The United States Registry for Fibromuscular Dysplasia

Results in the First 447 Patients

Jeffrey W. Olin, DO; James Froehlich, MD; Xiaokui Gu, MA; J. Michael Bacharach, MD, MPH; Kim Eagle, MD; Bruce H. Gray, DO; Michael R. Jaff, DO; Esther S.H. Kim, MD, MPH; Pam Mace, RN; Alan H. Matsumoto, MD; Robert D. McBane, MD; Eva Kline-Rogers, MS, RN; Christopher J. White, MD; Heather L. Gornik, MD, MHS

Background—Fibromuscular dysplasia (FMD), a noninflammatory disease of medium-size arteries, may lead to stenosis, occlusion, dissection, and/or aneurysm. There has been little progress in understanding the epidemiology, pathogenesis, and outcomes since its first description in 1938.

Methods and Results—Clinical features, presenting symptoms, and vascular events are reviewed for the first 447 patients enrolled in a national FMD registry from 9 US sites. Vascular beds were imaged selectively based on clinical presentation and local practice. The majority of patients were female (91%) with a mean age at diagnosis of 51.9 (SD 13.4 years; range, 5–83 years). Hypertension, headache, and pulsatile tinnitus were the most common presenting symptoms of the disease. Self-reported family history of stroke (53.5%), aneurysm (23.5%), and sudden death (19.8%) were common, but FMD in first- or second-degree relatives was reported only in 7.3%. FMD was identified in the renal artery in 294 patients, extracranial carotid arteries in 251 patients, and vertebral arteries in 82 patients. A past or presenting history of vascular events were common: 19.2% of patients had a transient ischemic attack or stroke, 19.7% had experienced arterial dissection(s), and 17% of patients had an aneurysm(s). The most frequent indications for therapy were hypertension, aneurysm, and dissection.

Conclusions—In this registry, FMD occurred primarily in middle-aged women, although it presents across the lifespan. Cerebrovascular FMD occurred as frequently as renal FMD. Although a significant proportion of FMD patients may present with a serious vascular event, many present with nonspecific symptoms and a subsequent delay in diagnosis. (Circulation. 2012;125:3182-3190.)

Key Words: aneurysm ■ dissection ■ fibromuscular dysplasia ■ hypertension ■ renal ■ stroke

Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory vascular disease that has been reported in virtually every arterial bed, but it most commonly affects the renal and extracranial carotid and vertebral arteries.1–4 FMD may cause stenosis, aneurysm, dissection, and/or occlusion of arteries.1 The clinical presentation of FMD is determined primarily by the distribution of arteries that are affected. When the renal arteries are involved, the patient may present with hypertension, whereas carotid artery involvement may lead to headache, pulsatile tinnitus, transient ischemic attack, or stroke. FMD may also be asymptomatic and only discovered incidentally when imaging is performed for another clinical indication.5–7

Clinical Perspective on p 3190

Although the prevalence of FMD in the general population is not known, it is considered to be rare by some investigators.8 Thus, diagnosis and treatment may be delayed, leading to potentially serious sequelae. Others have suggested that FMD is more common than previously recognized.5,6,9 The renal arteriograms of 1862 potential renal donors were examined, and FMD was found in 3.8%.6 A similar prevalence was found in a more recent study of potential kidney donors.5 No studies have investigated the prevalence of FMD in the general population.

Fibromuscular dysplasia was first described in 1938 by Leadbetter and Burkland10 and classified pathologically by...
The most common type of FMD is medial fibroplasia. The angiographic appearance of this type is the so-called string of beads, where the bead is larger than the normal caliber of the artery. The appearance of this type is the so-called string of beads, where the bead is larger than the normal caliber of the artery. Medial fibroplasia typically occurs in the mid and distal portion of the renal artery and in its branches. This is typical of intimal fibroplasia. The angiographic appearance of medial fibroplasia in the renal artery. Note the string of beads with the beading larger than the normal caliber of the artery (Figure, A). The appearance of beading is due to alternating areas of stenosis (from fibrous webs) and poststenotic dilatation. Less common types of FMD are intimal (Figure, B), perimedial, and adventitial (periarterial) fibroplasia. Since the early publications in the 1970s and early 1980s, subsequent publications have almost all been single case reports or small case series. There has been very little new information published about FMD in the past 30 years.

