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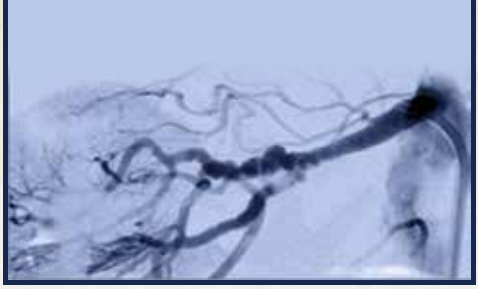
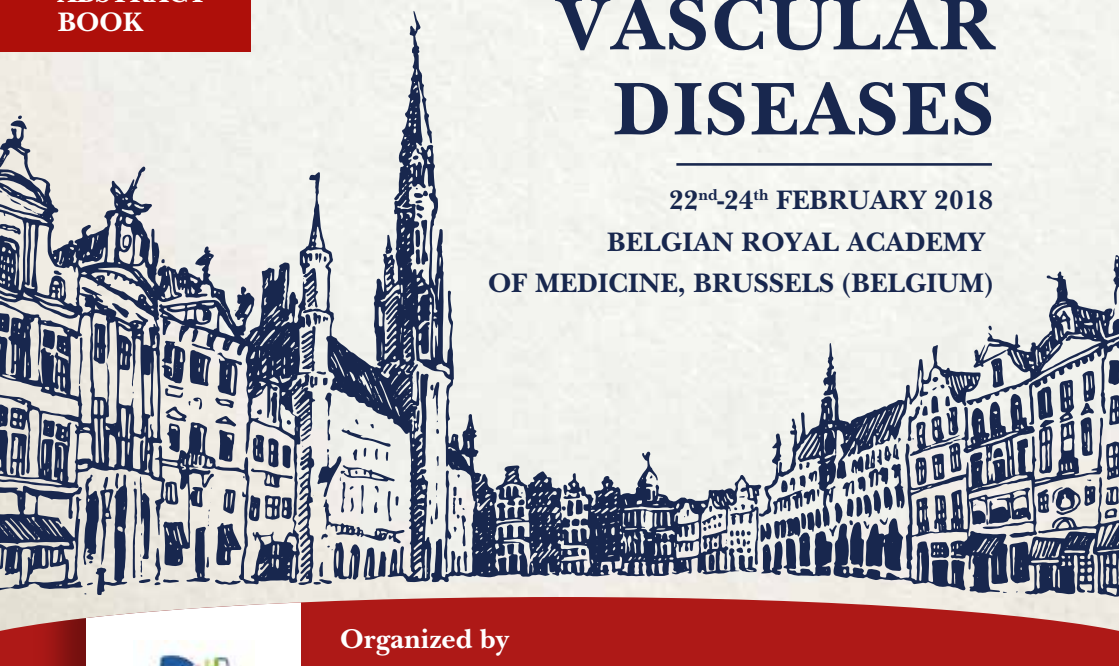


INTERNATIONAL SYMPOSIUM

REVISITING FIBROMUSCULAR DYSPLASIA & RELATED VASCULAR DISEASES

ABSTRACT BOOK



22nd-24th FEBRUARY 2018

BELGIAN ROYAL ACADEMY OF MEDICINE, BRUSSELS (BELGIUM)

Organized by

Cardiology Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

Cleveland Clinic Heart and Vascular Institute, Cleveland, Ohio, United States of America

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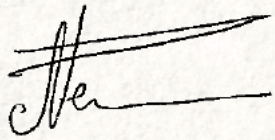
FINAL PROGRAMME

US and European registries are changing the image of Fibromuscular Dysplasia (FMD) from a rare, curable cause of renovascular hypertension mostly occurring in young women to a more common, diffuse, usually benign but sometimes devastating vascular disease, which may occur at all ages of life, both in men and women. International collaborative efforts are currently underway to unravel the genetics, pathophysiology and natural history of the disease, standardize diagnosis and management, and identify biomarkers and predictors of adverse vascular outcomes. This meeting will bring together leading international experts of FMD and related vascular diseases who will summarize current knowledge on FMD, present cutting edge research and identify clinical challenges and research priorities for the next years. It may interest nephrologists, neurologists, cardiologists, internists, paediatricians, radiologists, vascular medicine specialists, as well as basic and clinical researchers.



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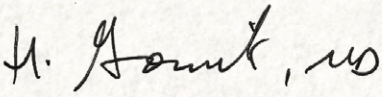

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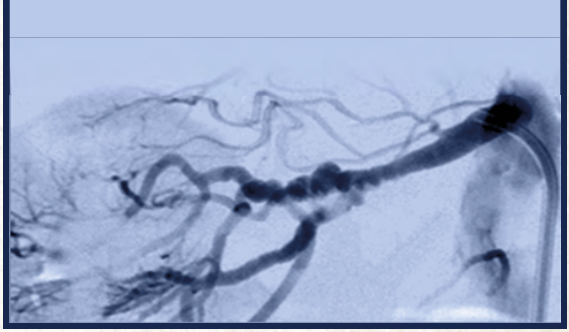
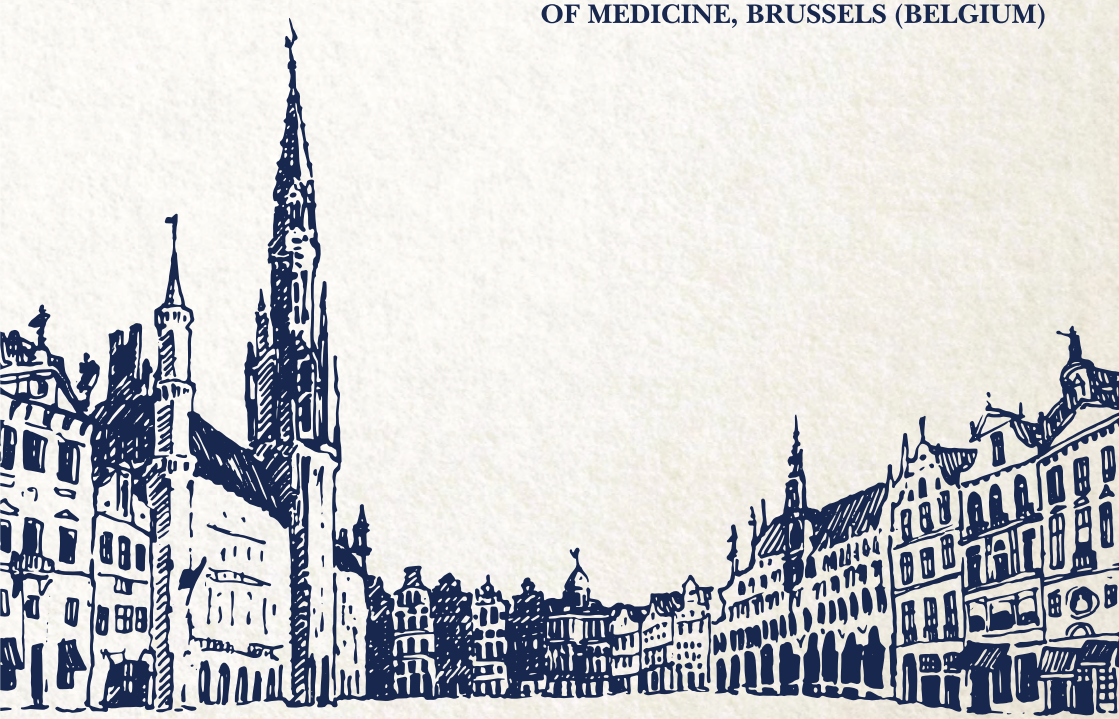


Abstract Book

22nd-24th FEBRUARY 2018

BELGIAN ROYAL ACADEMY

OF MEDICINE, BRUSSELS (BELGIUM)



25 YEARS OF FRENCH RESEARCH IN FIBROMUSCULAR DYSPLASIA

Pierre-François Plouin, Xavier Jeunemaitre, Michel Azizi, *Hypertension Unit, Department of Genetics and National Rare Vascular Diseases Reference Center, Hopital Européen G Pompidou (HEGP), Paris, France*

Fibromuscular dysplasia (FMD) has a long been considered in France as a rare disease causing renovascular hypertension in young women and appearing to be familial in 10 % of cases. Over the last 25 years, we learnt that (I) the condition is frequently overlooked, specifically when asymptomatic or presenting as neurological symptoms, (II) the mean age at diagnosis exceeds 50 years, (III) 2 of 3 patients have stenotic FMD lesions, aneurysms, or dissections that affect several vascular beds, and (IV) that about 2% of cases are familial.

From 1993 to 2009, a FMD registry was created at this institution to merge existing local FMD databases; to feed the French National Rare Vascular Diseases database and report local FMD activity; to prepare a registry usable at the French, then the European level; and to share data semantics with the FMD Society of America registry. The original FMD registry included data from 337 patients diagnosed with renal artery FMD on the basis of non-atherosclerotic stenotic lesions documented at angiography in the absence of aortic wall thickening or biochemical evidence of inflammation and of known syndromic arterial disease. FMD was classified as focal (a single stenosis on a given vessel) or multifocal (two or more stenoses on a given vessel segment), and familial if at least one first degree relative had documented FMD by angiography. In parallel, we found that subclinical lesions were present at arterial sites distant from the renal arteries, suggesting that renal artery FMD is a systemic arterial disease.

From 2010 to present, case-control studies were run at the HEGP to assess

biomarkers and noninvasive hemodynamics in FMD (MeDyA), as well as psychological traits associated with the condition (DYSPERS). In 12 French hypertension and neurovascular units, the ARCADIA registry and the nested PROFILE cohort included 500 new patients with renal and/or cervical artery FMD, along with a collection of leukocyte DNA. An international cooperation involving French geneticists showed that *PHACTR1* is a genetic susceptibility locus for FMD. Independent French groups described a carotid bulb variant of FMD and reported an intense intranuclear expression of progesterone receptors in smooth muscle cells of renal FMD.

