Prevalence, Presentation, and Associated Conditions of Patients With Fibromuscular Dysplasia

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Fibromuscular dysplasia (FMD) is defined by focal narrowing of small and medium-sized arteries due to an idiopathic, noninflammatory, nonatherosclerotic vascular disease. The population-based prevalence of FMD remains unknown. Using the National Inpatient Sample database, we evaluated the prevalence, clinical presentation, mortality, and associated conditions of FMD from January 1, 2004, to September 30, 2015. Among 2,420 patients who presented with FMD, 2,086 (86.20%) of patients were female. The mean age was 55.18 ± 18.99 years in men and 63.37 ± 17.10 years in women. FMD patients most commonly presented with hypertension (67.3%), transient ischemic attack (3.7%), headache (2.1%), dizziness (1.1%), abdominal pain (0.6%), or hematuria (0.3%). In-hospital mortality of FMD patients was 0.74%. In conclusion, FMD is a rare condition with low in-hospital mortality that may be considered among female patients presenting with hypertension. **(Am J Cardiol 2019;00:1−4)**

Though fibromuscular dysplasia (FMD) was first described in 1938 by Leadbetter and Burkland,[1] little is known about FMD within the medical community. The clinical manifestations of FMD are determined primarily by the vessels that are involved. FMD commonly presents as early or acute onset hypertension or renovascular hypertension,[2,3] but can also present with other symptoms. FMD patients may also have family history of stroke and cardiovascular disease.[4,5] While recent studies found that the large majority of patients are female (80% to 90%), the etiology and prevalence of FMD remain unknown.[2,6] Recent studies exploring the pathophysiological mechanisms of FMD suggest that it may be associated with other conditions such as spontaneous coronary artery dissection,[7] Marfan syndrome,[8] tuberous sclerosis,[9] Alport syndrome,[10] medullary sponge kidney,[11] pheochromocytoma,[12] cystic medial necrosis,[13] coarctation of the aorta,[14] alpha-1 antitrypsin deficiency,[15] Ehlers-Danlos syndrome,[16] neurofibromatosis type 1,[17] and Williams syndrome.[18] Environmental factors (e.g., smoking) may also be associated with FMD.[4,19,20] In this national population-based cohort study, we evaluated the prevalence, clinical presentations, mortality, and associated conditions of FMD.

Methods

We evaluated the National Inpatient Sample (NIS) database which is part of the Healthcare Cost and Utilization Project and includes data from hospitalized patients from a total of 46 states in the United States (http://www.hcupus.ahrq.gov/db/nation/nis/nisrelatedreports.jsp).

Patients with the principal diagnosis of FMD were identified from NIS between January 1, 2004, and September 30, 2015, using ICD-9 codes. All clinical presentations, comorbidities, associated conditions, and in-hospital outcomes were identified. The methodological standards have complied with the Agency for Healthcare Research and Quality's recommendations (Online Supplementary Table 1). A list of ICD-9-CM codes for the variables included in the current analysis is described in the online Supplementary Table 2. This study was approved by the Icahn School of Medicine at Mount Sinai institutional review board and determined to be exempt from review.

Descriptive statistical analysis of the prevalence, clinical presentations, mortality, and associated conditions of FMD were performed. Percentages and means ± standard deviations were computed for categorical and continuous variables, respectively. All analyses were conducted using R 3.4.0 and Stata version 14.2. All p values were 2-sided, and statistical significance was determined at the level of $p < 0.05$.

Results

A total of 2,420 patients had a diagnosis of FMD; of these, 86.20% were female. In-hospital mortality of FMD patients was 0.74% (Table 1). There were no sex differences in in-hospital mortality (female: 0.67% vs male: 1.20%,

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Table 1
The prevalence of FMD and percentage female (sampling weights)

Year	Number	Female (%)
2015	104	85 (81.73%)
2014	151	130 (86.09%)
2013	179	146 (81.56%)
2012	173	154 (89.02%)
2011	396	351 (88.64%)
2010	25	16 (64.00%)
2009	245	214 (87.35%)
2008	127	110 (86.61%)
2007	247	216 (87.45 %)
2006	289	252 (87.20%)
2005	228	196 (85.96%)
2004	256	216 (84.38%)

Table 2
Characteristics of FMD patients at presentation

Clinical presentation	Number (%)
Hypertension	67.3%
Headache	2.1%
Migraine	0.03%
Tension headache	0.14%
Pulsatile tinnitus	0.14%
Dizziness	1.12%
Neck pain	0.47%
Shortness of breath	0.01%
Transient ischemic attack	3.68%
Ischemic stroke	0.02%
Intracerebral hemorrhage	0.01%
Abdominal pain	0.56%
Hematuria	0.28%

$p = 0.30$). Hospital mortality over time varied from 0 to 4 cases (0% to 1.68%). The mean age was 62.25 ± 17.60 years with 59.56% of patients older than 60 years of age (Figure 1). The mean age of females was 63.37 ± 17.10 years. FMD patients were mainly white (84.45%) with African American (6.38%), Hispanic (4.86%), Asian (1.40%), and Native American (0.24%) being less common. Common associated co-morbidities included hyperlipidemia (31%), obesity (5.2%), chronic kidney disease (11.6%), diabetes mellitus (13.13%), history of smoking (11.6%), and family history of coronary artery disease (2.9%).

FMD patients most commonly presented with hypertension (67.3%), transient ischemic attack (3.7%), headache (2.1%), dizziness (1.1%), abdominal pain (0.6%), or hematuria (0.3%) (Table 2). A total of 4.3% had a history of renal infarction, 2.7% had a history of abdominal aneurysm, 1.6% had a history of renal dissection, 0.8% had a history of carotid artery dissection, 0.6% had a history of cerebral artery aneurysm, and 0.3% had a history of hyperaldosteronism.

