Brain-to-Pelvis Imaging Substantially Impacts Management of Patients With Fibromuscular Dysplasia

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During the past decade, and in the wake of French,[1] United States,[2] and more recently European/International[3] registries, our image of fibromuscular dysplasia (FMD) as a rare cause of renovascular hypertension in young women due to the iconic string-of-beads has evolved into a constellation of different clinical patterns. The latter include such diverse presentations as: focal stenosis in children or young men; multifocal FMD in older women coexisting with atherosclerotic lesions; carotid/vertebral, renal, or mesenteric arterial dissections leading to stroke, renal infarction, or mesenteric ischemia; cerebral aneurysms; and even arterial tortuosity.[4] Furthermore, in various cohorts of potential kidney donors, silent renal artery FMD lesions were found in 2.3% to 6.6% of subjects,[5] suggesting that symptomatic FMD is only the tip of the iceberg of a not so rare disease. Finally, it has been shown that FMD affects 2 or more arterial beds in 48% to 66% of patients according to cohort studied, definition of FMD, and screening modality.[1,2] Such novelties have been incorporated in the First International Consensus on the diagnosis and management of FMD.[6] According to the Consensus, while the diagnosis of FMD still requires presence of at least one string-of-beads or focal stenosis, in presence of such lesion(s), coexisting dissections, aneurysms, or tortuosity identified in other arterial beds are considered as additional manifestations of the disease (Figure). Furthermore, the Consensus recommends once a lifetime brain-to-pelvis CT-angiography (CTA) or contrast-enhanced MR angiography to detect additional FMD lesions, aneurysms, or dissections.[6]

While the International Consensus has been generally well received by clinical FMD experts, presentation of the consensus statement advocating brain-to-pelvis imaging in all patients with FMD to wider audiences has inevitably led to someone raising his/her hand asking: "how will this change patient management?".

The timely report the Assessment of Renal and Cervical Artery Dysplasia-Poland study (ARCADIA-POL) by Warchol-Celinska et al[7] in the current issue of *Hypertension* provides us important elements to answer that question based on data obtained in a near ideal setting: a cohort of 232 consecutive patients with FMD from all over Poland explored in a single institution using state-of the-art methods—including the recommended whole body CTA. The key findings are the following: (1) new FMD lesions were identified in 34% of patients; (2) new vascular complications (ie, dissections or aneurysms) in 25% and, most importantly, (3) 25% of all patients qualified for interventional treatment due to newly diagnosed FMD lesions or vascular complications.[7]

While the proportion of newly identified arterial abnormalities is not unexpected and consistent with or even lower than reported in previous studies,[8] the prevalence of patients requiring outright intervention—1 out of 4 patients[7] is surprisingly high and is not in line with our experience in Brussels or Cleveland. Indeed, while FMD is often discovered on the occasion of a work-up for hypertension or severe vascular complications such as cervical, renal, or coronary dissection, it is our experience that additional lesions detected by systematic CTA are often milder and seldom require immediate action. This seems to be even more the case when the initial lesion is discovered incidentally.

Several elements may have influenced the results of the ARCADIA-POL report[7]: (1) as indicated in the Limitations section, the cases referred to the Warsaw Institute of Cardiology for inclusion in ARCADIA-POL may be particularly symptomatic and/or severe (potential for referral bias); (2) as in most other European cohorts but in contrast with the US Registry for FMD,[2] patients included in ARCADIA-POL mostly presented with renovascular hypertension, the most frequent FMD-related symptom was hypertension (91%) and FMD lesions were most frequently found in renal arteries (88%). In addition, the prevalence of symptoms associated with cerebrovascular FMD, such as headache, dizziness, and pulsatile tinnitus was relatively low; (3) out of 59 lesions qualifying for endovascular intervention, 31 were newly diagnosed significant renal artery stenosis—which is not equivalent to newly diagnosed renal FMD; 9 of these lesions corresponded to restenosis of a previously revascularized lesion; (4) the other predominant intervention group consisted in aneurysms (n=25), mostly affecting intracranial (n=16) and renal (n=10) arterial beds. However, at least in the published version of the article, no detailed documentation of aneurysm size or individual rationale for intervention is available. It seems nevertheless that the size of aneurysm was not the primary criterion for intervention and that small or very small aneurysms were considered as eligible