There is a great need for additional research into the diagnostic approach, the natural history and the pathophysiology of FMD. A well-defined phenotype is a prerequisite for studies of the epidemiology, pathophysiology and genetics of the condition. A common registry would speed up such studies and increase their statistical power and external validity. The natural history of the condition should be better characterized, allowing development of optimal strategies for investigating, monitoring, following-up and treating patients with FMD. Biological and genetic studies should help improve understanding of the pathophysiology and genetic determinism of the condition and open new possibilities for therapy.

THE UNITED STATES REGISTRY FOR FIBROMUSCULAR DYSPLASIA

Heather L. Gornik, MD, *on behalf of the United States Registry for FMD Investigators*

The United States Registry for Fibromuscular Dysplasia (FMD) was formed in 2008 among 7 clinical centers. The Registry is funded by the FMD Society of America (FMDSA) and is maintained by the University of Michigan Cardiovascular Outcomes Research and Reporting Program (MCORRP). Since enrollment began in January, 2009, a total of **2003** patients have been enrolled (as of January 15, 2018), and the Registry has been expanded to 13 active clinical centers with others onboarding. There have been multiple poster and oral abstract presentations and 7 published peer reviewed manuscripts from the Registry with additional papers in process. A number of insights regarding FMD have been gleaned from the US Registry data, including:

- The most common clinical manifestations of FMD are hypertension and headache, followed by pulsatile tinnitus, dizziness, cervical bruit, and neck pain. 32.1% of patients report pulsatile tinnitus ("swooshing") in the ears as a presenting symptom of FMD.
- FMD is primarily a condition of middle age (mean at first symptom ~47 years), but can present across the life span, including in pediatric and elderly patients. Pediatric patients with FMD are less likely to have cerebrovascular involvement and are more likely to have renal or mesenteric involvement or middle aortic syndrome. Patients diagnosed with FMD at an older age (≥ 65 years) seem to have a more benign clinical course with fewer symptoms and lower likelihood of vascular events or procedures. The US Registry is capturing patients with FMD across the lifespan with median age of enrollment 55.6 years and range of ages of 2.8-90.2 years.
- Currently ~6% of patients enrolled in the Registry are male. Men with FMD are more likely to present with renal or visceral involvement and

have a two-fold prevalence of arterial dissection or aneurysm compared to women with FMD.

- Patients with FMD who have a history of smoking (current or former) are more likely to have an aneurysm or claudication and are more likely to have undergone a vascular procedure. 11.9% of Registrants actively smoke, and 34.5% have a history of smoking.
- FMD is an aggressive vascular disease. More than half of patients have more than 1 vascular bed involved. 41.7% of patients in the US Registry have had at least one arterial aneurysm or dissection. This statistic has led to a recommendation for all FMD patients to undergo one time brain to pelvis cross-sectional imaging (MRA or CTA) to screen for occult aneurysms or dissections.
- Among patients with FMD who have undergone intracranial imaging, 12.9% have at least one intracranial aneurysm and more than half of those with intracranial aneurysm had multiple aneurysms. 43% of intracranial aneurysms were ≥ 5 mm in diameter, a threshold at which repair is considered.
- Among all Registrants, 72.9% take an anti-platelet agent and 71.7% take at least one anti-hypertensive medication. 21.5% of patients take 3 or more anti-hypertensive medications.
- Approximately 50% of Registrants have undergone at least one therapeutic vascular procedure, >80% of which are catheter based. The renal artery was the target vessel in 73% of vascular procedures. A procedural complication was reported in ~10% of cases, most commonly an arterial dissection.

A current emphasis of the US Registry is on determination of the prevalence of major vascular events among patients with FMD and the incidence of new events in follow-up. Approximately 74% of patients enrolled in the Registry for more than 1 year have had at least one clinical follow-up visit reported, and some patients have been followed for eight or more years.

On behalf of the Steering Committee, the coordinating center (MCORRP), and the sponsor (FMDSA), we look forward to exploring collaborations between the US, European, and other international FMD registries.

THE EUROPEAN FIBROMUSCULAR DYSPLASIA INITIATIVE

Alexandre Persu[1], Laurent Toubiana[2], *[1]Division of Cardiology, Cliniques Universitaires Saint-Luc and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium ; [2] INSERM UMRS 1142 « LIMICS », Paris, France.*

The main aims of the European Fibromuscular Dysplasia (FMD) Initiative, coordinated by A. Persu (UCL, Brussels, Belgium) in tight collaboration with M. Azizi, X. Jeunemaitre and P.-F. Plouin (HEGP, Paris, France) are to (I) standardize clinical practice / update the European consensus on FMD (Persu et al., *J Hypertens* 2014 Jul;32:1367-78); (II) establish a network of expert centers in Europe; (III) establish a European patient association; (IV) establish a European FMD registry; (V) facilitate coordination of research on FMD in Europe; (VI) facilitate interactions with the ESC-ACCA SCAD Study Group (Chair: D. Adlam, Leicester, UK), the US FMD registry, and other related initiatives all over the world.

The European FMD registry (Persu et al., Hypertension. 2016; 68:832-9), launched on the occasion of the first national FMD meeting in Brussels (12th December 2015) and subsequently endorsed by the European Society of Hypertension (http://www.eshonline.org/esh-content/uploads/2016/10/Call-FMD-registry-2016.pdf) is at the crossroads of these different objectives. It has been adapted from the French FMD registry (coord. P.-F. Plouin), created in 2010 to merge existing local FMD databases, and includes over 50 items covering demographic and clinical characteristics of FMD, family history, type, localization, associated complications and interventions. It is both retrospective and prospective, is linked with a DNA/RNA biobank and, since October 2017, a bank of images. A flexible, user-friendly online platform has been developed by the team of L. Toubiana (LIMICS/IRSAN, Paris, France), which allows adding an indefinite number of new events

during follow-up of individual patients (Toubiana et al., *Stud Health Technol Inform.* 2015; 210:887-91). Specific modules can be developed according to local interests.

Since its creation 2 years ago, the European FMD registry includes 687 patients (609 patients with "classical" FMD and 78 with SCAD) from 17 countries, including 3 extra-European countries: Argentina, Japan and Tunisia. The main characteristics of patients included in the registry and other preliminary analysis will be shown for the first time at the meeting.

Lucas S. Aparicio, *Médico de Planta Sección Hipertensión Arterial Servicio de Clínica Médica, Hospital Italiano de Buenos Aires Juan D. Perón 4190 (C1181ACH), Buenos Aires, Argentina*

The Argentine FMD registry was initiated in October 2015. It is operationally based in Buenos Aires but has achieved nationwide scope due to the recognition and sponsoring of the Argentine Society of hypertension (SAHA). It has been christened with the acronym SAHARA-DF (i.e. SAHA-Republica-Argentina-Displasia-Fibromuscular), and has online access for data entry through the official webpage (www.saha.org.ar). Up to this date, the registry includes 44 patients diagnosed with FMD by their treating physicians (90.7% women, mean age at FMD diagnosis 45 y.,mean years from hypertension to FMD diagnosis 5 y.). 29 patients have available images confirming FMD, 14 need further confirmation and image retrieval is in progress.

Dr. Constantina Chrysochou MBChB MRCP PhD, *Consultant Renal Physician and Honorary Lecturer Trust Speak Up Guardian Salford Royal Hospital NHS Foundation Trust*

Fibromuscular dysplasia has historically been thought to carry a benign prognosis and as such research in this area has lagged behind. However, we now know FMD can be associated with severe hypertension, ischaemic or haemorrhagic stroke, myocardial Infarction and end stage renal disease, particularly in young females. New research has suggested a potential genetic link in some individuals.

The condition can lead to invasive procedures such as percutaneous

angioplasty, reconstructive surgery, or intracranial aneurysm clipping. Thus, both the disease and its treatment can lead to significant morbidity and mortality.

A UK FMD specialist interest group was formed in 2016. FMD has been adopted on to the rare disease (RADAR) portfolio in 2016 which allows for national uploading of patients with the condition. Since then the specialist interest group has grown to include a pediatric nephrologist, interventional radiologists and links with cardiologists and neurologists. This session will provide an update on the progress of the UK FMD group.

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http://rarerenal.org/rare-disease-groups/fibromuscular-dysplasia-rdg/

Faiçal Jarraya, Hanen Chaker, Jamil Hachicha, *Research unit UR12ES14 and Nephrology Dpt. Faculty of Medicine, Sfax University, SFax, Tunisia.*

FibroMuscular Dysplasia (FMD), a non-inflammatory and non-atherosclerotic arterial disease, mainly affecting the renal and carotid arteries, has regained a lot of interest in recent decades; it is currently conceived as a systemic disease with a genetic substratum.

In Tunisia, it stills just a renal artery disease investigated when hypertension is diagnosed in young ladies and children. Its systematic check is even declining considering its rarity and the increasing obesity as a cause of hypertension in children and young ladies. If vascular medicine is well developed in our country in contrast to many other countries and imaging techniques are available, awareness of the disease still the major barrier to go ahead with this disease. Progress from a renal disease to a systemic disease will improve awareness and gain interest to this not so rare disease. Joining the European initiative will help this Task and help to investigate Tunisian patients

As part of the European initiative to develop a registry on FDM, we

have already collected 4 patients of middle age 41years (24 to 54 years). Hypertension (HTN) was present in all cases. The mean time between the diagnosis of HTN and renal artery FMD was 24 months (12-36 months). Mean creatinine was 99.5µmol/l (53-170µmol/l). Mean GFR(MDRD) 78 ml/mn/1.73m² (24-130ml/mn/1.73m²). Arterial renal involvement was present in all cases. It was unilateral in 3 cases, affecting the right renal artery in 1 case. It was bilateral in 1 case. The typical appearance in pearl necklace was present in 2 cases; the tubing aspect was present in 1 case. Extra-renal involvement was not detected. Angioplasty was performed in 2 cases, with success in 1 case and failure in 1 case. Angioplasty was not performed in one case because of impaired renal function. Vascular surgery was performed on left renal artery in 1986, with an angioplasty in the right renal artery in the year 2000.

