	1991	66	100	39	59	2	39 (1–121)	13
Bonelli et al.[60]	1995	105	89	22	63	15	43 (0–168)	11 (major)
Jensen et al.[61]	1995	30	97	39	47	14	12 (NR)	3 (major) 12 (minor)
Davidson et al.[62]	1996	23	100	52	22	26	NR	13
Klow et al.[63]	1998	49	98	26	44	30	9 (1–96)	0
Birrer et al.[64]	2002	27	100	74†		26	10 (NR)	7.4
Surowiec et al.[65]	2003	14	95	79†		21	NR	28.5
de Fraissinette et al.[66]	2003	70	94	14	74	12	39 (1–204)	11

* NR denotes not reported.
† The percentage shown is the total for cured and improved.

vertigo, lightheadedness, and syncope.[8,75,76] The more specific neurologic syndromes of transient ischemic attack, amaurosis fugax, stroke, Horner's syndrome, and cranial-nerve palsies may be the first presentation of fibromuscular dysplasia involving the carotid or vertebral arteries[8,76] (Fig. 3). Cerebrovascular symptoms may be related to critical stenosis or occlusions of major arteries, rupture of an intracranial aneurysm, or cerebral embolism originating from intravascular thrombi in stenotic regions.[77] Intracranial or extracranial cerebrovascular fibromuscular dysplasia may also be discovered incidentally as the cause of a cervical bruit or when angiography or some other imaging method is performed for unrelated reasons. The mean age of patients with cerebrovascular fibromuscular dysplasia is approximately 50 years. The natural history of cerebrovascular fibromuscular dysplasia of the medial type is generally benign.[78-80]

Several imaging methods may be used for the detection of intracranial or extracranial cerebrovascular fibromuscular dysplasia. Duplex ultrasonography of the carotid arteries may demonstrate irregular patterns of stenosis and aneurysm[81] (Fig. 1D), but color-coded duplex ultrasonography has a lower sensitivity than angiography for the detection of cerebrovascular fibromuscular dysplasia.[81] Since fibromuscular dysplasia affects the middle and distal portions of the carotid and vertebral arteries at the level of the first and second cervical vertebrae,[82] it may be difficult to visualize these lesions by means of duplex ultrasonography. There has been little experience with computed tomographic angiography (Fig. 1C) or magnetic resonance angiography for the detection of cerebrovascular fibromuscular dysplasia; however, magnetic resonance angiography should be performed to rule out the presence of intracranial aneurysms in patients with such dysplasia.

Before the use of percutaneous revascularization became widespread, surgery was the mainstay of therapy for patients with symptomatic cerebrovascular fibromuscular dysplasia. The surgical technique used depended on the type of lesion and its location, but the most widely used procedure was graduated intraluminal dilatation.[82-85] Other procedures that have been used include intraoperative balloon angioplasty,[86] placement of a polytetrafluoroethylene-covered endograft,[87] resection of the diseased segment and primary anastomosis (Fig. 3C), grafting of autogenous saphenous vein, resection of the aneurysm, and carotid endarterectomy.[82,88,89]

During the past 10 years, percutaneous angioplasty has become the preferred treatment for symptomatic cerebrovascular fibromuscular dysplasia[90-97] (Fig. 3A and 3B). There have been no randomized, controlled trials comparing surgery with balloon angioplasty in this condition. Studies in patients with atherosclerotic carotid artery disease suggest that the use of cerebral protection devices may reduce the frequency of ischemic neurologic events during stenting of the carotid artery.[98-100] When these devices receive approval from the Food and Drug Administration, they will probably be used during percutaneous intervention for the treatment of fibromuscular dysplasia in the carotid artery.

FIBROMUSCULAR DYSPLASIA IN OTHER VASCULAR TERRITORIES

Of the arteries that supply blood to the lower extremities, the iliac arteries are the most likely to be affected by fibromuscular dysplasia, although this condition has been described in the femoral, popliteal, and tibioperoneal arteries as well.[9,101] Patients with fibromuscular dysplasia in the pelvic or leg arteries may present with intermittent claudication, critical limb ischemia, or peripheral microembolism that manifests as pain and cyanosis in the toes. In the arms, fibromuscular dysplasia is identified most frequently in the subclavian arteries but has also been described in the brachial and axillary arteries.[5,6] In severe cases, patients have weakness, paresthesias, or claudication in their arms. For symptomatic fibromuscular dysplasia in the arms or legs, treatment consists of percutaneous balloon angioplasty.[102,103]

Fibromuscular dysplasia in the visceral arteries typically involves the celiac, superior mesenteric, inferior mesenteric, hepatic, and splenic arteries.[2,104] Intestinal angina may occur when at least two of the major mesenteric arteries are obstructed. In unusual cases, the stenosis progresses to total occlusion, leading to acute intestinal ischemia.[105,106] Treatment options include percutaneous intervention and surgical bypass.

As is the case with most rare diseases, it is difficult to conduct a prospective study of various treatment options. Therefore, most treatment decisions are based on data derived from retrospective case series and anecdotal reports. Thanks to advances in imaging methods and enhancement of the interventional armamentarium, treatment has become less invasive and is now at least as effective as previous

surgical approaches while being associated with lower morbidity. Future studies will involve the use of protection devices at the time of percutaneous intervention in order to prevent distal embolization. There is no role for stent implantation as a primary treatment for fibromuscular dysplasia, since angioplasty alone is quite effective. Further study of the pathogenesis of fibromuscular dysplasia is needed so that we may gain a better understanding of this disease.

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