Fibromuscular Dysplasia: More Questions Than Answers

Robert D McBane, MD: I am Rob McBane, a vascular specialist at Mayo Clinic in Rochester, Minnesota. Today we are going to discuss a very interesting topic — fibromuscular dysplasia (FMD). Three renowned experts have joined me for this roundtable, and they know this disease well. On my far right is Dr Thom Rooke, from the department of vascular medicine at Mayo Clinic; Dr Sanjay Misra, one of our interventional colleagues with a great deal of experience in catheter-based therapies for FMD; and Dr Iftikhar Kullo, who has a strong research program in vascular disease and specifically in FMD.

My first question will be to Dr Rooke. Can you tell us about FMD? It’s gaining a lot of press lately. What is this disease? Who develops it? How would you classify this unusual entity?

Thom W Rooke, MD: It is an unusual entity. I’m probably going to let some people down by not being able to provide all the answers at this stage. It’s a mystery of vascular medicine.

FMD is probably a congenital condition[1](something we are born with), but it doesn’t necessarily manifest until we age. We used to think of it as a disease of young people, but that is changing.

There are several types of FMD. The most common is medial dysplasia, which affects the medial layer of the arteries and results in abnormal arrangements of the smooth muscle that can lead to stenotic lesions, aneurysms, dilatations—a variety of problems. It is these changes in the artery that ultimately get people into trouble.

The Female Factor

Dr McBane: Approximately 90% of patients with FMD are women. Dr Kullo, do you have any sense of why women seem to be overrepresented in this disease entity?

Iftikhar J Kullo, MD: We don’t know fully why there is such a strong predilection in women. It’s been shown in multiple studies, and there has been a humoral hypothesis that some of the clinical manifestations are related to hormones. Support for this hypothesis comes from studies that show that these individuals have also a high incidence of having taken hormone-replacement therapy.[2]

However, going against the humoral hypothesis is the fact that pregnancy doesn’t seem to necessarily exacerbate FMD, and parity, for example, is not associated with a higher rate of FMD.[3]

It’s an intriguing observation, and as yet, it’s not clear why women are more prone to FMD. There may be an interaction of the genetic susceptibility variance with sex that then leads to the manifestation of the disease in women.

The Natural History of FMD

Dr McBane: Dr Misra, you have done a lot of invasive studies in patients with FMD, with cross-sectional CT and ultrasound. Is there any evidence that FMD becomes worse over time? Is this a disease that we are born with, and then it progresses, as Dr Rooke mentioned?
Dr Misra: It’s complicated. We have seen people who are 80 years old with FMD and atherosclerosis involving the renal arteries, and conversely, we have seen nine- and 10-year-olds with FMD. It is probably congenital, although it’s hard to know. We have looked at 2600 CAT scans from patients who had donated kidneys and found a small incidence of renal-artery FMD.[4] We know people have it, and they don’t know they have it. We have seen it at all ages, from childhood and adolescence all the way up to the 80s and 90s.

We have looked at our own database from the Olmsted epidemiology registry to understand how many patients have FMDs in Olmsted County and what the prevalence is. Over the past 20 years, the point prevalence is increasing, and we are looking at this to understand the natural history. What happens once you get it? Is it treated, and what are the ramifications of the management of FMD? Do you do procedures or do patients do fine with medications? It’s a big unsolved mystery.

A Spectrum of Severity

Dr McBane: As Sanjay has recently published and others have shown, perhaps as many as 4% of the general public may have this disease.[5] On one end of the spectrum, we see patients who present with dissections, renal infarctions, and stroke, and on the other hand, we see patients who don’t have any symptoms. What is your sense? Is this a benign disease? Where does FMD fall on the scale of serious diseases?

Dr Rooke: It certainly can be serious. That is the problem here. There is general agreement that most FMD is benign and asymptomatic and doesn’t cause problems. That is probably true of almost anything that causes mild stenotic or mild dilatations in arteries.

The problem is that we haven’t yet learned how to predict who is going to develop problems with FMD and who isn’t. When problems occur, they can be absolutely catastrophic, and those are the patients who typically are showing up on our doorsteps; the patients who have symptoms related either to stenotic lesions leading to ischemia or to aneurysms that can dissect. Those are the patients we are seeing. It’s a small number, but it biases our view of the severity of FMD.

Dr McBane: In recent months and years, a very specific disease called segmental arterial mediolysis (SAM, a disease of dissections) has been discussed, which, at least on angiographic and CT imaging, looks like FMD but behaves very malignantly, with dissections and infarctions. Are these the same or different diseases? Are these just manifestations on a spectrum?