Genetic sampling was performed in all patients after their informed consent and proposed to the Human Molecular Genetics Laboratory at the Institute Duve, Brussels.

From this institutional participation to the European Initiative, we try to increase awareness about this disease by giving lectures to other medical core who can face such a disease, we make a call to nephrologists to join this initiative and try to create a multidisciplinary group working in this field.

Yoshio Iwashima, MD, PhD, FAHA, FACC, ISH member, *Division of Hypertension and Nephrology, Department of Medicine, National Cerebral and Cardiovascular Center, Suita, Japan.*

Renal artery stenosis (RAS) is associated with secondary hypertension, which is often resistant to antihypertensive medication. The most common cause of RAS is atherosclerotic, and fibromuscular dysplasia (FMD) comprises most of the remaining causes. The most frequent clinical presentation of FMD is renovascular hypertension secondary to renal artery involvement; however, it is also well known that cervicocephalic FMD can result in ischemic or hemorrhagic stroke, cervical artery dissection, and risk of subarachnoid

hemorrhage. Although renal FMD had been considered a rare disease, recent data suggest that FMD is much more common. In Japan, only a limited number of physicians were interested in FMD, and nationwide registry for FMD was not established yet. Therefore, we did not know whether the frequency, demographic characteristics, or pathophysiology of FMD in Japan differ to those in the other countries. Percutaneous transluminal renal angioplasty (PTA) is one of the standard treatments for renal FMD, and in my presentation, I will report on the recent outcome studies of my institute which focused on the renal PTA.

References:

fibromuscular dysplasia, renovascular hypertension, percutaneous transluminal renal angioplasty.

Jianzhong Xu, MD, Ph D, *Department of Hypertension, Shanghai Institute of Hypertension, Ruijin Hosptial, Shanghai*

Renal artery fibromuscular dysplasia (FMD) is a group of idiopathic, segmental, primarily nonatherosclerotic diseases that may result in renal arterial stenosis, occlusion, aneurysm, or dissection. We documented therapeutic management in patients with renal artery FMD, by analyzing the medical records of hypertensive patients diagnosed with FMD at a single center from 2010 to 2016.

A total of 53 subjects (67.9% female) were included in the analysis. Mean age was 25±6 years, 100% had hypertension, 25.4% had resistant hypertension, 63.3% had a history of secondary aldosteronism, and 1.9% had a history of cerebrovasular disease (CAD). Dual anti-platelet agents were administered to 100% of patients in three month after percutaneous transluminal renal angioplasty (PTRA). 84.9% PTRA patients keep anti-platelet with aspirin for one year.

All patients underwent renal artery angiography. Among them, 25(47.2%) presented “string of beads”, 22 (41.5%) presented unifocal, 6 (11.3%)

presented tubural type.

Intravascular ultrasound (IVUS) is a useful tool, in addition to the angiography for evaluation of the anatomical changes of structures of the vessel layer. Sixteen patients with renal artery FMD were performed IVUS. The multifocal type, with multiple stenoses and the 'string-of-beads' appearance, was present in 8 cases (50.0%); the focal type was present in 6 cases (37.5%); the tubular type was present in 2 cases (12.5%). All 8 multifocal stenoses were associated with IVUS medial FMD, whereas focal and tubular stenoses were not specifically associated with IVUS type.

32 patients were finished one year follow up after PTRA. The mean systolic BP decreased from 158 ± 16 to 122 ± 15 mmHg (P<0.001), and the mean diastolic BP decreased from 101 ± 11 to 82 ± 9 mmHg (P<0.001) at 12 months. After 1 year, 14 (43.8%) patients were cured, 13(40.6%) patients were improved and 5 (15.6%)patients blood pressure has no change. In cured FMD patients, FMD with "string of beads" type was 57% , unifocal was 43%, and no tubular case could be cure after PTRA ; In improved group, FMD with "string of beads" type was 50%, unifocal was 42% and tubular was 8%; Tubular type was 80% and unifocal was 20% in the patients who had no effect after PTRA.

The potential value of IVUS classification is investigated as a way to overcome the limitations of angiography in FMD. The prognosis of FMD patients was related to the subtype, and the patients with multiple lesions had better prognosis.

Scott Wilson, *B.Med.Sci (Hons) MB.BS (Hons) PhD FRACP FASN*

Until recently, and despite an active and organised patient self-advocacy group, fibromuscular dysplasia (FMD) was a relatively orphan disease in the Australian medical landscape. There was no identifiable location of expertise or resource for patients, nor capacity to monitor quality and outcomes of FMD care. We sought to rectify this through the establishment of the Alfred Health FMD service and the inclusion of FMD as one of the foundation

diseases in the clinical quality registry 'ROKD' (Registry of Kidney Disease – http://rokd.org.au/).

ROKD engages consumer representation in its governance, and individuals with FMD consistently express their interest in greater exposure to, with option to participate in, clinical research. Consent for future contact regarding additional research projects is established upfront on an 'opt-out' basis after provision of detailed written information. Data is held in a secure redcap platform domiciled in the Department of Epidemiology at Monash University in Melbourne. Following establishment of the minimal dataset, initiation of the registry has been an extremely challenging exercise in terms of ongoing funding and wider engagement, though we now obtained HREC approval milestones for recruitment at 11 different sites. Multiple models of centralised and decentralised patient enrolment strategies have been considered and currently participants are recruited on a case-by-case basis in the clinical setting – many self-referring to travel cross-country for clinical opinion and enrolment with registry investigators. As momentum builds, further subspecialty groups in other states have engaged to contribute to the registry.

The primary objectives of ROKD-FMD are to recruit patients at earlier stages after diagnosis, accurately describe disease progression, evaluate, standardise and improve the quality of medical care (in particular with regard to promulgation of head-to-pelvis arterial screening recommendations) and disseminate significant international observations and consensus. The broader aspiration is as an aggregation platform to build a suitable cohort for future research, in particular therapeutic trials and contributions to joint efforts with international registries.
Our recent experience moving from an idea through start-up phase into fledgling and now established registry in a high-governance environment may be instructive for those with earlier phase registries or interested in establishing a local registry.

CERVICO-CEPHALIC FMD: FROM SYMPTOMS TO COMPLICATIONS

Stéphanie Debette, M.D., Ph.D *Department of Neurology, Bordeaux University Hospital; Inserm U1219, Bordeaux Population Health, Dir. of team on vascular and neurological diseases: integrative and genetic epidemiology; Bordeaux University, Bordeaux, France*
Adjunct Assoc. Prof., Department of Neurology, Boston University School of Medicine, the Framingham Heart Study, Boston, USA

Fibromuscular dysplasia (FMD) affects primarily renal and cervico-cephalic (carotid and vertebral) arteries, with both sites being affected concomitantly in ~65% of patients in the US registry. Cervico-cephalic FMD is often asymptomatic, or can be associated with headache, pulsatile tinnitus, or carotid bruit. The main complications include cervical artery dissection (CeAD) and stroke (mostly but not exclusively caused by CeAD). Cervico-cephalic FMD has also been associated with a higher prevalence of intracranial aneurysms that can lead to subarachnoid haemorrhage. The frequency of CeAD is estimated at ~15-20% in FMD patients. Both FMD and CeAD mostly occur in apparently healthy individuals with few or no "traditional" vascular risk factors. Their underlying mechanisms and risk factors are still poorly understood, but there is converging evidence from epidemiological and genetic studies that FMD and CeAD share some common biological pathways. Both can occur in the setting of rare inherited connective tissue disorders, such as vascular Ehlers-Danlos syndrome. Recently the two first genome-wide association studies for CeAD and FMD (mostly renal) have led to the independent identification of an association with the same genetic polymorphism in the PHACTR1 gene. This provides further evidence for shared mechanisms at the molecular level between both conditions and warrants a more systematic exploration of shared genetic determinants. Recommendations on management of cervical FMD and its main complication, CeAD, are mainly based on empirical data.

CAROTID BULB DIAPHRAGM: IS THIS A VARIANT OF FIBROMUSCULAR DYSPLASIA? HOW SHOULD THIS ENTITY BE MANAGED?

Marion Boulanger, *Normandie University, UNICAEN, INSERM U1237, Caen, France*

Carotid bulb diaphragm, also known as "arterial web", was first described in 1967.[1] It corresponds to a linear filling defect usually on the posterolateral side of the carotid bulb, just beyond the carotid bifurcation, that does not change or disappear after modification of the
patient's head position.[2, 3] Although the presence of diaphragm was first described on conventional angiography, its identification has become more commonly reported on computed tomographic angiography (CTA) with the improvement in resolution of imaging.