To better understand the epidemiology, clinical characteristics, management, and outcomes of patients with FMD, a multicenter registry involving 9 centers in the United States was instituted in 2008 (online-only Data Supplement Appendix). This report includes the first 447 patients entered into the registry. Because the duration of follow-up is short, the authors plan to report on the endovascular and surgical intervention. Less common types of FMD are intimal fibroplasia, perimedial fibroplasia, and adventitial fibroplasia. The definitions for the various types of FMD were as follows: medial fibroplasia, “string of beads” appearance with beading larger than the normal caliber of the artery (Figure, A). The beading represents areas of stenosis alternating with dilatation. This occurs in the mid and distal part of the renal or carotid/vertebral arteries; intimal fibroplasia, an area of long smooth narrowing (tubular stenosis) or a focal bandlike constriction; perimedial fibroplasia, there are beads smaller than the normal caliber of the artery and less numerous. There is usually collateralization around the stenosis. Medial hyperplasia and adventitial fibroplasia can only be reliably diagnosed with histopathology.

Methods

In 2008, 7 US sites agreed to participate in a FMD registry with coordination by the Michigan Cardiovascular Outcomes Research and Reporting Program. Two additional sites were added after 2010. The 9 centers were selected for inclusion in the registry based on an established history of clinical experience in the care of patients with FMD. Each of these centers identified patients by use of 1 or more of 3 mechanisms: (1) query of clinic or hospital databases or of the electronic medical records to identify patients with confirmed FMD; (2) enrollment of established FMD patients when the patients return for follow-up visits; (3) all centers approached patients with newly diagnosed FMD and patients with established FMD newly referred to their practices for consent to enroll in the registry.

Each center had its own specific referral pattern. Many patients were referred by their physicians to a clinical center for more specialized FMD diagnosis, education, and treatment. A significant number of patients were self-referred after searching the Internet for a center with expertise in FMD, whereas others contacted the Fibromuscular Dysplasia Society of America and obtained more information about FMD and about participating registry centers. The mode of referral for each individual patient is not available in the database at this time. Of the 447 patients enrolled in the registry, 378 (85%) were prospectively enrolled. Of the patients asked to participate, >95% agreed to do so.

FMD patients were eligible for enrollment in the registry on assessment by one of the registry investigators. Because histopathology is rarely available (owing to the large majority of patients either being treated medically or by an endovascular procedure), the diagnosis was made on the basis of angiographic (invasive or noninvasive) imaging.

A standardized FMD data form of definitions was used for each component of the data collection form. This was formulated before the start of the registry and was last updated on December 8, 2010.

Each participating center submitted the protocol to its respective institutional review board. In addition, a Data Use Agreement was signed between participating institutions and the coordinating center to ensure appropriate use of data obtained.

An initial data form was completed by a registry investigator for each patient at the time of enrollment in the registry. A follow-up data form with emphasis on interval diagnostic testing, therapeutic procedures, change in symptoms, and interval clinical outcomes, was completed at the time of each clinical follow-up visit or at another follow-up interval at the discretion of the center investigator.
An on-line database was designed at the coordinating center with the use of Drupal as the web development environment and MySQL database. A list of frequently asked questions is available on the web site to assist with clarification of data variables. To further enhance data validity, several data constraints are programmed on-line to filter and alert the data abstractor if erroneous data have been entered.

Queries are generated by the coordinating center staff and sent to site coordinators for resolution. Once all data queries are resolved, data are analyzed by the coordinating center statistician (X.G.) by using SAS (SAS Institute, Inc, Cary, NC).

Statistical Analysis
Summary statistics are presented as frequencies and percentages, also as ranges, means, and standard deviations. Two-sample t tests were performed to examine differences in continuous variables, whereas \( \chi^2 \) testing was used to test differences in proportions.

