Is Fibromuscular Dysplasia a Single Disease?

Jeffrey W. Olin, DO

There is a dearth of new information about fibromuscular dysplasia (FMD). Although the disease was first described in 1938 in a 5-year-old boy with malignant hypertension, it was nearly 25 years before the pathology and angiographic correlates were described in detail. From 1966 to the early 1980s there were multiple articles on the classification and treatment of patients with fibromuscular dysplasia. There is disparity and complexity among the 5 classification schemes, and thus no consensus as to the most accurate way to classify this disease exists.

In the last 30 years there has been no new information regarding the cause and pathophysiology and little new information on the genetics and treatment of patients with FMD. The literature is inundated with single case reports and small case series, most adding little to the understanding of this uncommon disease. However, in the last 3 years there has been a resurgence of interest in FMD, leading to a better understanding of this condition. In 2012, the findings from the Registry for Fibromuscular Dysplasia were reported on the first 447 patients entered into the registry. Additionally, a multidisciplinary State of the Science paper on FMD was commissioned by the American Heart Association, and those findings will be published in 2013.

It is therefore timely that in this issue of Circulation, an experienced group of investigators in Paris published a provocative study that provides a plethora of important new information related to the classification and phenotypic expression of FMD. Because pathological specimens are rarely available as a result of technical advances in endovascular therapy, Savard and his associates investigated whether using a binary angiographic classification would accurately discriminate between 2 distinct clinical phenotypes.

The most common angiographic appearance in patients with fibromuscular dysplasia is an artery that looks like a string of beads. In the renal and internal carotid arteries, this occurs in the mid and distal portion of the artery, whereas with atherosclerosis the stenosis is at the origin or proximal portion of the artery. The pathological correlate to the string of beads is medial fibroplasia, and this was present in 82% of patients in the series by Savard et al. The authors call this multifocal FMD. The next most common angiographic appearance is that showing a focal or tubular stenosis, which the authors call unifocal FMD. There is a third angiographic appearance that does not fit nicely into this classification, called perimedial FMD. This occurs most often in children and may cause hypertension and renal impairment. Perimedial fibroplasia was identified in only 2 of 577 (0.3%) patients in the U.S. Registry for fibromuscular dysplasia. Because perimedial fibroplasia is so uncommon in adults, it is reasonable to omit this subtype from the simplified classification as proposed by Savard and colleagues.

The majority of patients with renal artery FMD who require treatment for control of hypertension undergo percutaneous balloon angioplasty. In adults with FMD, the only indications for surgical revascularization are failed balloon angioplasty or for the treatment of aneurysms associated with FMD. Therefore, because there is no tissue obtained, it is not possible to know definitively the pathological type of FMD. Whereas medial fibroplasia has a distinct angiographic appearance (string of beads), several of the other pathological types of FMD (intimal fibroplasia, medial hyperplasia, adventitial [periarterial] fibroplasia) may be indistinguishable on angiography. By simplifying classification into 2 groups, the authors have made several important observations about the clinical characteristics of fibromuscular dysplasia, and their findings raise an important question: Is fibromuscular dysplasia a single disease, or is it a heterogeneous group of disorders with similar clinical characteristics, but quite different in regards to etiology and genetics?

Important Points Worth Emphasizing

Although Savard and associates have provided an excellent starting point for a universally accepted classification for fibromuscular dysplasia, there are several points that need to be further clarified so that consensus can be achieved.

- A small number of patients have the angiographic appearance of 2 different types of FMD. How should a patient with unifocal disease in 1 arterial bed and multifocal disease in another be classified?
- The term unifocal implies there is a focal area of stenosis in 1 region. There are patients who have unifocal disease in several arterial beds. Perhaps dropping the prefix and terming these lesions as focal would more accurately reflect the angiographic appearance.
- All 337 patients in the current series were referred for hypertension and renal artery FMD. Therefore, it is difficult to know whether the clinical characteristics are the same for patients referred for FMD in other locations. It is known from the U.S. registry on FMD that among patients with renal artery FMD, coexistent extracranial carotid or vertebral artery disease was present in 142 of the 210 (64.8%) patients who...
underwent neuroimaging; and among patients with extracranial carotid or vertebral artery disease, coexistent renal artery FMD was present in 142 of 220 (64.5%) patients who underwent renal imaging. Many of the registry sites now routinely image other vascular beds (even in the absence of symptoms or signs) because of this apparently high rate of disease in multiple vascular territories.