Sensitivity of MR angiography (MRA) seems lower than those of CTA3 and performance of ultrasound might be insufficient in the absence of a stenosis.[4, 5] Other locations of cervical diaphragm have been described, especially in the vertebral artery (ostium and V3 segment).[3, 4]

Carotid bulb diaphragm and typical fibromuscular dysplasia share similar histological findings with intimal fibrosis or hyperplasia without atheromatous or inflammatory lesions.[4, 6, 7] Because pathophysiology, demographics characteristics and clinical presentation differ between typical fibromuscular dysplasia and carotid bulb diaphragm, this entity has been classified as a variant of fibromuscular dysplasia by some authors. Unlike cerebral ischemia in typical fibromuscular dysplasia that is mainly caused by hypoperfusion resulting from arterial stenosis, cerebral ischemia in carotid bulb diaphragm is estimated to be mediated by an embolic mechanism, because of stasis of blood flow at the site of the bulb.[2, 7] Regarding the clinical characteristics, the population with diaphragm is young (<55 years) adults, with no atherosclerotic risk factors and no signs of typical cervical/intracranial fibromuscular dysplasia lesions (such as cervical stenosis or dissection and intracranial aneurysm).[4]

Women tend to be overrepresented and almost all cases were described

in African or Afro-Caribbean population.[4, 8] The main clinical presentation is Transient Ischaemic Attack (TIA) or ischaemic stroke ipsilateral to the diaphragm and a strong association between carotid bulb diaphragm and ischaemic stroke has been reported in a population-based case-control study in the French West Indies.[9] In the presence of ischaemic stroke, bilateral diaphragms do not seem to be uncommon.[4, 8]

Description of patients with ischaemic stroke attributable to cervical (carotid or vertebral) diaphragm mainly comes from small cases series, with a total of approximately 50 cases reported in the literature, and the optimal management of these patients remains uncertain.

The rate of recurrent cerebral ischaemic events in the same territory seems particular high, even in patients on antiplatelet therapy,[2, 4, 8] reaching 30% at 1 year of follow-up in the largest study.[4] Other therapeutic alternatives include anticoagulant therapy,[7] surgical excision of the diaphragm and stenting. Long-term anticoagulant therapy might be effective since the mechanism is estimated to be artery-to-artery embolism.[7] However, this option is rarely opted for in clinical practice because of the patients 'young age. No recurrence has been reported after surgery in the largest cohort of 6 patients with a median follow-up of 14 months[4] and after stenting in the largest cohort of 16 patients with follow-up ranging from 3 to 12 months.[8]

Carotid diaphragm could be a common cause of carotid-territory TIA or ischaemic stroke in young Afro-Caribbeans adults. Further research is needed to determine the optimal treatment.

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DIGESTIVE FMD: FROM ASYMPTOMATIC DISORDER TO VASCULAR EMERGENCY

P. Van der Niepen, *Head of nephrology and hypertension department University Hospital Brussels - Belgium*

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, non-atherosclerotic and non-inflammatory disease of the musculature of arterial walls, leading to stenosis of small and medium-sized arteries, mostly involving renal and extracranial arteries. As a result of better and more systematic screening, it appears that involvement of the visceral vascular beds is more frequent than originally assumed. The prevalence of visceral FMD is estimated to be 15-20% (range: 9 – 50%).
The clinical picture is very diverse. FMD may be clinically silent and discovered incidentally, because patients are often asymptomatic due to the double hepatic and collateral blood flows. Patients may be symptomatic as well and can even die due to eg. a ruptured aneurysm or critical bowel ischemia and visceral gangrene. The classical triad including postprandial abdominal pain, weight loss and abdominal bruit, is the most common clinical presentation, indicating severe stenosis at the origin of visceral ischemia.

In visceral FMD, intimal fibroplasia is the most common histological variant, producing unifocal [a discrete area of a single] stenosis, especially in the mesenteric artery; multifocal stenosis [string of beads] is less frequent, but also occlusion, dissection, aneurysm and arterial tortuosity can be seen.

There are no specific guidelines for the diagnosis and treatment of visceral FMD, which is at least partly explained by the absence of randomized clinical trials. Most of the evidence derives from cohorts (French and US registries), case reports and expert opinions. In 2015, a European registry has been established (Persu 2016). Currently, it includes over 550 cases from 13 countries (A. Persu, personal communication). The gold standard

for diagnosis is conventional catheter-based angiography, and remains the first choice in symptomatic patients. CT- and MR-angiography are reliable screening examinations. However definitive diagnosis is challenging, as visceral FMD can closely mimic vasculitis as well as atherosclerosis. Screening for visceral FMD is advised in renal FMD and in case of aneurysms and/ or dissections in other, especially cervico-cephalic vascular beds, to prevent complications. Treatment depends on the clinical picture (symptomatology, type/localization and extent of the arterial involvement, the presence of aneurysms, prior vascular events, comorbid conditions and age of the patient) and may include optimal medical FU and/ or revascularization with PTAS with or without coil embolization, aneurysm clipping or reconstructive vascular surgery. However, the level of evidence is low and much of the common practice is extrapolated from visceral atherosclerotic disease.

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NEWLY DISCOVERED TARGETS OF FMD : FINDINGS OF ARCADIA-POL

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ARCADIA-POL study was instituted in January 2015 on the basis of Polish-French collaboration in the Institute of Cardiology , Warsaw , Poland to better understand the epidemiology , clinical characteristics , management and outcomes of patients with FMD . This report includes the first 280 patients who entered the multicenter registry involving 32 centers in Poland with coordination of Department of Hypertension . Each of these centers followed referral pattern and identified patients with newly diagnosed or established renal FMD , FMD in any vascular bed or with spontaneous artery dissection particularly in carotid , vertebral or coronary arteries. All patients underwent detailed clinical evaluation including ABPM, biochemical evaluation, biobanking, duplex Doppler of carotid . Along with the main goals , ARCADIA-POL is also focused on newly discovered targets which include evaluation of: 1) clinical characteristics, potential associated factor and incidence of FMD in patients with spontaneous cervical artery dissection (sCAD) . The causes of sCAD are poorly understood and very rarely may by associated with FMD . 2) blood pressure levels and profile - clinical evaluation based on office and ABPM allows to characterize hypertension , hypertension control and dipping / non-dipping pattern of BP particularly at night , which has been reported as a feature of patients with atherosclerotic RAS . 3) subclinical target organ damage in the heart, vessels and kidney . Available evidence on the association between renal FMD and cardiac changes (LV structure and function) , IMT of carotid arteries , parameters of intrarenal blood flow (RI) and albuminuria are scant . 4) retinal microperfusion and arterioral structure in patients with FMD and to compare with those of essential hypertension using scanning laser Doppler flowmetry (SLDF). The parameters of retinal morphology : outer diameter (AD), lumen diameter (LD), wall/lumen ratio (WLR), wall

thickness (WT), and wall cross-sectional area (WCSA) were determined by automatic full-field perfusion imaging analysis (AFFPIA V.4.011) 5) clinical characteristics of women with FMD including : detailed clinical , ultrasound gynecological and hormonal profile evaluations . 6) coronary arteries of all consequtive patients included to the ARCADIA-POL . Coronary CT will be performed with 3rd generation dual-source scanner, the prospective ECG triggering acquisition protocol were used. The arteries will be analysed according AHA coronary segments classification, with SyngoVia software.

FIBROMUSCULAR DYSPLASIA AND PERSONALITY IN WOMEN: THE DYSPERS CASE-CONTROL STUDY

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Psychological characteristics of patients with fibromuscular dysplasia (FMD) have never been studied. Based on the clinical impression of several specialized physicians, we aimed to test the hypothesis that patients with FMD will display high levels of histrionic traits and/or subthreshold manic symptoms. Our population consisted in 101 women with hypertension: 51 women with FMD (cases) were compared to 50 women with essential hypertension (controls) matched for age. Beside clinical and sociodemographic variables, psychological characteristics were assessed with the Personality Diagnostic Questionnaire - Version 4, the Hospital Anxiety and Depression Scale and the Mood Disorder Questionnaire.

Histrionic personality score was significantly higher in cases vs. controls [Odds-Ratio (95% Confidence Interval): 1.56 (1.13-2.15), p=0.007), as was anxiety score [1.16 (1.03-1.31); p=0.012). No difference was observed between the two groups regarding depression or manic symptoms. Smoking status and antihypertensive drugs use also differentiated cases from controls [5.13 (2.07-12.70); p<0.001 and 0.27 (0.09-0.80); p = 0.019, respectively). In a multivariable binary logistic regression including potential confounders, histrionic personality score still predicted belonging to the FMD group with the same effect size [1.56 (1.03-2.36); p = 0.034].

Our study confirmed the clinical intuition of physicians about the high levels of histrionic traits in women with hypertension secondary to FMD, compared to women with essential hypertension. Further studies are necessary to explore the pathways that may potentially explain this association.

GENETICS OF ARTERIAL DYSPLASIA

Santhi K. Ganesh, *Associate Professor Cardiovascular Medicine, Department of Internal Medicine Department of Human Genetics University of Michigan*

The University of Michigan Arterial Dysplasia Study continues to enroll subjects. We are using a number of complementary genetic approaches to study FMD. Our most recent efforts focus on the identification of rare variants underlying FMD in sporadic and familial cases of FMD, and we are additional undertaking larger scale studies to identify further common variants. Our studies include case control approaches, analyses aimed at quantifying familial risk and the role of specific genetic variants. We are pleased to participate in several successful collaborations on our studies as well as corollary studies led by collaborators. We have previously proposed a consortium approach and will review enabling technologies to facilitate collaborations. We are grateful to the Doris Duke Charitable Foundation, National Institutes of Health and the Frankel Cardiovascular Center at the University of Michigan for funding grants to support this work.

PHACTR1 AND OTHER RECENTLY IDENTIFIED SUSCEPTIBILITY GENES

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Fibromuscular Dysplasia (FMD) is a neglected vascular disease with severe health consequences. The genetic investigation of FMD has been challenging despite evidence for the existence of a genetic basis supported by declared and assessed intra-familial recurrence. Our recent identification of a common genetic locus that increases the risk of FMD by 40% provides first evidence for the existence of a complex genetic pattern on inheritance for FMD. Moreover, this finding connects for the first time FMD to other neurovascular and cardiovascular diseases providing new avenues to the physiopathology of arterial stenosis that characterizes FMD. Here I will provide arguments in favor of the existence of a large number of genetic determinants for FMD, describe our first genome-wide association study involving the PHACTR1 locus in FMD and more recently in SCAD, in addition to an overview of recently published functional genomics work on this locus linking the genetic variants with putative regulators of the Endothelin gene. I will also and our scientific approach that aims to decipher the genetic basis of this genetically and clinically intriguing vascular disease.