Results
Demographics and Comorbidities
Table 1 presents demographic and medical history for 447 patients in the registry as of October 5, 2011. Mean patient age was 55.7 years (SD 13.1) at the time of enrollment, and the majority of patients were white and female. Although men comprised a minority of this cohort, there was no statistically significant difference in age at enrollment or age at first diagnosis of FMD among male patients in comparison with female patients (age at enrollment 55.7 years for both men and women, \( P=0.99 \)) nor age at diagnosis of FMD (54.0 years for men versus 51.6 years for women, \( P=0.29 \)).

Hypertension was highly prevalent, with a median of 2 (interquartile range 1–3) medications required for blood pressure control. Headaches were a common symptom (60.0% of patients), with classical migraine-type headaches reported in 32.2%. Severe headaches occurred weekly in 13.1% of patients and daily in 12.5% of patients. In addition to hypertension, traditional cardiovascular risk factors were prevalent in this population. Approximately one-third of patients were current or former smokers with mean 22.4 pack-years of tobacco use (SD 23.1). Nearly half of patients were on lipid-lowering therapy.

There was exposure to either oral contraceptives or hormone replacement therapy in 69.6% of women, with 13.5% of women receiving systemic 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 FMD registry. Sixty-five percent of women were postmenopausal at the time of entry into the registry.

Family History
Self-reported family history data for first- and second-degree relatives of FMD patients are provided in Table 2. Only 7.3% of FMD patients reported a confirmed diagnosis by a physician of FMD among a family member. In contrast, there was a high prevalence of a family history of stroke (53.5%), aneurysm (23.5%), and sudden death (19.8%). Family histories of hypertension and hyperlipidemia were also common.

Presenting Symptoms and Initial FMD Diagnosis
The mean patient age at first symptom or sign due to FMD was 47.2 years (SD 14.6) with a wide range of age at first symptom (range, 5–83 years). Mean age at first clinical diagnosis of FMD was 51.9 years (SD 13.4). The mean time from first clinical symptom or sign to diagnosis of FMD was 4.1 years (SD 8; range, 0–54 years). The frequency of presenting symptoms and clinical signs leading to the diagnosis of FMD is shown in Table 3. The mean and median number of symptoms/signs at time of diagnosis were 3.5 (SD 2.4; range, 0–12) and 3 (interquartile range 2–5 symptoms), respectively. Twenty-five (5.6%) patients were asymptomatic at the time of diagnosis. These asymptomatic patients were

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( n ) (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, mean( \pm )SD</td>
<td>55.7( \pm )13.1 y (range, 18–86)</td>
</tr>
<tr>
<td>Age at first FMD-related symptom, mean( \pm )SD</td>
<td>47.2( \pm )14.6</td>
</tr>
<tr>
<td>Age at diagnosis of FMD, mean( \pm )SD</td>
<td>51.9( \pm )13.4 y (range, 5–83)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>395/414 (95.4)</td>
</tr>
<tr>
<td>Black</td>
<td>9/414 (2.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6/414 (1.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>2/414 (0.5)</td>
</tr>
<tr>
<td>Other</td>
<td>2/414 (0.5)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>322/447 (72.0)</td>
</tr>
<tr>
<td>Age at onset, mean( \pm )SD</td>
<td>43.1( \pm )14.9 y (range, 4–79)</td>
</tr>
<tr>
<td>Median number of BP medications</td>
<td>2 (IQR 1–3)</td>
</tr>
<tr>
<td>Significant headaches</td>
<td>216/360 (60.0)</td>
</tr>
<tr>
<td>Migraine type</td>
<td>116/360 (32.2)</td>
</tr>
<tr>
<td>Weekly</td>
<td>47/360 (13.1)</td>
</tr>
<tr>
<td>Daily</td>
<td>45/360 (12.5)</td>
</tr>
<tr>
<td>Require suppressive medication</td>
<td>45/360 (12.5)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>190/262 (65.1)</td>
</tr>
<tr>
<td>History of hormonal therapy†</td>
<td>204/293 (69.6)</td>
</tr>
<tr>
<td>Current estrogen replacement</td>
<td>44/325 (13.5)</td>
</tr>
<tr>
<td>Tobacco history</td>
<td></td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>147/395 (37.2)</td>
</tr>
<tr>
<td>No. of pack-years smoked, mean( \pm )SD</td>
<td>22.4( \pm )23.1 pack-years (range, 1–120)</td>
</tr>
<tr>
<td>Drug therapy for hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>164/390 (42.1)</td>
</tr>
<tr>
<td>Other cholesterol-lowering agents</td>
<td>41/372 (11.0)</td>
</tr>
</tbody>
</table>

FMD indicates fibromuscular dysplasia; BP, blood pressure; IQR, interquartile range.