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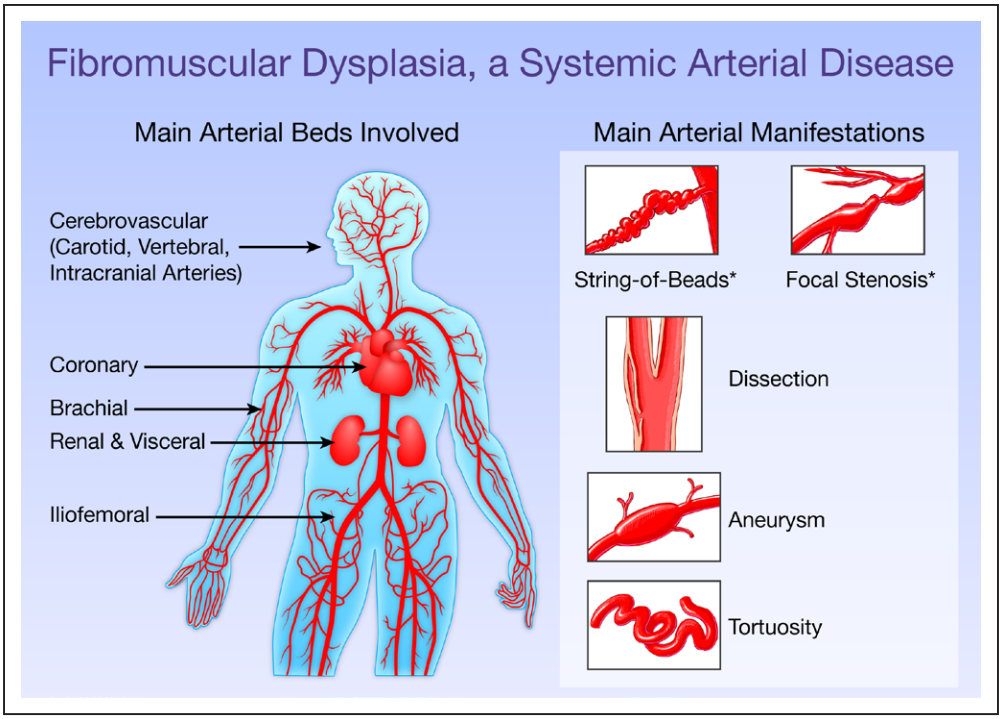

Figure. Main arterial beds potentially affected by fibromuscular dysplasia (FMD) and main arterial manifestations of the disease. The presence of a least one stenotic lesion (string-of-beads in the case of multifocal FMD or focal stenosis in the case of the less frequent focal FMD) is required to establish the diagnosis (*). In presence of such lesions, coexisting arterial dissections, aneurysms, or arterial tortuosity are considered to be additional manifestations of the disease.[6]

for intervention if found in young women, especially of childbearing age and/or associated with hypertension. The comment that "patients with small aneurysms (<2 mm) presented a challenging clinical dilemma"[7] suggests that slightly larger aneurysms (still considered small by most clinical standards) were considered as straightforward candidates for revascularization in presence of additional risk factors.

While these elements may have contributed to an increase in the proportion of patients requiring intervention following vascular assessment, the relatively low prevalence of multivessel disease in the ARCADIA-POL cohort (44% versus 66% in the French-Belgian ARCADIA study,[1] 55% in the US Registry for FMD,[2,6] and 57% in the European/International FMD Registry; A. Persu, personal communication) may have decreased the yield of systematic vascular exploration.

The work of Warchol-Celinska et al[7] sets a benchmark against which other studies aiming to document the impact of whole-body CTA on management of FMD patients will be measured. Nevertheless, for aforementioned reasons, replication in other cohorts is warranted. In our opinion, future studies should (1) include a more balanced group of patients presenting with cerebrovascular as well as renal FMD; (2) consider only the interventions due to identification of new FMD lesions rather than to progression of previously known lesions (eg, progression of initially mild renal FMD or restenosis after angioplasty)—as the latter may have been detected by standard vessel-centered follow-up; (3) report the severity of lesions (eg, the diameter of aneurysms or translesional renal artery pressure gradients) and the associated factors leading to the decision for revascularization in all cases in order to facilitate comparison between studies; (4) include data regarding the cost effectiveness of brain-to-pelvis imaging relative to the finding of clinically significant vascular lesions, including those which warrant interventional therapy.