GENETIC AND ACQUIRED CAUSES OF VASCULAR TORTUOSITY

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Arterial tortuosity can be simply defined as the property of the artery having many turns and appears as twisting and winding of the arteries on imaging studies. More recently attempts to quantify the arterial tortuosity have defined an arterial tortuosity index. This arterial tortuosity is the consequence of an abnormal gradual lengthening of the arteries in a fixed space, leading to forced curving of the arteries. Several hypotheses, involving maladaptation to axial tension or increased TGFbeta signaling have been put forward as possible etiologies, but the exact cause remains elusive.

Historically, studies have focused on the role of aging, hypertension and atherosclerosis but more recently more attention is given to arterial tortuosity in connective tissue disorders such as cutis laxa, arterial tortuosity syndrome, Marfan syndrome and Loeys-Dietz syndrome. But also other genetic conditions such as Menkes/occipital horn syndrome, Turner syndrome, filaminopathies and non-syndromic forms of thoracic aortic aneurysm and dissection have been associated with increased incidence of arterial tortuosity. Recent papers have also suggested increased arterial tortuosity as a prognostic marker for the risk of arterial and aortic dissection. Whether the degree of tortuosity will ultimately become a helpful component of the medical or surgical decision making will rely on better standardization of tortuosity quantification and studies in larger cohorts.

WHAT CAN WE LEARN ABOUT FIBROMUSCULAR DYSPLASIA FROM HEREDITARY VASCULOPATHIES?

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We have recruited families with multiple affected members with vascular diseases to identify mutated genes that confer a high risk for vascular diseases. Using families with multiple members with thoracic aortic aneurysms, leading to acute aortic dissections, we identified *ACTA2* mutations as a cause of both thoracic aortic disease and occlusive lesions in large and medium sized arteries, including moyamoya disease (MMD)-like cerebrovascular disease[1]. *ACTA2* encodes the smooth muscle cell (SMC)-specific isoform of actin, SMC α-actin, the major protein in vascular SMCs. Arterial lesions in patients with *ACTA2* mutations are characterized by thickening of the medial layer, neointimal proliferation of cells that stain for SMC markers, and absence of pathologic features typical of atherosclerotic disease, such as cholesterol deposition and inflammation[2]. Supporting these pathologic findings, SMCs from both affected patients and *ACTA2* mutant mice proliferate and migrate more rapidly than control cells. More recently, we and others have identified additional novel genes for MMD, including *RNF213*, *GUCY1A3* and *SETD5*, which implicate nitric oxide synthesis and chromatin remodeling in cerebrovascular disease. Finally, we identified recessive loss-of-function mutations in YY1AP1 in patients with Grange syndrome[3], characterized by early-onset and widespread occlusive arterial disease of the renal, vertebral, internal carotid, mesenteric and coronary arteries with angiographic appearance similar to FMD. We determined that YY1AP1 localizes to the nucleus and is a component of the INO80 chromatin remodeling complex responsible for transcriptional regulation, DNA repair, and replication. Additionally, molecular studies revealed that loss of YY1AP1 in vascular SMCs leads to cell cycle arrest and disrupts TGF–α

ß driven differentiation of SMCs. In summary, the genes identified to date for hereditary occlusive/stenotic vasculopathies provide insights as to what molecular pathways are altered and predispose to these diseases.

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TRIPLE SIGNAL IN FIBROMUSCULAR DYSPLASIA: AN INTRIGUING PHENOTYPE

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Fibromuscular dysplasia is a non-atherosclerotic, non-inflammatory disease affecting medium size arteries. FMD has long being considered as a focal disease with predilection sites such as renal arteries and cervical vessels. FMD is most of the time paucisymptomatic, however, when symptoms occur they are linked to the occurrence of stenosis and subsequent organ ischemia. Although familial cases were described, few evidences were available for FMD being a systemic disease. After studying large groups of patients using high definition echotracking devices, we could demonstrate that the echostructure of large and medium size artery was not normal in FMD, compared to matched controls. Indeed, the normal echostructure corresponds to a double line, the first line representing the blood-intima interface and the second (denser) line corresponding to the media-adventitia interface. In a significant part of FMD patients, we could find additional lines (usual 3 lines total) which we called triple signal. In a careful study of cases and controls, after blinding the reading of ultrasound scans, we could demonstate that triple signal was 7 time more frequent in FMD than in controls (Boutouyrie 2003). Following this seminal study, we could show that this trait had a family transmission compatible with autosomal dominant (Perdu 2007). Since then, this observation has been confirmed in independent cohorts and in our center in different patients sets. However, we could also observe triple signals in some normal controls and some essential hypertensives. This triple signal occurred more frequently in older subjects with obesity, showing that triple signal is not specific for FMD or at least that this is a continuous trait more frequently observed in FMD. The anatomical correlates of triple signal is not yet known. In vitro studies show that triple signal is observed in muscular arteries rather than in elastic arteries (Sarkola 2013). The additional signal must correspond to additional

acoustic interfaces, which may correspond to focal points of sclerosis within the media. Functional correlates have been recently studied in our group. Patients with triple signal have thicker, stiffer arteries, and altered endothelial function. The utilization of triple signal for diagnosis might evolve since higher definition ultrasound scanners are available, which allow better definition images and confirm the triple signal pattern on smaller vessels. Its use is still hampered by the subjective nature of the pattern, which rendered difficult the generalization of its use.

ULTRA-HIGH FREQUENCY ULTRASOUND FOR VASCULAR PHENOTYPING IN FMD

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Increasing evidence from large registries point out that FMD is a systemic disease, with a very high prevalence of multiple districts involvement. The consolidation of this knowledge opens new perspectives for the FMD clinical work-up, thorugh the exploration of easily accessible, but usually not affected arterial districts. Indeed, the study of non-affected and easily accessible medium and small-sized arteries, such as the radial artery, with similar diameter and histology of affected arteries such as the renal, cerebral and coronary arteries, might be informative in FMD. This approach has been recently made possible by the commercial availability of ultra-high frequency ultrasound for human use. The machine is equipped with transducers up to 70 MHz and allows imaging superficial tissues with a spatial resolution up to 30 μm (axial) and 65 μm (lateral). Preliminary results obtained by using ultrahigh frequency ultrasound, confirmed an increased radial wall thickness in FMD patients in comparison to age-, sex- and BP-matched controls. Most strikingly, wall ultrastructure was extensively subverted in FMD patients: the echogenic layers identified in normal radial arteries presented a lower echogenicity and a greater inhomogeneity as compared to healthy individuals. Interestingly, similar alterations were found in SCAD patients. It is important to underline that these preliminary results need to be replicated in larger, independent cohorts. Furthermore, the anatomical correlates of radial artery disarray in FMD need to be fully clarified. Though considering these limitations, the technique is promising and has several advantages, including easiness of use and non-invasiveness.

CIRCULATING MICROVESICLES (C-MVS) LEVELS IN PATIENTS WITH MULTIFOCAL FIBROMUSCULAR DYSPLASIA (FMD): A CROSS-SECTIONAL STUDY

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FMD is an idiopathic, segmental, non-atherosclerotic non-inflammatory arterial disease of unknown origin which occurs mostly in middle-aged women and affects medium-sized arteries (renal and carotid arteries in particular). The objective of the study was to identify new biological biomarkers of the pathology. We investigated c-MVs from different vascular cell origins.

We conducted a cross sectional study with 50 patients with multifocal FMD, 50 essential hypertensive (EH) patients matched for age, sex, ethnicity and BP and 50 healthy subjects (HS) matched for age, sex and ethnicity. Exclusion criteria were: tobacco consumption, hypercholesterolemia, diabetes, aspirin or statin treatment. We measured endothelial and smooth-cell derived MVs plasma concentrations by flow cytometry analysis of human platelet free plasma blind to the phenotype.

Results: FMD, EH and HS were well matched. FMD and EH had significantly higher SBP than HS despite antihypertensive treatments. Circulating levels of total MVs (annexinV+MVs), endothelial MVs (CD144+MVs, CD62E+MVs and CD31+CD41-MVs), CD11a+MVs and smooth muscle derived MVs (SMA (smooth muscle actin)+MVs) displayed large between-subject variability within each group and did not significantly differ between groups.

In conclusion, we could not identify specific changes in c-MVs levels of endothelial or smooth muscle origin in patients with FMD when compared with age-, sex-, and ethnicity-matched patients with EH or HS.

	FMD	EH	HS
Age, yrs	52±9	52±9	52±9
Women, n (%)	43 (86%)	43 (86%)	42 (84%)
Caucasian, n (%)	38 (76%)	38 (76%)	42 (84%)
Office SBP, mmHg	125±15***	121±12***	113±10
Antihypertensive drugs, n (range)	2 (1-4)	2 (1-4)	0
Annexin V+ MVs (number/μL)	2875 (1441; 4589)	3135 (2098; 4823)	2399 (1543; 3904)
CD11a+ MVs (number/μL)	0 (0; 64)	14 (0; 36)	4 (0; 36)
CD144+ MVs (number/μL)	23 (0; 65)	17 (6; 43)	14 (0; 61)
CD41+ MVs (number/μL)	1417 (668; 3082)	1591 (588; 2460)	1370 (596; 3301)
CD41-CD31+ MVs (number/μL)	102 (18; 251)	104 (31; 234)	97 (21; 207)
CD62e+ MVs (number/μL)	0 (0; 48)	0 (0; 30)	0 (0; 37)
SMA+ MVs (number/μL)	19 (16; 54)	19 (16; 57)	39 (18; 65)

Data are mean±SD or median(IQR). *** P<0.001 vs. HS

WHAT CAN WE LEARN FROM THE FIBROBLAST? THE DEFINE STUDY

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The DEFINE-FMD study is aiming to use disease-relevant samples from FMD patients and matched healthy control subjects to DEFINE the molecular and cellular basis of FMD. As suggested by the name **Fibro**muscular Dysplasia, it is likely that **fibro**blast cells play an important role in this disease. In the DEFINE-FMD study, we are collecting DNA, plasma, serum, fibroblast cells (via skin punch biopsy) and culture supernatant from rigorously phenotyped FMD patients with multifocal disease and healthy controls. Healthy controls are also carefully screened, and are matched to FMD patients by gender, race/ethnicity, age, smoking status, body mass index and number of anti-hypertensive medications. All fibroblasts are grown from skin biopsy samples under standardized conditions by a single person, and fibroblast RNA is then harvested for high-throughput transcriptomic analysis using RNA sequencing. As of January 2018, 320 subjects have been enrolled and recruitment is ongoing.