*Denominator of reported responses is reported if different than total cohort size of \( N = 447 \) patients to account for missing data.
†Includes oral contraceptive therapy or systemic postmenopausal hormone replacement therapy (excluding vaginal topical estrogen preparations).
Table 2. Self-Reported Family History of Vascular Disease or Risk Factors Among First- and Second-Degree Relatives of FMD Patients

<table>
<thead>
<tr>
<th>Family History</th>
<th>n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>289/366 (79.0)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>171/302 (56.6)</td>
</tr>
<tr>
<td>Stroke</td>
<td>175/327 (53.5)</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>76/323 (23.5)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>60/303 (19.8)</td>
</tr>
<tr>
<td>FMD</td>
<td>26/354 (7.3)</td>
</tr>
<tr>
<td>Dissection</td>
<td>6/303 (2.0)</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>2/299 (0.7)</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>1/302 (0.3)</td>
</tr>
</tbody>
</table>

FMD indicates fibromuscular dysplasia.

*Denominator of reported responses is reported as different than total cohort size of N = 447 patients to account for missing data.

Either discovered to have a bruit during a physical examination or incidentally when imaging was performed for another indication. Hypertension, headaches, pulsatile tinnitus (an abnormal swooshing or whooshing sound in the ears), and dizziness were the most common presenting symptoms, followed by cervical bruit, neck pain, and nonpulsatile tinnitus. Carotid or vertebral artery dissection was a presenting manifestation in 12.1% of patients, and other cerebrovascular events, including hemispheric transient ischemic attack (8.7%), stroke (6.9%), or amaurosis fugax (5.2%), were initial clinical manifestations of FMD in a significant percentage of patients. Chest pain or shortness of breath was reported as a presenting symptom in 16.1% of patients, and myocardial infarction was reported as a presenting clinical syndrome in 1.8%.

Findings on Physical Examination

Physical examination findings at the time of enrollment were available for 414 patients (92.6%). Mean body mass index was 25.5 kg/m² (SD 5.2), and 48.8% of patients had a body mass index >25 kg/m². Mean blood pressure was 130/75 mm Hg (SD 20/12). Findings consistent with Horner syndrome (pupil abnormality or ptosis) were reported in 12.4% of patients. Cranial nerve abnormalities were reported in 9.4%, and other focal neurological deficits were reported in 13.6%. Bruits were reported over the carotid arteries (30.5%; 18.1% bilateral), epigastrium (17.5%), and flanks (6.1%). Among 306 patients with reported imaging of the extracranial circulation (carotid and vertebral) and a documented physical examination for carotid bruits, 227 (74.2%) had FMD. The sensitivity of a carotid bruit for extracranial FMD was 103/227 (45.4%), and the specificity was 74/79 (93.3%). Among 337 patients with renal or mesenteric imaging and a documented physical examination for epigastric or flank bruits, 262 (77.7%) had FMD. The sensitivity of an epigastric or flank bruit for identifying renal or mesenteric FMD was 63/262 (24.0%) with a specificity of 70/75 (93.3%). Peripheral pulse deficits were uncommon and were documented at the doralis pedis and/or posterior tibial arteries in 5.0% and brachial and/or radial arteries in 0.9% of patients.

Vascular Bed Involvement and Type of FMD

The anatomic distribution of vascular involvement based on imaging is shown in Table 4. Three hundred forty-two patients had imaging of the extracranial carotid/vertebral arteries (73% ultrasound, 30% magnetic resonance angiogram, 28% computed tomographic angiography, and 28% catheter-based angiography).

