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The United States Registry for Fibromuscular Dysplasia: New Findings and Breaking Myths

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Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory arterial disease predominantly seen in women. Most FMD cases are classified as medial fibroplasia, which has the appearance of a string of beads on angiography. Until recently, FMD was thought to be seen in women in their 20s and 30s, with more than 60%-75% of cases occurring in the renal artery and 25% of cases in the carotid artery. Hypertension was regarded as the primary symptom seen in these patients followed by a small number of patients presenting with intracranial aneurysms with subarachnoid hemorrhage. The United States Registry of FMD, a patient registry, has broken many preconceived notions as well as provided more in-depth knowledge of this uncommon disorder. In this review, we discuss the findings of this registry and its use in understanding this disorder. In addition to the registry, we review other recent studies and future directions in the diagnosis and management of this disorder.

KEYWORDS Fibromuscular dysplasia, FMDSA, registry, dissections, aneurysms, FMD

Introduction

Fibromuscular dysplasia (FMD) is a rare nonatherosclerotic, noninflammatory arterial disease.[1] It was first described by Leadbetter and Burkland[2] at John Hopkins Medical Center in 1938 in the renal artery of a 5.5-year-old boy with severe uncontrolled hypertension, which was cured with nephrectomy. FMD is known to cause stenosis, aneurysms, dissections, and occlusions of the arteries involved.[1] Its clinical presentation typically depends on the location of the disease. For years, it was thought to occur predominantly in the renal arteries (RA), with the internal carotid artery being a distant second, and it was felt that this disease most often occurred in only 1 vascular territory.[3] Most of the data on this disorder were obtained from retrospective case series from single centers.

In 2008, 7 medical centers collaborated to participate in the FMD registry, coordinated by Michigan Cardiovascular Outcomes Research and Reporting Program. Now, there are 14 centers participating in the registry with more than a thousand patients enrolled. These centers are Cleveland Clinic, Mount Sinai School of Medicine, University of Virginia, University of Michigan, Baptist Hospital of Miami, Children's Hospital of Philadelphia, Massachusetts General, Mayo Clinic, Ochsner Clinic, North Central Heart Institute, South Carolina Greenville Hospital System, UC Davis Vascular Center, University of Kansas, and Vanderbilt University. Each registry site has approval from its local institutional review board. Data are collected prospectively and retrospectively. A standardized data form is available for initial and follow-up data. Initial data form consists of family, personal past medical, and presenting history as well as medications; physical examination; imaging identifying and excluding FMD in various locations; type of FMD; genetic testing for other vascular connective tissue disorders; creatinine level and lipid testing; and finally FMD-related therapeutic procedures along with outcomes and complications. Follow-up form, which is collected at least once a year, comprises interval diagnostic testing, therapeutic procedures, change in symptoms, and interval clinical outcomes. The registry has enrolled more than a thousand patients, and while doing so, it has published numerous articles and abstracts on its findings. Many of these findings have questioned various preconceived notions and have brought into attention certain novel findings.

Demographics and Clinical Presentation

FMD was previously described as a disease of women who were in their 20s and 30s; however, data from the US FMD

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registry provided very interesting results. In 2012, Olin et al described demographics and clinical characteristics in the first 447 patients in the US FMD registry. They noted that the mean age was 51.9 years (standard deviation = 13.4 years, range: 5-83 years) rather than 20s and 30s.[4] This was an interesting and unexpected finding. Most patients were women as expected (91%).[4]

Although hypertension was the most common presenting symptom seen in 63.8% of patients, there were numerous other symptoms and signs reported in the registry. These were headaches (52.4%), pulsatile tinnitus (27.5%), dizziness (26%), cervical bruit (22%), neck pain (22.2%), tinnitus (18.8%), chest pain or shortness of breath (16.1%), flank or abdominal pain (15.7%), aneurysms (14.1%), and cervical artery dissection (12.1%). Registry also highlighted that women are more likely to present with symptoms and signs related to extracranial cerebrovascular involvement compared with men, with increased rates of pulsatile tinnitus (35.7% vs 9.1%, $P = 0.0002$), cervical bruit (26.8% vs 4.5%, $P = 0.0004$), and neck pain (28.6% vs 13.3%, $P = 0.034$).[5] Men were more likely to present with signs and symptoms of renal artery FMD compared with women, with higher rates of flank or abdominal pain or both (43.8% vs 14.3%, $P < 0.0001$), renal insufficiency (9.1% vs 2.2%, $P = 0.026$), and renal infarction (42.9% vs 4.3%, $P = 0.0067$).[5] In addition, patients with pulsatile tinnitus also have headaches, neck pain, and dizziness and are less likely to have hypertension.[6] They are also more likely to have transient ischemic attack (TIA), cervical bruit, cervical artery dissection, and Horner syndrome, with more involvement of the cerebrovascular arteries rather than the RA.[6] The registry clearly highlights that FMD presents with a heterogeneous group of symptoms in most patients, with predominance of certain presenting features based on their sex. Another interesting finding was the lack of any symptoms in 5.6% of patients who were diagnosed with FMD, incidentally identifying either asymptomatic form or dormant phase of this disorder.[4]