- There are other angiographic findings in patients with FMD that are often not recognized. In the current study, patients with dissection, or aneurysm, were only included if they had the typical angiographic findings for FMD. What about the patient with typical FMD in the renal artery and a less commonly appreciated finding such as extreme tortuosity (S Curve) in the carotid or vertebral arteries? Does this finding represent FMD in multiple territories? Do patients with this imaging characteristic have different clinical manifestations than those without tortuosity? We have shown that FMD patients exhibit the S Curve much more frequently than age- and sex-matched controls (odds ratio, 18.76; 95% confidence interval, 4.36–80.79; \( P < 0.001 \)) and patients \( > 70 \) years of age and sex matched (odds ratio, 2.69; 95% confidence interval, 1.29–5.61; \( P < 0.001 \)). Although extreme tortuosity is not specific for FMD, it occurs with a much higher frequency in FMD patients compared with those without FMD and may in fact be another angiographic manifestation of FMD.

Clinical Differences Suggest the Possibility of 2 Different Diseases

The authors have shown that there are important clinical differences between patients with multifocal and unifocal FMD. Savard et al reported that 31% of unifocal FMD patients were male, whereas only 17% of multifocal FMD patients were male. This apparent difference in sex according to FMD type was not demonstrated in the U.S. Registry, where 91.5% were female. It is not clear why there is a significantly higher percentage of females than in the study by Savard and colleagues. This may be related to the fact that all patients in the current study had renal artery FMD and hypertension, whereas in the U.S. Registry, patients with FMD in any vascular territory were included.

It is important to recognize that the median age of hypertension onset was 26 years in those with unifocal FMD, whereas it was 40 years in patients with multifocal FMD. In other words, 82% of the patients in the series by Savard et al had an onset of hypertension in the age range consistent with primary (essential) hypertension. Similar findings were present in the FMD registry. This underscores how difficult it may be to diagnose FMD in a timely fashion. It is noteworthy that in the U.S. Registry, there was nearly a 5-year delay from the onset of the first clinical manifestation of FMD until the diagnosis was made. In the current series, there was a median 4-year delay from the onset of hypertension until the diagnosis of FMD was made in patients with unifocal FMD and a median 9-year delay in those subjects with multifocal FMD. This has important implications in that the delay in diagnosis may increase the risk of adverse cardiovascular events from suboptimally controlled hypertension, expose the patient to other manifestations of FMD such as unrecognized aneu-

rysms, and make it less likely that the patient will have a favorable response to balloon angioplasty of the renal arteries. The longer the duration of hypertension, the less likely angioplasty will cure they hypertension.

A point worth emphasizing is that it is easy to determine the degree of stenosis on angiography in the patient with unifocal FMD, whereas it is not possible in multifocal FMD. In multifocal FMD, the only way to accurately assess the degree of stenosis is by measuring the translesional gradient or using intravascular ultrasound. This may be one of several possible reasons why 87% of patients with unifocal FMD had renal artery revascularization, whereas only 38% of those with multifocal FMD had revascularization. Additionally, the higher cure rate of hypertension in patients undergoing intervention with unifocal FMD (54%) compared with those with multifocal FMD (26%) may be related to the fact that patients with unifocal disease were younger, had a shorter duration, and more severe hypertension, making a favorable response to balloon angioplasty more likely. The authors point out that the larger decrease in blood pressure and number of antihypertensive agents in patients with unifocal FMD was a result of the higher percentage of patients undergoing intervention. If only patients who underwent intervention were analyzed, there was a similar decrease in blood pressure in the unifocal and multifocal patients with FMD.

Further Simplifying Classification

There are 4 minor changes that could be made to further simplify the classification of FMD without sacrificing accuracy, or the ability to differentiate different phenotypes. The scoring system could be deleted because it does not help to further characterize the clinical manifestations of FMD. In addition, because many patients with FMD will have disease in multiple vascular territories, classification according to the burden of disease using a scoring system would be overly complex. Second, there is no practical purpose in distinguishing multifocal disease with the string of beads and without the string of beads. I contend that both of these angiographic appearances (Figure 1D and 1F in the article by Savard et al) show a string of beads, and are only different by degrees. They both demonstrate multiple areas of constriction followed by dilatation. Intravascular ultrasound would show the same abnormality, webs causing narrowing followed by enlargement of the artery. The authors have shown that clinically (Table I in the online-only Data Supplement), these 2 angiographic appearances are exactly the same. The third change would be to delete perimedial FMD from the classification. As previously noted, it is extremely rare in adults, and it behaves so differently from multifocal FMD that it is not worth including in a classification that is trying to simplify rather than complicate. And lastly, changing unifo-

cal to focal makes sense for the reasons discussed previously.

Savard and colleagues have made a very important contribution to the FMD literature. They have proposed a straightforward and simple binary angiographic classification, and they have clearly shown that the clinical manifestations associated with each angiographic appearance are different enough from one another to suggest that this may not represent a single disease.
Studies elucidating the genetics and cause of FMD will help to determine answers to some of these questions.

Disclosures
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References

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