Three hundred seventy-four patients had imaging of the renal, mesenteric, and/or abdominal aorta (71% ultrasound, 50% catheter-based angiogram, 28% computed tomographic angiography, and 12% magnetic resonance angiogram). Because all vascular beds were not imaged, the prevalence of FMD in multiple vascular beds in the whole cohort could not be determined. However, of 357 patients having 2 or more vascular beds imaged, 126 (35.3%) had FMD in 2 vascular beds. Of 292 patients having 3 or more vascular beds imaged, 64 (21.9%) had FMD in 3 vascular beds. Of 232 patients having 4 or more vascular beds imaged, 21 (9.1%) had FMD in 4 vascular beds.

Intracranial FMD, primarily manifesting as intracranial aneurysms, was reported in 8.3% of patients. Among patients with renal artery FMD, coexistent extracranial carotid or vertebral artery disease was present in 142 of 210 (64.8%)...
patients who underwent neuroimaging; among patients with extracranial carotid or vertebral artery disease, coexistent renal FMD was present in 142 of 220 (64.5%) patients who underwent renal imaging. No cases of aortic FMD were identified, although aortic aneurysm was present in 3.4% of patients and accounted for 19.7% of all aneurysms. A discrete data field for documentation of coronary involvement was not present in the data collection form at the time of this first publication, but has been subsequently incorporated; thus, it is not possible to determine whether the coronary artery involvement (Table 5) was due to atherosclerosis or fibromuscular dysplasia. Histopathologic confirmation of the diagnosis of FMD was available in only 14 patients (3.3%). In the overwhelming majority of patients, diagnosis was based on angiographic or noninvasive imaging and classification of disease according to previously published histopathologic-angiographic correlates.11,12,14,23 The type of FMD was recorded in 302 (67.6%) patients. Among these, medial fibroplasia was by far the most common subtype (91.4%) followed by intimal (7.0%) and perimedial disease (0.7%), and 3 (1%) patients had features of both medial and intimal disease.

### Vascular Events

Table 5 summarizes the number of patients with a past or presenting history of vascular events and complications including all events up to the time of initial enrollment in the registry. Myocardial infarction was uncommon (3.1%) and 1.3% of patients had undergone coronary revascularization. A cerebrovascular event, including stroke or transient ischemic attack (19.2%), or less commonly amaurosis fugax (6.0%), occurred in approximately 1 in every 4 patients. Subarachnoid hemorrhage was uncommon, occurring in 5 (1.1%) patients. Renal failure or infarction and mesenteric ischemia were both uncommon events.

### Dissection and Aneurysm

Dissection and aneurysm were identified in 19.7% and 17.0% of FMD patients, respectively. Although all vascular beds were not imaged in every patient, the anatomic distribution of dissections and aneurysms is shown in Table 6. Among patients with dissection, 18.5% had dissection of 1 vessel (maximum 3 dissections per patient reported). The 3 majority of patients, diagnosis was based on angiographic or noninvasive imaging and classification of disease according to previously published histopathologic-angiographic correlates.11,12,14,23 The type of FMD was recorded in 302 (67.6%) patients. Among these, medial fibroplasia was by far the most common subtype (91.4%) followed by intimal (7.0%) and perimedial disease (0.7%), and 3 (1%) patients had features of both medial and intimal disease.

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common sites for dissection were the carotid arteries (14.8% of all patients enrolled), followed by renal arteries (4.3%) and vertebral arteries (3.4%). Aneurysms were reported in 17% of FMD patients, with the renal (5.6% of patients enrolled) and carotid arteries (3.6%) as the most common sites. Aortic aneurysms were identified in 15 (3.4%) patients, with both thoracic (10 patients) and abdominal aortic aneurysms (5 patients) reported. Among patients with aneurysm, 17.3% had >1 vascular bed involved (maximum 4 aneurysm locations per patient reported).

