PERSPECTIVES IN HYPERTENSION

Fibromuscular Dysplasia – personal trajectory and joint achievements

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I have been interested by Fibromuscular Dysplasia (FMD) since my mentor Prof. Jean-François De Plaen (Nephrology Department, Cliniques Universitaires Saint-Luc, Université catholique de Louvain) involved me in the diagnosis and follow-up of several complex cases in the 1990s. By that time, FMD was still considered by many solely as a rare cause of renovascular hypertension in young women.

Since then, mostly thanks to the contribution of the French and US FMD registries, the outlook on FMD has evolved to a systematic, not so rare arterial disease affecting virtually all middle-sized arteries of the body, with a wide range of presentations going from an asymptomatic, silent condition to a severe disease leading to resistant hypertension, renal infarction, carotid dissection or subarachnoid haemorrhage. Besides stenotic lesions, the most frequent being the so-called string of beads, characterized by an alternation of arterial narrowing and dilations (Figure), the clinical picture of FMD has been progressively extended to include aneurysms, dissections and arterial tortuosity.[1] However, despite recent genetic breakthroughs,[2-3] the aetiology and pathophysiology of FMD remain elusive, and management of FMD has not substantially changed since the early 2000.

My view on FMD has been shaped by fruitful contacts with experts from both France and the United States: the French highly cartesian school (Pierre-François Plouin, Michel Azizi, Xavier Jeunemaitre) and the US more empiric but equally successful approach (Heather Gornik, Jeffrey Olin). I was privileged to coordinate the First International Consensus on FMD[1] with Heather Gornik (Cleveland, Ohio), which as of today remains the main source for clinical management of the disease. In the wake of this publication, with a number of motivated experts, we developed the European International FMD registry and initiative (FEIRI) which over the years evolved from a Belgian to a European and now international initiative, including Argentina (PI: Lucas Aparicio), China (PI: Jiguang Wang), Japan (PI: Kan Zen) and Québec (PI: Sébastien Savard).

As of today, the achievements of the FEIRI initiative include, between others:

1. large-scale confirmation of the differences between multifocal and focal FMD, and of the association of arterial dissection with male gender in FMD patients;[4]
2. demonstration of an increased risk of hypertensive disorders of pregnancy in women subsequently diagnosed with FMD;[5]
3. identification of a tentative urinary proteomic signature of FMD, mainly constituted of collagen peptides.[6]

Furthermore, with David Adlam, lead of the EORP-SCAD registry, we analysed in depth extra-coronary FMD lesions in patients with Spontaneous Coronary Artery Dissection (SCAD) and healthy controls from the United Kingdom.

We documented a lower proportion of widespread and complicated FMD, aneurysms and extra-coronary dissections in patients with SCAD compared with patients with primary FMD.[7] Along with genetic and pathologic findings, these results suggest that SCAD and FMD are distinct though overlapping entities rather than different presentations of the same disease. Analysis of proteomic profile of SCAD patients with or without extra-coronary FMD compared with primary FMD may shed more light on the extent of the overlap (submitted manuscript).

Still, a number of major issues relevant to clinical practice remain to be clarified.

First, over 90% of available data on FMD are derived from subjects of Caucasian descent.[1] We recently performed a meta-analysis suggesting a distinct clinical presentation of FMD in patients of Asian descent[8] and are planning to compare characteristics of Asian versus Caucasian patients within the FEIRI registry. Further analysis of FMD presentation in patients of different ethnicities will be needed to understand regional variations in presentation of FMD and to propose truly global recommendations for the diagnosis and management of the disease.

Secondly, there is currently no non-invasive way to assess the haemodynamic significance of renal FMD-related stenosis, and therefore to decide which patients may benefit from angioplasty. Renal Duplex is highly operator-dependent and cut-offs for haemodynamic significance are extrapolated from atherosclerotic renal artery stenosis. The use of pressure gradient measurements during catheter-based angiography has been recommended[1] but due to limited availability, time and money constraints is in reality seldom used. Based on anatomical quantification of lesions and application of fluid dynamics laws in collaboration with engineers, we are currently attempting to predict pressure gradients and therefore response to angioplasty based on non-invasive imaging, with promising preliminary results.[9,10]

Third, compared to analysis of coronary arteries in the context of ischemic heart disease, analysis of images in extra-coronary arteries affected by FMD is clearly lagging behind. For decades, the dichotomic classification of FMD has allowed a welcome standardisation but it does not account for the high variety of clinical presentations of FMD. Based on the imaging resource associated with the FEIRI registry, we are currently developing a novel, more granular and inclusive classification. In association with quantitative assessment of lesions,[9,10] enhanced or not by artificial intelligence, it may prove instrumental to develop a common language across different registries, establish correlations between morphology and clinical presentation, genetic and proteomic profile and to assess progression of lesions over time.

Finally, many patients currently referred to expert centres are in a grey zone: young patients with multiple aneurysms or dissections but without typical string of beads or focal stenosis, in the absence of argument for early atherosclerosis, inflammatory disease or inherited arteriopathy. We are currently unable to answer their questions: do I have FMD, which follow-up should be proposed, and what is my prognosis? Again, baseline characterization of these patients by advanced imaging methods and proteomic profiling combined with extended follow-up may help to address these questions in the next decade.

Past and ongoing work performed within FEIRI rests on collaboration with expert teams from all over the world. The support and contribution provided by centres such as Brussels (PIs: Tom Robberechts and Patricia Van der Niepen), Warsaw (PI: Andrzej Januszewicz), Maastricht (PI: Peter de Leeuw), Reggio Emilia (PI: Marialuisa Zedde) or Manchester (PI: Constantina Chrysochou) and the corresponding national initiatives is invaluable.

Also invaluable is the support of patient-led initiatives, such as BEL-FMD and FMD-EU, developed with an incredible efficiency and dedication by Mrs Cathlin Jamison.

Finally, I would like to express my gratitude to the numerous investigators who are not explicitly mentioned in this short outline. Their names are or will be acknowledged in current or future publications.

While this article is in the first person and attempts to explain my own trajectory, it is obvious for me that our achievements are the result of a collaborative endeavour involving trust, hard work, exchange of ideas and experience. Which may be the nicest part of the story.

10 facts about FMD

1. The diagnosis is based on the presence of the so-called string of beads (multifocal FMD) (Figure) or less frequently of a focal or tubular stenosis (focal FMD). This dichotomous classification does not account for the whole spectrum of clinical presentations of the disease.
2. Besides stenotic lesions, FMD is often associated with arterial dissections, aneurysms and marked arterial tortuosity.
3. Up to 5% of apparently healthy subjects may harbour FMD lesions.
4. The mean age at diagnosis of FMD in current registries is ~50 years.
5. Despite the overall female predominance of FMD, coexistence of arterial dissection with FMD is strongly associated with male gender. The proportion of males is also higher among children/adolescents with FMD, patients with focal FMD and patients of Asian descent.
6. In more than half of patients, FMD is present in two or more arterial beds. Renal and cerebrovascular arteries are the most frequently affected.
7. Women with undiagnosed FMD at the time of pregnancy are at increased risk of gestational hypertension, preterm birth and, to a lesser extent, preeclampsia.
8. While a substantial proportion of patients with Spontaneous Coronary Artery Dissection (SCAD) have FMD-like lesions of extra-coronary arteries, the relation between both entities remains controversial.
9. Patients with FMD appear to display a unique urinary proteomic profile, which may be indicative of an increased collagen turnover.
10. Quantitative assessment of renal FMD lesions may allow predicting their haemodynamic significance, and therefore orient the decision to perform renal angioplasty.

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