Dr Rooke: This is one of the big controversies that we have to wrestle with. I had a great mentor years ago, an interventional radiologist, who used to tell me, "You can easily tell a difference between FMD and segmental arterial mediolysis, because FMD never dissects and SAM does." If it dissected, then by definition it’s SAM.

We don’t yet know what subtle differences in the dysplastic components or the localization of the disease might lead to the clinical differences that we see in FMD and SAM. An ongoing national effort to learn more about these conditions is picking up steam.

Dr McBane: In the national registry, a number of patients had a history of tobacco exposure; some had hypertension (possibly a renal manifestation of FMD) or dyslipidemia.[2] How do these factors
relate to atherosclerosis? Is this just sample bias, or do these risk factors have any relevance to this disease?

Dr Kullo: By definition, FMD is supposed to be a bland arteriopathy without any inflammation or atherosclerosis. Having said that, there is an interesting association between risk factors and dysplastic or aneurysmal disease. Patients with diabetes are protected against aneurysms, particularly abdominal aortic aneurysms. Even higher lipid levels may not necessarily predispose to aneurysms.

So there is this dichotomy in how risk factors behave toward FMD. The only observational finding of merit is a higher prevalence of smoking, which may contribute to either the development or progression of FMD.

By definition, FMD is not atherosclerotic, so we have to look at other risk factors, whether they are genetic, hormonal, or mechanical, for example. As we discover more of these 80-year-olds with FMD, we will see patients who have both FMD and atherosclerosis.

When and How To Intervene

Dr McBane: I want to move very briefly to treatment and first talk about medical treatment and then interventional treatment.

Dr Misra: We looked at about 1500 renal angioplasties and stents performed in Rochester, Scottsdale, and Jacksonville. About 10% had arteriosclerosis obliterans and FMD. That is often forgotten. We have some data on how FMD behaves in older vs younger patients and those who undergo angioplasty vs those who don’t.

Dr McBane: If you see a patient with FMD, how do you manage that individual, knowing that typically these are young women who may not have any symptoms? What are your recommendations?

Dr Rooke: The first thing that drives your recommendation is the presence or absence of symptoms. The two most common areas where we find the disease are the renal arteries and carotid arteries, in a nearly equal distribution.

If the renal disease is symptomatic, you can treat it with conservative medical therapy. If the patient is hypertensive, you can start standard antihypertensive drugs, using the same rules that we follow for atherosclerotic renal disease—if you can control a disease with medication, you are doing well.

I have trouble with that approach because so many of these people are young and you are committing them to a lifetime of medication when at least traditionally we have thought of this as being something that can be managed a little easier than other vasculopathies.

Carotid or extracranial cerebral vascular disease is more problematic because we don't have as good a medical therapy for that disease. If the patient is symptomatic, we often look at some type of interventional treatment.

I consider FMD a risk factor for developing atherosclerosis down the road. I don't know whether that is true, but I automatically move such patients in my mind to a higher-risk category, so that I am a
little more aggressive and liberal with the aspirin, statins, and other drugs that I might prescribe for people with higher-grade risk factors.

**Dr McBane:** The standard mantra in patients with FMD who are undergoing endovascular management is to do angioplasty without stenting. Can you comment upon that, Dr Misra?

**Dr Misra:** That has been our mantra for as long as I remember. In a group of patients, especially those in the sixth and seventh decades of life, balloon-only angioplasty failures occur much faster than it does in 20- to 30-year-old patients. Angioplasty is probably safe in this group. It's not like patients with atherosclerotic disease, in whom you run the risk of more dissections and other embolizations.

For a young patient who is symptomatic and hypertensive with FMD, angioplasty works very well. When you get in the sixth, seventh, or eighth decades, it fails. We published a study on the high risk of failure as patients age, but it’s unclear why that happens.[6]

**Dr McBane:** Can each of you make final comment about FMD and areas for future research?

**Dr Kullo:** There is a lot that we don't know. One area that we really need to understand better is the genetic basis of the disease. Those activities are ongoing at Mayo Clinic and elsewhere.

**Dr Misra:** I would like to understand the natural history better. After diagnosis, what happens? Is the patient at risk for aneurysms? What is that level of risk, so that we can better counsel our patients?

**Dr Rooke:** The natural history is clearly our big weakness right now, and fortunately, there is a registry. They have begun to publish some of their data, and I am cautiously optimistic that as we follow this registry over time we will understand more about the natural history of FMD and from that what we ought to be doing about it.

**Dr McBane:** There is so much to talk about and many avenues that we haven’t had time to broach with this discussion. I would like to thank each of our discussants and our audience for watching this very interesting roundtable discussion. I encourage you to continue to follow us at theheart.org on Medscape.