Discussion

To our knowledge, this is the largest study to date evaluating FMD patients at a national level. There were 3 main findings. First, we found that sex and racial distributions in FMD patients were consistent with previous reports. Our study showed 85.6% of FMD patients were female. Previous studies which reported 80% to 90% were female,[2,21] while data from the United States and French registry reported 83.7% female prevalence.[22] There is no evidence to support racial or ethnic propensity, but white patients are more likely to be affected than other ethnicities. Although

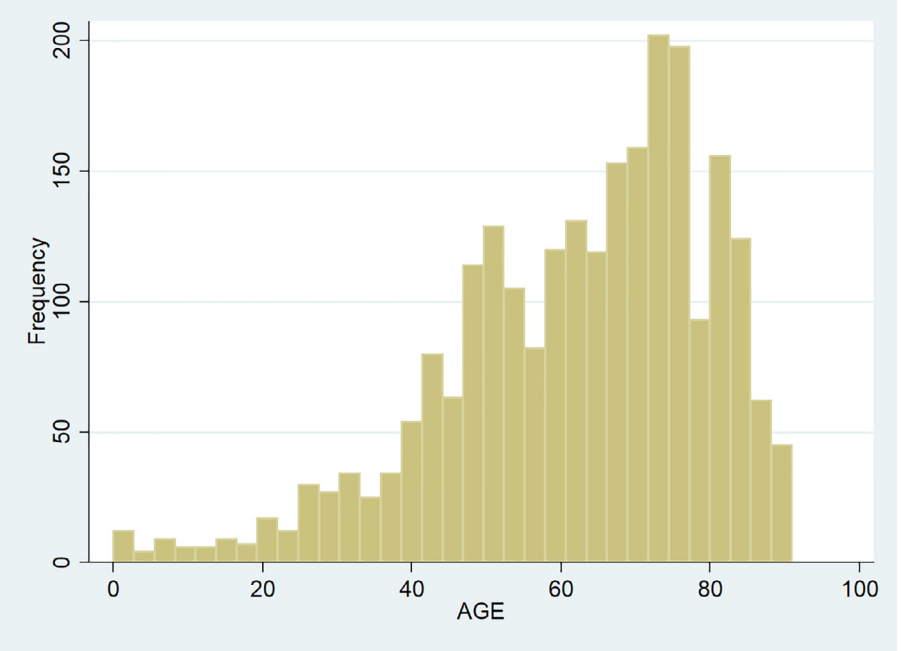

Figure 1. Age distribution in FMD patients from 2004 to 2015.

FMD cases have been reported in infants, children, and older patients, it was previously thought that FMD was a disease of young women. Interestingly, our results showed that most FMD patients are middle aged. This is consistent with findings[2,23] from the United States Registry for FMD involving 9 centers which reported a mean age at diagnosis of 51.9 years with a range of 5 to 86 years.[2]

Second, we demonstrated that more than half of patients with FMD had hypertension, 30% had hyperlipidemia, and 10% had a history of smoking or diabetes. In a retrospective cross-sectional study of 337 patients diagnosed with FMD, Savard et al[19] found that 30% of FMD patients were current smokers compared with 18% in a control group. Preventive strategies in high-risk patients with FMD such as controlling blood pressure, diet, exercise, and smoking cessation may be useful in preventing the development of or complications from FMD. The current scientific statement from the American Heart Association[24] suggests that antihypertensive medications such as angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are the drugs of choice because FMD is thought to be associated with the activation of the renin-angiotensin-aldosterone system in response to renal ischemia. Some FMD phenotypes such as hyperaldosteronism-related FMD might benefit more from an ACEI/ARB. Although FMD is related to hyperlipidemia, statin treatment in FMD is controversial[25] and in some observational studies has been associated with harm.[26]

Third, some conditions such as renal infarction, TIA, and stroke may be associated with FMD. This suggests that while FMD is postulated to be a systemic disease,[16] its involvement can be heterogeneous. Previous studies have reported that the prevalence of renal FMD is 0.4%, whereas the estimated prevalence of craniocervical FMD is much lower at 0.1%.[27] Stroke risk factor modification and antiplatelet agents may be useful in management of cerebral FMD and require further study.

There are certain limitations in this cohort. First, we could not differentiate congenital disorders using ICD-9 codes. For example, an ICD-9 code of 759.89 (for other specified congenital anomalies) could not be classified into Williams syndrome or Alport syndrome. This may be avoided in future studies utilizing ICD-10 codes which differentiate between these rare syndromes. Second, we could not identify the presence of classic physical exam findings (e.g., carotid bruit) from ICD-9 codes. Third, we could not evaluate admission medications from the NIS database to identify types of medications which could be related to outcomes or mortality. Fourth, we could not identify genetic factors which could be related to FMD. Lastly, it is possible that the true prevalence of FMD is underrepresented in this analysis because the gold standard of diagnosis is angiography. For example, studies showed that the prevalence of FMD among kidney donors who underwent angiography varied between 2% and 6.6%.[26,28–30]

In conclusion, FMD should be considered in female patients presenting with hypertension. In-hospital mortality of FMD patients today is relatively low. Controlling blood pressure, diet, exercise, and smoking cessation are potentially important management strategies for FMD.

Conflict of Interest Disclosures

Dr. Deepak L. Bhatt discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda. None of the other authors have any disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.12.045.

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