The results from the US registry for FMD identified a delay in diagnosis and showed a mean time of 3.6 ± 7.4 years between presenting symptoms and diagnosis of FMD.[7] Factors associated with delay in the diagnosis were presenting with hypertension and being on multiple antihypertensive medications during diagnosis. However, patients presenting with arterial dissections have a shorter time interval between presenting symptoms and diagnosis of FMD and were more likely to have a timely diagnosis.[7] The delay in diagnosis in patients presenting with hypertension raises the concern for delay in evaluation of FMD as secondary cause of hypertension.

The US FMD registry identified abnormal physical findings in a large number of patients. Cervical or epigastric bruit led to diagnosis of FMD in 22.2% and 9.4% of patients, respectively.[8] Positive predictive value (PPV) and negative predictive value (NPV) of carotid bruit in predicting extracranial carotid FMD were 95.4% and 37.4%, respectively. The PPV and NPV of epigastric and flank bruit or both in predicting renal and mesenteric FMD were 92.6%, and 26.0%, respectively.[8] Horner syndrome, cranial nerve abnormalities, and other focal neurologic deficits were reported in 12.4%, 9.4%, and 13.6% of patients, respectively.[8] Horner syndrome can be a sign of vertebral artery dissection.[8] Clearly, a presence of physical findings was more predictive of FMD, but a lack of them was a poor predictor of its absence.

Etiology

The cause of FMD is unknown, but possible etiologies such as smoking, estrogen, and genetic factors have been considered. Smoking has been found to be more common in patients with FMD than the general population. Among patients in the US registry, 37.2% were current or former smokers.[4] In a European study of 337 patients with FMD, current smokers had been diagnosed with hypertension and FMD earlier than nonsmokers.[9] This reflects that smokers have a more severe presentation and are therefore more likely to be diagnosed with FMD. Estrogen level has been proposed as a factor owing to the high proportion of female patients with FMD. Exposure to oral contraceptives or hormonal replacement therapy was recorded for 69.6% of women in the US registry.[1] Prior studies on inherited factors relating to FMD have shown mixed results. An early study of 20 patients diagnosed with FMD showed that 60% of them had at least 1 family member with the disease.[10] Recent studies such as by Perdu et al[11] and the US FMD registry have shown more modest familial associations (11% and 7.3%, respectively).[4] The US FMD registry revealed a strong family history of vascular outcomes with stroke, aneurysm, and sudden death seen in 53.5%, 23.5%, and 19.8% of family members, respectively, indicating an underlying inherited vasculopathy.[4] A study from Cleveland Clinic evaluated patients with FMD for established connective tissue disorders such as vascular type of Ehlers-Danlos syndrome or Loeys-Dietz syndrome and only identified 2 of 216 patients with FMD with known vascular connective diseases.[12] Interestingly, a recent publication by Santhi et al also noted increased production of transforming growth factor β (TGF-β) 1 and 2 in fibroblast and elevated TGF-β 1 and 2 levels in plasma in patients with FMD, identifying a potential TGF-β pathway for this disorder.[13]

Vascular Distribution

Contrary to the belief that FMD occurred in the RA in most cases, the US FMD registry identified that cerebrovascular FMD was almost as common as renal FMD, and in fact, a large number of patients had FMD in multiple vascular beds.[3,4] In the US FMD registry, FMD was seen in the RA in 79.7% of 369 patients with renal imaging and in the carotid arteries of 74.3% of 338 patients with carotid imaging. In addition to it, FMD was seen in vertebral arteries (36.6%; 82 of 224 cases imaged), mesenteric arteries (26.3%; 52 of the 198 cases images), lower extremity arteries (60%; 42 of the 70 cases images),