Besides its contribution to the literature on patients with confirmed diagnosis of FMD, one of the most attractive features of ARCADIA-POL is inclusion of a number of patients with cerebrovascular or coronary artery dissection but without a string-of-beads or focal stenosis, a wide group of patients with FMD-like phenotypes which is of increasing interest among FMD experts.[9] Future perspectives may include investigation of the impact of brain-to-pelvis imaging in these FMD-like subgroups, as well as in children (in whom no firm evidence about the yield of systematic vascular exploration exists) and in patients with focal versus multifocal FMD. Other areas of research may include direct comparison of CTA with contrast-enhanced MR angiography, which has the advantage of being nonirradiating, non-nephrotoxic, and with a much lower risk of allergic reaction. Such studies could address the question: does MR-angiography miss clinically significant arterial lesions requiring intervention? Finally, the study of Warchol-Celinska et al[7] is cross-sectional, and the mid-to-long term cost-effectiveness and clinical impact of identification of additional lesions by systematic CTA or MR-angiography in patients with FMD remains to be established longitudinally. This last issue is tightly linked with the burning question of predictors of progression (…or occurrence of progression at all) of FMD lesions.

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References

1. Plouin PF, Baguet JP, Thony F, Ormezzano O, Azarine A, Silhol F, Oppenheim C, Bouhanick B, Boyer L, Persu A, et al; ARCADIA Investigators. High prevalence of multiple arterial bed lesions in patients with fibromuscular dysplasia: the ARCADIA Registry (Assessment of Renal and Cervical Artery Dysplasia). *Hypertension*. 2017;70:652–658. doi: 10.1161/HYPERTENSIONAHA.117.09539
2. Olin JW, Froehlich J, Gu X, Bacharach JM, Eagle K, Gray BH, Jaff MR, Kim ES, Mace P, Matsumoto AH, et al. The United States Registry for fibromuscular dysplasia: results in the first 447 patients. *Circulation*. 2012;125:3182–3190. doi: 10.1161/CIRCULATIONAHA.112.091223
3. Persu A, Van der Niepen P, Touzé E, Gevaert S, Berra E, Mace P, Plouin PF, Jeunemaitre X; Working Group "Hypertension and the Kidney" of the European Society of Hypertension and the European Fibromuscular Dysplasia Initiative. Revisiting fibromuscular dysplasia: rationale of the European fibromuscular dysplasia initiative. *Hypertension*. 2016;68:832–839. doi: 10.1161/HYPERTENSIONAHA.116.07543
4. Sethi SS, Lau JF, Godbold J, Gustavson S, Olin JW. The S curve: a novel morphological finding in the internal carotid artery in patients with fibromuscular dysplasia. *Vasc Med*. 2014;19:356–362. doi: 10.1177/1358863X14547122
5. Hendricks NJ, Matsumoto AH, Angle JF, Baheti A, Sabri SS, Park AW, Stone JR, Patrie JT, Dworkin L, Cooper CJ, et al. Is fibromuscular dysplasia underdiagnosed? A comparison of the prevalence of FMD seen in CORAL trial participants versus a single institution population of renal donor candidates. *Vasc Med*. 2014;19:363–367. doi: 10.1177/1358863X14544715
6. Gornik HL, Persu A, Adlam D, Aparicio LS, Azizi M, Boulanger M, Bruno RM, de Leeuw P, Fendrikova-Mahlay N, Froehlich J, et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. *Vasc Med*. 2019;24:164–189. doi: 10.1177/1358863X18821816
7. Warchol-Celinska E, Prejbisz A, Dobrowolski P, Klisiewicz A, Kadziela J, Florczak E, et al. Systematic and multidisciplinary evaluation of fibromuscular dysplasia patients reveals high prevalence of previously undetected fibromuscular dysplasia lesions and affects clinical decisions: the ARCADIA-POL Study. *Hypertension*. 2020;75:1102-1109. doi: 10.1161/HYPERTENSIONAHA.119.13239
8. Bolen MA, Brinza E, Renapurkar RD, Kim ESH, Gornik HL. Screening CT angiography of the aorta, visceral branch vessels, and pelvic arteries in fibromuscular dysplasia. *JACC Cardiovasc Imaging*. 2017;10:554–561. doi: 10.1016/j.jcmg.2016.04.010
9. Bruno RM, Mischak H, Persu A. Multi-omics applied to fibromuscular dysplasia: first steps on a new research avenue. *Cardiovasc Res*. 2020;116:4–5. doi: 10.1093/cvr/cvz307