Discussion
Of the first 447 patients entered into the FMD registry, 91% were women. The mean age at diagnosis for the entire cohort was 51.9 years (SD 13.4; median, 52; range, 5–83 years), and there was no significant difference in age at diagnosis between men and women. In an earlier study, Stanley and Fry22 reported on 106 female and 7 male patients with FMD who had undergone surgery for occlusive or aneurysmal disease. The mean age for the women was 38.9 years (SD 8.9), and the mean age for the men was 26.1 years (SD 6.9). Unlike previous reports suggesting that FMD is a disease of young women,2,3, 22,24,25 the current study showed that FMD is predominately a disease of middle age but may occur in any age group.

Much of the previous literature reported that FMD most commonly affected the renal arteries (70%) and less frequently the carotid and vertebral arteries (25%–30%).3,5,12,16,19,22,26–31 In contrast, in this registry, the extracranial carotid and vertebral arteries were nearly as frequently involved as the renal arteries (Table 4). The reason for this disparity is not known, but it may be due to improved noninvasive imaging techniques, and to more thorough screening for extent of disease involvement in FMD patients, as well, even in the absence of neurovascular symptoms. It is notable that the prevalence of multivessel FMD was higher than reported elsewhere,2 and ~65% of patients with renal FMD had evidence of cerebrovascular FMD and visa versa.

There was a significant delay in diagnosis from the first onset of clinical symptoms/signs of 4.4 years in men and 4.1 years in women. There are several possible reasons for such a delay, including the possibility that FMD was not considered in the differential diagnosis of a patient’s symptoms because of underrecognition of this disorder, the mistaken belief that FMD is predominately a disease of young patients, and the fact that many of the signs and symptoms of FMD are nonspecific, such as dizziness, tinnitus, and headaches. In addition, it is important to note that, among FMD patients with hypertension, the mean age of onset was 43.1 years (SD 14.9; median, 44.5 years). Because the age of onset of hypertension overlaps with the age of onset of essential (primary) hypertension,2 additional clues to the presence of FMD are abdominal, flank, or neck bruits, headaches, pulsatile tinnitus, or resistant hypertension.

On the basis of these registry data, we propose key clinical scenarios that may help the clinician more readily consider the diagnosis of FMD, thus leading to earlier diagnosis and treatment with a goal of improved outcome and fewer adverse vascular events (Table 7). However, these are nonspecific and

Table 7. Consider the Diagnosis of FMD in the Following Circumstances

| Onset of hypertension at <35 years of age |
| Resistant hypertension (ie, hypertension that cannot be controlled to goal despite at least 3 medications with different mechanisms of action and one of the medications is a diuretic) |
| Epigastric bruit and high blood pressure |
| Cervical bruit in a patient <60 years of age |
| Pulsatile tinnitus (swooshing or whooshing sound in the ear[s]) |
| Severe and recurrent headaches, especially migraine type |
| TIA or stroke in a patient <60 years of age |
| Dissection of a peripheral artery (carotid, vertebral, renal) |
| Aneurysm in a visceral or intracranial vessel |
| Aortic aneurysm in a patient <60 years of age |
| Subarachnoid hemorrhage |
| Renal infarction |

FMD indicates fibromuscular dysplasia; TIA, transient ischemic attack.

their value in the primary care setting or other populations with a low prevalence of FMD is uncertain.

Because histopathology was rarely available in this cohort owing to the infrequency of open surgery and because the pathological type of FMD may be difficult to discern on angiography, the classification of FMD type as promulgated by Harrison and McCormick may need to be revised.11,14,33 In previous reports and in the current series, medial fibroplasia was the most common type encountered. Intimal fibroplasia was encountered in 21 patients (7.0%), and there were only 2 (0.7%) patients with perimedial disease in the current series. Nearly one third of all patients could not be definitively classified with the use of angiographic criteria. The reason for this is not known, but it should be emphasized that intimal fibroplasia and medial hyperplasia have similar angiographic appearances, and, although adventitial fibroplasia has a distinct angiographic appearance, there is considerable angiographic overlap among the 3 pathological types. Several other angiographic classifications have been proposed, but none have been uniformly adopted.20,34–37 There is a need for modernization and standardization of the classification system for FMD, particularly given the rarity of histopathology among patients in current medical practice and the differing prognosis and response to therapy among the different types of FMD.4,38,39