As a pilot study and to prove proof-of-concept, we processed DNA and fibroblast RNA from the first 104 subjects (57 FMD patients and 47 controls). From this analysis we identified 274 genes with different expression levels in fibroblasts from FMD patients versus controls. A systems-based bioinformatics approach was then applied to construct Bayesian gene regulatory networks. We are now engaged in detailed investigations of these gene networks, and their potential role in FMD.

DIAGNOSIS OF FMD OF RENAL ARTERIES, THE CASE FOR CTA

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We evaluated computed tomography angiography (CTA) with submillimetric slices versus digital subtraction angiography (DSA) for the diagnosis and the evaluation of stenosis of renal arteries in patients with FMD. From the prospective multicentric register (ARCADIA), 43 FMD patients, who underwent CTA and DSA within 6 months, without renal artery angioplasty in between, were included. For each artery, the positive diagnosis, the angiographic subtype and the stenosis severity were blindly and independently analysed. We found FMD lesions in 55 out of 95 renal arteries, 44 multifocal and 11 unifocal subtype. Se and Spe of CTA for the diagnosis of FMD were respectively 87-93% and 90-98% with an excellent reproducibility.

For significant stenosis >50%, PNV was 93-97% with better Se for the expert reader 92% vs 76%.

CTA with submillimetric slices have a good accuracy to diagnose and to identify significant renal arteries stenosis.

Prof. dr. Tine De Backer, MD, PhD, *Cardiovascular Center Heymans Institute of Clinical Pharmacology University Hospital Ghent*

Medical therapy and clinical surveillance is one of the main options in the treatment of FMD.
Pharmacological management of FMD is mainly based on expert opinion and consensus given the lack of randomized controlled trials in FMD patients and given the shortage in knowledge of the real underlying pathophysiology and natural history of the disease.

Cardiovascular risk control

Although FMD is a noninflammatory, nonatherosclerotic vascular disease, cardiovascular risk control is advised in order to prevent potential other vascular disease, especially atherosclerotic disease. Smoking cessation and healthy physical exercise are main recommendations. Statin therapy is debatable. Antihypertensive treatment and prevention of thrombosis are proven effective interventions overall and should be applied in FMD patients when considered appropriate.

Antihypertensive treatment

Hypertension is a considerable risk factor in stroke and cardiovascular events overall. FMD-induced hypertension is partially mediated by the renin-angiotensin-aldosterone system. All classes of antihypertensives can be considered, although RAAS blockers (ACE-Inhibitors and angiotensin receptor blockers) might be favored. Angioplasty or surgery of the renal artery with FMD should only be considered when strictly indicated.

Antithrombotic treatment: Antiplatelet and anticoagulant treatment

Following the guidelines antiplatelet and /or anticoagulant therapy is recommended in all symptomatic peripheral vascular diseases for the reduction of cardiovascular events. Again in FMD patients there is no proven evidence due to a lack of RCTs. Still, antiplatelet therapy, aspirin 75-325 mg/d or clopidogrel 75 mg/d (in case of aspirin intolerance), should be considered in FMD patients with cerebrovascular, renal, mesenteric or peripheral arterial disease of the lower limbs. In case of the presence of dissection and or thrombus, anticoagulant therapy with heparin and warfarin should be considered. The use of non-vitamin K or direct oral anticoagulants (NOACS/DOACs) in this setting is not established yet. After angioplasty with or without stenting the same treatment is applied as in patients with atherosclerotic disease.

Till now a curative therapy of vascular disease due to FMD does not exist.

RENIN-ANGIOTENSIN SYSTEM ACTIVITY AND RENAL HEMODYNAMICS IN MULTIFOCAL FIBROMUSCULAR DYSPLASIA

dr. D.J.L. van Twist, *internist – vascular medicine specialist, Zuyderland Medical Centre, Sittard/Heerlen, The Netherlands.*

Fibromuscular dysplasia (FMD) is the second most common cause of renovascular hypertension. Nonetheless, knowledge on the renal microvasculature, renin-angiotensin system (RAS) activity, and mechanisms leading to hypertension in kidneys with FMD is scarce. As the blood-pressure lowering effect of revascularization in renal artery FMD appears to fairly good [especially as compared to that in atherosclerotic renal artery stenosis (ARAS)], we hypothesized that renal microvasculature and intrarenal RAS are relatively spared in kidneys with FMD. Furthermore, we questioned whether the commonly held hypothesis that FMD causes hypertension via similar mechanisms as ARAS is true.

Therefore, we measured renal blood flow (133Xenon washout method), glomerular filtration rate, and renin secretion per kidney in a cohort of patients with multifocal FMD (off medication, prior to revascularization). We compared them to matched controls with essential hypertension and to a cohort of patients with ARAS. In a subgroup, we also measured changes in renal blood flow in response to intrarenal infusion of several vasoactive agents. This led to several interesting insights:

First, intrarenal microvasculature appears to be relatively preserved in kidneys with multifocal FMD. In FMD, renal blood flow is significantly higher as compared to that in ARAS and comparable to that in matched controls. Moreover, in patients with unilateral FMD, renal blood flow, and glomerular filtration rate are comparable between the affected and unaffected kidney, suggesting that the presence of a string-of-beads does not seriously affect local renal perfusion. We also found that the hemodynamic response to infusion of vasoactive agents in FMD is comparable to that in controls and substantially higher than in ARAS. These findings indicate that, in contrast to ARAS, microvascular and endothelial function is more or less intact in kidneys with FMD.

Second, intrarenal renin-angiotensin system (RAS) activity is relatively normal in kidneys with FMD. We found that systemic renin levels and renin secretion in FMD were comparable to that in matched controls. Moreover, in patients with unilateral FMD, no differences in renin-secretion were observed between the affected and unaffected kidney, this in contrast to ARAS. In addition, the response to RAS-modulation (by infusion of several RAS-components) intact and comparable to that in controls.

Third, several findings argue against the prevailing concept that FMD causes hypertension via similar mechanisms as ARAS, i.e. due to a decrease in renal blood flow, resulting in increased renin secretion, which on its turn increases blood pressure. As discussed above, renal perfusion is not reduced and renin secretion is not increased in FMD. Furthermore, the relation between renin levels and blood pressure in FMD (the higher the blood pressure, the lower the renin levels) is inverse to that in ARAS.

In conclusion, intrarenal microvascular function is more or less intact in kidneys with multifocal FMD. Renin secretion is not increased and intrarenal RAS activity is not disturbed. Furthermore, it appears that the prevailing concept that FMD induces hypertension due to reduced renal perfusion and subsequently increased renin secretion needs revision.

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Renal Artery Stenosis: Fibromuscular dysplasia (FMD) frequently affects the renal arteries (RA). Multifocal disease is most common with unilateral involvement in 68% and bilateral involvement in 32%. The secondary RA branches can also be involved along with the main RA. Hypertension that is poorly controlled with medication, or loss in kidney mass with serial evaluation are the usual indications to intervene since azotemia is uncommonly seen in RA-FMD.

Duplex ultrasound is used to screen for stenotic disease followed by CTA or MRI. Angiography is reserved for symptomatic patients. At the time of selective renal arteriography the hemodynamic significance of the disease should be established. Balloon angioplasty (PTA) is used to resolve the pressure gradient and stenting is reserved for complications associated with stand-alone PTA. The resolution of the translesional gradient is also the best endpoint of intervention rather than the angiographic appearance.

The literature includes about ~1600 patients who have undergone RA-FMD PTA. Cure of hypertension with PTA has ranged widely from 5-64% with Improvement in 5-76% and failure to respond in 0-79%. Complications are infrequent and usually minor.

Renal artery aneurysms (RAA): RAA do occur and have been seen in the main RA, secondary and parenchymal branches. Asymptomatic RAA of > 2 cm should be treated particularly in younger patients. Any symptomatic aneurysm or pseudoaneurysm should be treated. Occluded aneurysms do not require intervention. Both endovascular and surgical techniques should be considered in the treatment decision. The best technique minimizes risk,

excludes the aneurysm without sacrificing significant renal parenchyma. Endovascular treatment is very effective for RAA in the main RA and is considered low risk. Intermediate risk is estimated in small segmental or intralobar arteries and high risk are RAA at the renal artery bifurcation.

Intravascular ultrasound provides accurate detail to facilitate the sizing of aneurysms for covered stents. Excellent quality imaging is necessary. In general, covered stents are used in main RA and parenchymal RAAs; coil embolization for narrow-necked saccular aneurysms and stent-assisted coil embolization for wide-necked aneurysms. Pseudoaneurysms should not be treated with coil embolization.