The most frequent presenting signs and symptoms of FMD in this registry were hypertension, headache, pulsatile tinnitus, and dizziness (Table 3). However, 25 (5.6%) patients had no signs or symptoms and were discovered incidentally when imaging was performed for another reason. In 80% of patients, multiple clinical symptoms/signs were present. Among 265 patients who had either carotid or vertebral artery FMD, 189 (71.9%) patients experienced headaches. Of the 294 patients with renal artery involvement, 174 (59.2%) patients reported the presence of headaches. In Mettinger and Ericson’s series,16 25 of 32 (78%) patients with carotid or vertebral FMD reported headaches, most commonly of the migraine type. Foster and associates40 noted the occurrence of headaches in 50 of 56 (89%) patients with FMD of the renal
arteries. It should be noted that there were missing data regarding headaches in 87 patients. Thus, the prevalence of headaches in the current series may be overestimated. However, if none of these 87 patients with missing data had headaches (which is very unlikely), the prevalence would still be quite high, approaching 50%. The etiology of headache among patients with FMD is not known, but it does not appear to be related to blood pressure levels in most patients. Why 1 patient with carotid FMD has severe pulsatile tinnitus and headache while another is asymptomatic is not known.

Although the sensitivity of a carotid or epigastric bruit is quite low in FMD patients, the specificity is high; thus, the presence of a bruit in a young or middle-aged patient should trigger the clinician to investigate further.

There are several interesting and somewhat surprising findings from the registry data. The self-reported presence of a family history of FMD in this cohort is lower (7.3%) than reported in several studies (Table 2). Pannier-Moreau et al41 reported a prevalence of 11%, and Perdu and colleagues42 reported that relatives of patients with FMD had asymptomatic abnormalities of the carotid artery at a much higher frequency than a control group. It is possible that the true prevalence of FMD in first- and second-degree relatives is higher, but was not identified because relatives were not consistently screened for FMD. Perhaps even more striking is the extremely high prevalence of stroke (53.5%), aneurysm (23.5%), and sudden death (19.8%) among family members of FMD patients. These family history events were not adjudicated; thus, the accuracy of these numbers cannot be assured. If in fact these data are correct, it would indicate that FMD may be associated with an inherited systemic arteriopathy with heterogeneous vascular manifestations.42

Dissection (19.7%) and aneurysm (17.0%) occurred frequently with carotid artery dissection, accounting for 75% of all dissections followed by renal artery (22% of dissections) and vertebral arteries (17% of dissections) (Table 6). It is interesting to note that abdominal and thoracic aortic aneurysms occurred with a higher frequency than expected for primarily female patients with a mean age of 55.8 years, the majority of whom have never smoked. Because not all patients had the thoracic or abdominal aorta imaged, the frequency of aortic aneurysms in FMD patients may even be higher than reported in this series. The cause of the increased frequency of aortic aneurysms is not known, but it may again represent FMD as a manifestation of a more generalized arteriopathy.

In comparison with the general population, there is an increased prevalence of intracranial aneurysms in patients with extracranial cerebrovascular FMD.

In a meta-analysis of 18 studies involving 615 patients with carotid or vertebral artery FMD, the overall prevalence of intracranial aneurysms was 22%. However, when patients presenting with subarachnoid hemorrhage were excluded, the prevalence of intracranial aneurysms was only 7.3%, much lower than the 22% to 51% prevalence reported by other investigators.16,19,28,36,43 This may explain the reported low prevalence of subarachnoid hemorrhage (5 patients) in this series.

**Limitations**

Although the US FMD Registry is the largest series of FMD patients reported to date, there are limitations to these data. There may be referral bias in that the most symptomatic of the FMD patients or those who have had a vascular event may be more likely to be evaluated at one of the centers included in this registry. Thus, we are unable to determine whether asymptomatic and/or undiagnosed patients with FMD have the same characteristics as those with symptoms and vascular events, nor are we able to determine the true prevalence of FMD. Additionally, the lack of an age- and sex-matched control group makes it harder define the association of aneurysms, dissections, hypertension, headaches, and pulsatile tinnitus or the apparently high rates of strokes and sudden death in family members.