Conclusion: The workup of RA FMD involves multiple modalities. When therapeutically necessary to treat RA FMD then first establish the hemodynamic significance, normalize this with PTA and avoid stenting. Consider bypass for small arteries or recurrent disease. RAA can be treated with endovascular techniques, but always consider the surgical option.

PAEDIATRIC FMD AND MID-AORTIC SYNDROME

Kjell Tullus, *Consultant Paediatric Nephrologist - Nephrology Unit- Great Ormond Street Hospital For Children - London - England*

FMD is the commonest cause (80%) of renovascular hypertension (RVH) and mid-aortic syndrome in children. RVH causes 10% of secondary hypertension in childhood. About 50% of all hypertension in children has a defined cause.

Children with FMD present mainly with very high blood pressure, often 200 mmHg systolic. Many have severe cerebral or cardiac symptoms but 35% of the children are asymptomatic and discovered during a routine investigation. Disease onset varies between a few weeks of age to the teenage years. Children with FMD in their renal arteries have in 24% mid-aortic syndrome, in 30% mesenteric artery disease and in 21% cerebrovascular problems.

Takaysu Arteritis is an important differential diagnosis in these children and the diagnosis made in children with severe hypertension varies markedly around the world perhaps not only due to medical findings but also diagnostic traditions.

The diagnosis is made on digital subtraction angiography. CTA and MRA are not sensitive enough to detect more than 75-80% of cases while doppler US finds only 50-60%.

Medical treatment is virtually never enough in hypertension due to FMD and angioplasty is the method of choice. Surgery has an important place in selected cases.

OPTIMAL MANAGEMENT OF SCAD:

Fernando Alfonso, MD, PhD FESC *Hospital Universitario de la Princesa. Madrid. Spain*

Spontaneous coronary artery dissection (SCAD) is a rare clinical entity of unknown etiology. From a pathophysiological perspective SCAD occur either in patients with an intimal tear (the classic angiographic "flap" with 2 lumens) or in patients without intimal rupture (intramural hematoma). Intracoronary diagnostic techniques (intravascular ultrasound and optical coherence tomography) complement coronary angiography and provide unique diagnostic insights on this elusive entity. Growing evidence suggest an association between SCAD and fibromuscular dysplasia in non-coronary territories. Until very recently information on SCAD management was based exclusively on multiple small case-series. In the last decade, however, data from large registries have cast new light on this challenging disease. Although SCAD was classically thought to occur in young females without risk factors recent reports suggest a broader clinical spectrum encompassing older patients with risk factors. Early angiography complemented with intracoronary imaging when indicated is required for diagnosis. Revascularization, however, should be restricted only to patients with ongoing or refractory ischemia. In these selected cases coronary stenting should be considered as the first option whereas coronary surgery should be offered to unstable patients with left main or severe multivessel disease. Patients should be monitored in a coronary care unit in the acute phase following a conservative approach (watchful waiting strategy). Medical therapy remains largely empirical. In most cases dual antiplatelet therapy should be considered. Novel potent antiplatelets are usually not indicated and IIbIIIa inhibitors or fibrinolysis appeared contraindicated. Betablockers are usually indicated. Conservative medical management should be offered to most patients following clinical stabilization as vessel healing leading to vascular restoration is expected to occur spontaneously in most cases during clinical follow-up.

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Non-atherosclerotic spontaneous coronary artery dissection (SCAD) is now known to be a far less "rare" etiology of myocardial infarction than previously appreciated; its demographics and pathophysiology are better understood and its association with fibromuscular dysplasia (FMD) has been confirmed by many investigators and clinicians. Patient-initiated research, improved diagnostic definitions and tools, and a growing awareness among healthcare providers have also propelled our understanding of SCAD. Crucial differences in pathophysiology, response to treatment, and clinical outcomes between SCAD and atherosclerotic disease have been described and inform current practice. To provide a synthesis of what is known about SCAD, The American Heart Association commissioned a Scientific Statement entitled *Spontaneous Coronary Artery Dissection: Current State of the Science*. The statement, authored by an international multidisciplinary expert writing group provides a consensus among cardiologists, and specialists in vascular medicine, genetics, obstetrics and gynecology, and psychology. This presentation will provide an overview of the AHA Statement, especially as it relates to the association between SCAD and FMD as well as highlight gaps in our knowledge and future research opportunities.

Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, Ganesh SK, Gulati R, Lindsay ME, Mieres JH, Naderi S, Shah S, Thaler DE, Tweet MS, Wood MJ. **Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement from the American Heart Association.** Circulation, 2018 *(in press)*

David Adlam, *Chair ESC-ACCA SCAD Study Group - Associate Professor of Acute and Interventional Cardiology - Honorary Consultant Interventional Cardiologist - University of Leicester UK*

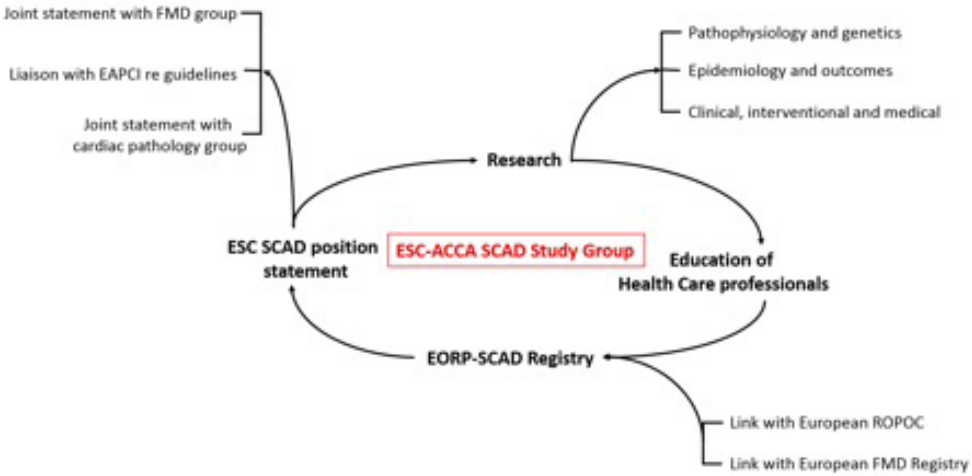
To date Spontaneous Coronary Artery Dissection (SCAD) research in Europe has been limited to a number of national registries, small clinical studies and case series. Despite recent progress, understanding the pathophysiology and optimal management of SCAD remains limited. As a result SCAD represents a substantial area of unmet clinical need. Globally there is a strong recognition that the next stage of SCAD research requires a larger international series with earlier (prospective) recruitment.

There is therefore an urgent necessity to coordinate research internationally to enable larger numbers of patients to be studied. This will advance our knowledge of the epidemiology, pathophysiology and clinical management of SCAD. With this aim we have established the SCAD Study Group within the Acute Cardiovascular Care Association of the ESC (ACCA). Support from: the European Association for Percutaneous Coronary Interventions; the European Fibromusclular Dysplasia (FMD) Group; the European Association of Cardiovascular Pathology and our SCAD-survivor groups at EURORDIS and BeatSCAD is especially welcome. The aims of the Study Group are:

- To establish a collaborative partnership to advance research into SCAD
- To maintain a European registry of SCAD patients to advance understanding of epidemiology and variations in patient management and outcomes
- To coordinate and support clinical and pre-clinical research into SCAD
- To formulate and disseminate a European consensus on the diagnosis and management of SCAD
- To improve accurate diagnosis by raising awareness of SCAD
- To support patients with this condition

The Study Group welcomes any interested clinicians to make contact and hope by working together we can make an important contribution to better understanding SCAD and improving our care and support for SCAD-survivors.

Figure: ESC-ACCA SCAD Study group and affiliated groups



Heather Gornik[1], Alexandre Persu[2], *[1]Department of Cardiovascular Medicine, Cleveland Clinic Heart and Vascular Institute, Cleveland, Ohio, United States; [2]Division of Cardiology, Cliniques Universitaires Saint-Luc and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium*

In 2014, expert panels from Europe (Persu et al., *J Hypertens* 2014;32:1367-78) and the United States (Olin, Gornik et al., Circulation. 2014;129:1048-78) independently published consensus statements devoted to the diagnosis and management of Fibromuscular Dysplasia (FMD). These documents have contributed to raise awareness about FMD, improve screening and harmonize management of the disease. However, in view of recent advances in the understanding of the disease ("systemic" character, links with SCAD...), also including identification of the first genetic susceptibility locus and novel biomarkers, both documents have become partly obsolete and therefore need updating. Furthermore, while these statements have much in common, the approaches proposed on both sides of the Atlantic differ slightly in terms of classification, preferred imaging modalities for screening and follow-up, and medical management.

Building upon the prior European and US documents, a writing committee was commissioned by the Working Group "Hypertension and the Kidney" of the European Society of Hypertension (ESH) and the Society for Vascular Medicine (SVM) to update recommendations and reach consensus where needed, in order to create a single, up-to-date expert consensus document on FMD. Writing committee members were selected by each society based upon extensive experience in the care of patients with FMD and/or research contributions to the field, including participation in international FMD Registries. Besides European and US specialists, the panel includes a number of experts from other regions of the world and representatives of patient advocacy groups. Consensus has now been reached on all critical points and the manuscript is expected to be finalized in March. The presentation will summarize the main consensus points and a few other highlights of this new consensus.

Pamela Mace, RN, *Executive Director, FMDSA ROCKY RIVER - OHIO - USA*

FMDSA was founded in March of 2003 and is classified as a tax-exempt organization under the United States Internal Revenue Code Section 501(c)(3) as a "public charity". In 2003, Fibromuscular Dysplasia was considered a very rare disease and was (and remains) poorly understood. As a result, our initial goal was to provide a place where patients would have access to the limited information that was available and to validate our disease within the medical community. In addition, FMDSA set out to raise awareness and create a physician education program.