This registry includes data that were collected retrospectively (15%) and prospectively (85%), and, thus, some of the information requested for our data forms was either not available or difficult to interpret. In addition, there was no standardized approach in regard to imaging of specific arterial beds. There are currently no national standards or published practice guidelines as to the recommendations for the extent of vascular imaging for patients with FMD. It is anticipated that data from this registry, and other published data, as well, will be used to address guidelines for care of FMD patients.4 The high prevalence of dissection and aneurysms in this series has already changed the way patients with FMD are evaluated among many of the investigators in this registry. For example, if an aneurysm is discovered after imaging a particular vascular territory, a decision is made as to the most appropriate management, depending on the size and configuration of the aneurysm and the specific circumstances (ie, future pregnancy, age, location of aneurysm) of an individual patient. The patient will either be placed in an imaging surveillance program to detect enlargement of the aneurysm or a decision is made to treat the aneurysm by surgical or endovascular means.

As this registry matures, more centers and patients will be added, and data forms will be further refined. It should be emphasized that this initial report presents only baseline data recorded at the time of enrollment in the FMD patient registry. Future publications will present subsequent follow-up data, including interval vascular events, mortality, therapeutic procedures performed, and the outcomes from these procedures.

Patients <18 years of age were excluded from this report. Although FMD does occur in the pediatric population, the characteristics are unique and different from the adult population with the disease. Thus, these data are not applicable to the pediatric FMD population. Future reports of characteristics in the pediatric FMD population are anticipated as more centers with clinical focus in pediatric FMD are added.

Despite these limitations, this large cohort of FMD patients has provided a vast array of new information particularly regarding the epidemiology, presenting signs and symptoms, and vascular complications related to FMD.
Conclusions
Fibromuscular dysplasia is a nonatherosclerotic, noninflammatory vascular disease that primarily affects women in the prime of their life. It most commonly affects the renal, carotid, and vertebral arteries, but it may occur in virtually every artery of the body. Multivessel involvement is common. The most common clinical manifestations of FMD are hypertension, headaches, pulsatile tinnitus, and dizziness, but dissection, aneurysm, transient ischemic attack, and stroke also occur with a high frequency. This multicenter registry provides data on the largest cohort of FMD patients to date. As more centers and patients are added and followed longitudinally, more information will be available on the natural history of this disease, optimal methods of diagnosis and treatment, and perhaps ultimately the discovery of genetic and environmental influences that may be important in the pathogenesis of FMD.

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Disclosures
Drs Gornik and Olin are volunteer (noncompensated) medical advisory board members to the Fibromuscular Dysplasia Study of America (FMDSA). Pamela Mace, RN, is a paid employee of FMDSA.

References
Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory vascular disease that primarily affects women in the prime of their life. There is an average delay of 5 years from the onset of symptoms until the diagnosis of FMD is made. FMD most commonly affects the renal, carotid, and vertebral arteries but may occur in virtually every artery of the body. Multivessel involvement is common. The most common clinical manifestations of FMD are hypertension, headaches, pulsatile tinnitus, and dizziness. However, 1 in 5 patients experience a dissection, and 17% have one or more aneurysms. A cerebrovascular event including transient ischemic attack, stroke, and/or amaurosis fugax occur in 1 of every 4 patients with FMD. The presence of a carotid bruit in a patient under 60 or an epigastric bruit in a patient with hypertension should alert the clinician to the possible diagnosis of FMD. Earlier diagnosis may prevent the consequences of poorly controlled hypertension, and allow for the identification of aneurysms and dissections and their appropriate treatment.

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Supplemental Material

Appendix:

United States FMD Patient Registry Sites (Investigators; number of patients): Cleveland Clinic (HL Gornik, ESH Kim, 187), Mt. Sinai Medical Center (JW Olin; 76), University of Michigan (J Froehlich; 51), Greenville Health System (B. H. Gray; 32), Mayo Clinic (R. McBane, 31), North Central Heart, Sioux Falls (M Bacharach; 21), Ochsner Clinic (C.J. White, M. Grise 19), Massachusetts General Hospital (MR Jaff, 18), University of Virginia (AH. Matsumoto, 12).