15 years later, FMDSA is well established as the most extensive FMD patient resource in the world. We have seen the diagnosis rate and medical knowledge of the disease grow in direct proportion to the growth of our programs, patient registry and other activities. Our website includes patient information, resources and educational content. We also have an established Research Network Page where research publications can be found making them easily accessible to the medical and patient community.

Some of the more impactful programs that lead to our success included the development and funding of the United States Registry for Fibromuscular Dysplasia, our annual patient conference, and our public awareness and physician education programs. We never expected that so many patients would be diagnosed with the disease but as each program progressed we saw a dramatic increase in newly diagnosed patients contacting us.Patient support is one of the most requested services that we offer.

Identified early on, was the lack of resources for our international patients which prompted us to engage patient volunteers to assist with newly diagnosed patients within their countries. Initially, most request that we received were from patients in Canada and Australia. Starting with those volunteers we

worked together to try to identify physicians knowledgeable of the disease or ones that were willing to assist us. We recruited more volunteers and established our Network Group Leader program, by doing so we have been able to assist with and engage many resources all over the world, giving us and them the ability to help patients on a global level. As more and more patients are being diagnosed with FMD there is a greater demand and need for patient resources and associations.

Several of our colleagues have since succeeded in establishing local groups or organizations but they struggle as we did to identify resources, funding and volunteers to assist with their endeavors. We are all committed to working together and together we have worked to identify our patient's unmet needs and resources to address these needs.

Cathlin Jamison, *(FMD-Be) on behalf of* ***Véronique Godin*** *(FMD-Be) and* **Madelon Bouwmeester** *(FMDGroepNL)*
Cathlin Jamison, *Member Of Fmd-Be - Belgium*
Madelon Bouwmeester, *President Of The Fmdgroep Nederland–The Netherlands*

We will present the existing European patient network, and the steps being taken to help expand and improve access for patients across Europe.

Europe now has two established national FMD patient associations, and four International FMDSA volunteers in Europe. There is also a Fibromuscular Dysplasia community on rareconnect, an online forum for rare disease patients hosted by EURODIS (Rare Diseases Europe)

FMDGroepNL (*www.fmdgroep.nl*) established in 2014 by two patients who contacted each other via social media, and then found support from an FMD experienced physician in the Netherlands. The need for better FMD awareness in the Netherlands, and for Dutch patients to be included in the European registry research was a major motivator for the formation of the association. FMDGroepNL became a non-profit organisation (ANBI) in 2017 and hosted an FMD/SCAD patient information day in Nijmegen in November 2017, with an attendance of over 60 patients and family members.

FMD-Be (*www.fmd-be.be*) formed in 2016, in Belgium, three patients backed by a scientific committee, to provide valid and up to date information in French, Dutch and English initially for Belgian/Belgian based patients, as well as a support network for those being diagnosed or living with FMD. The Facebook group now has members from outside of Belgium, from the UK, France, Switzerland, Canada and Germany. This highlights that for many European patients there is a lack of support/ information in their own countries, and shows the need for a more extensive European patient network.

FMDSA International volunteers in Europe (*www.fmdsa.org*)
There are currently volunteer contacts for the UK, Belgium, the Netherlands, and Switzerland, with contact details listed on the FMDSA website (http://www.fmdsa.org/patient_support/support_groups)

rareconnect.org (*http://www.rareconnect.org/en/community/fibromuscular-dysplasia*)
The FMD community on rareconnect.org attracts contact from patients internationally.

These groups and volunteers are working closely together, and in conjunction with the FMDSA to support patients, and provide information in several languages. We are continually working to expand our visibility both via other relevant patient associations (e.g. SCAD groups, rare disease associations Eurodis.org etc.) other online forums and also through FMD specialists. We are also working with the European FMD Initiative and Registry members with the aim of supporting patient participation in ongoing research.

Véronique Godin, *(FMD-Be) Responsible For The Medical Education Department - Université Catholique De Louvain –Brussels - Belgium and* **Cathlin Jamison** *(FMD-Be) Member Of Fmd-Be - Belgium*

In March 2016 three FMD patients met to discuss the idea of starting a Belgian patient association.
Patient orientated Fibromuscular Dysplasia information was available in English (through the FMDSA *www.fmdsa.org*) or in Dutch (from FMDGroepNL *www.fmdgroep.nl*) but nothing existed for French speakers.
It was decided that one of the main objectives of the group would be to provide up to date and validated information concerning FMD in French, and also in Dutch and English.
The idea of creating a website was discussed, along with a Facebook group to provide a space for discussion and support.
In Dec 2016 at the second Belgian FMD symposium FMD-Be was launched.
Just over a year later the Facebook group has grown to over 50 members, including members from outside of Belgium. The website has to date had over 35,000 hits.
We are continually updating and adding information to the site, posting articles and links, along with other relevant information through the website (*www.fmd-be.be*) or via the Facebook group (FMD.Be.Patients)
We work in close contact with the FMDSA and FMDGroepNL and, following in their footsteps, this first FMD-Be patient meeting will be not only an opportunity for patients to hear from prominent FMD specialists, but also a chance to meet others affected by FMD.

FIBROMUSCULAR DYSPLASIA: AN OVERVIEW

P. Van der Niepen, *Head of nephrology and hypertension department University Hospital Brussels - Belgium*

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, non-atherosclerotic and non-inflammatory disease of the musculature of arterial walls, leading to stenosis of small and medium-sized arteries. FMD has become a "systemic" vascular disease affecting renal, cervico-cephalic, visceral, lower and upper limb and even coronary arteries. Multi-vascular FMD (≥2 vascular beds) is found in >30% of cases. The prevalence of FMD in the general population is probably around 4%. Besides female sex and repeated mechanical trauma (increased mobility of kidneys or neck arteries), a genetic susceptibility, as well as a contribution of smoking in the progression of the disease is suggested. The diagnosis of FMD can be made by using noninvasive imaging studies, including duplex ultrasonography, and angiography by computed tomography or magnetic resonance. However, the gold standard remains catheter-based angiography.

Renal FMD may lead to hypertension. Less frequently, flank pain may be a manifestation of renal artery dissection, renal infarction, and aneurysm rupture. Renal insufficiency is uncommon and progression to end-stage renal disease is very rare. The treatment of patients with renal FMD may include medical therapy (blood pressure lowering drugs) with surveillance, endovascular therapy (angioplasty without stenting in association with antiplatelet or antithrombotic drugs), or surgery. The decision depends on the nature and location of vascular lesions (stenosis/dissection/aneurysm), the presence and severity of symptoms, prior vascular events related to FMD, and comorbid conditions.

Cervico-cephalic FMD can result in ischemic or hemorrhagic stroke, cervical artery dissection, and may be associated with intracerebral aneurysms and risk of subarachnoid bleeding. Though interventional treatment is seldom required, detection of cervical FMD has implications for the patients as it may help to improve primary and secondary prevention of cerebrovascular events

and lead to the diagnosis of FMD of other vascular beds. Diagnosis of cervico-cephalic FMD is often incidental, or following screening in patients with renal FMD. Symptoms are often aspecific, e.g. pulsatile tinnitus, headache. In most cases, treatment of cervico-cephalic FMD is conservative (antithrombotic drugs and control of cardiovascular risk factors (especially smoking). Severe stenotic cervical FMD lesions with ischemic or hemodynamic manifestations (pulsatile tinnitus) may require angioplasty. FMD-related aneurysms may be treated endovascular or surgical.

Visceral FMD may be clinically silent and discovered incidentally as well. Symptoms can be due to eg. a ruptured aneurysm or critical bowel ischemia. The classical triad including postprandial abdominal pain, weight loss and abdominal bruit, is the most common clinical presentation, indicating a severe arterial stenosis. Treatment depends on the clinical picture and may include optimal medical FU and/ or endovascular or surgical revascularization.

Typical FMD lesions of the coronary arteries appear to be exceptional, but there is probably a link between FMD and spontaneous coronary artery dissection. The latter causes an acute coronary event (cardiac infarction or arrest) especially in young or middle-aged women with no or few cardiovascular risk factors.

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THE BELGIAN AND EUROPEAN FIBROMUSCULAR DYSPLASIA INITIATIVES

Alexandre Persu, *Division of Cardiology, Cliniques Universitaires Saint-Luc and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium.*

The Belgian Fibromuscular Dysplasia (FMD) Initiative, coordinated by A. Persu (UCL) and P. Van der Niepen (VUB) is a national initiative aiming at increasing awareness and knowledge about FMD, improving and harmonizing management of the disease and promoting related research initiatives. Since its creation in 2015, two national meetings covering various aspects of the disease have been organized, with participation of experts from Belgium and abroad. The Belgian FMD initiative is working jointly with the Belgian patient association FMD-Be to provide validated information for patients in French, Dutch and English. Finally, the Belgian FMD initiative is at the origin of BEL-FMD, a "Belgian multicentric cohort of patients with Fibromuscular Dysplasia and/or Spontaneous Coronary Artery Dissection" linked with a DNA/RNA biobank. BEL-FMD is endorsed by the Belgian Hypertension Committee. BEL-FMD includes PIs from 7 Academic centres, namely A. Persu (UCL), P. Van der Niepen (VUB), P. Verhamme (KUL), H. Heuten (UA), T. De Backer (UG), J.-C. Wautrecht (ULB) and J.-M. Krzesinski (ULg). Local teams involved in BEL-FMD include nephrologists, cardiologists, neurologists, radiologists and vascular surgeons. Two years after its creation, the BEL-FMD cohort includes 160 patients, and this number is steadily increasing. The BEL-FMD cohort is nested within the European FMD registry, and the Belgian FMD initiative is one of the driving forces of the European FMD initiative. The aims and current achievements of the European FMD initiative are summarized in the abstract of the communication "The European FMD initiative" by A. Persu and L. Toubiana.

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