Fibromuscular Dysplasia

State of the Art

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Université Catholique de Louvain
Brussels, Belgium

No conflict of interest
Definition of Fibromuscular Dysplasia

An idiopathic, segmental, nonatherosclerotic and non inflammatory disease of the musculature of arterial walls, leading to stenosis of small and medium-sized arteries.

The diagnosis of FMD requires exclusion of renal artery spasm, arterial diseases of monogenic origin, and inflammatory arterial diseases.

Prevalence of renal FMD

**Symptomatic FMD** (Plouin et al., Orphanet JRD 2007, 2:28)

Estimated to ~0.02-0.08%

(based on the prevalence of HTN in middle-aged subjects, the prevalence of renovascular HTN in hypertensive patients and the proportion of renal artery stenosis due to FMD).

**Silent FMD** (Hendricks et al., Vascular Medicine 2014;19: 363-367)

Meta-analysis of data from kidney donors: ~4%

CORAL database: 5.8%
FMD: not only a disease of young women

### Table 1. Demographics and Comorbidities of Patients With FMD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>55.7±13.1 y (range, 18–86)</td>
</tr>
<tr>
<td>Age at first FMD-related symptom, mean±SD</td>
<td>47.2±14.6</td>
</tr>
<tr>
<td>Age at diagnosis of FMD, mean±SD</td>
<td>51.9±13.4 y (range, 5–83)</td>
</tr>
<tr>
<td>Female</td>
<td>406/447 (91)</td>
</tr>
</tbody>
</table>

FMD in a 65 yo man with Coronary Heart Disease
FMD in an 85 yo woman
Provisional recommendations for screening

- Recommended in hypertensive patients aged < 50 years, especially women and/or patients with severe/resistant hypertension
- CTA (or if CI MRA) preferable to renal Duplex as first-line test, especially if high diagnostic probability/ low expected performance of renal Duplex
- Increase awareness of radiologists and clinicians!

Persu et al., FMD deserves to be revisited, submitted 2016
Differences according to the radiological classification

**Angiographic**

<table>
<thead>
<tr>
<th></th>
<th>Multifocal, 276</th>
<th>Focal, 61</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>47 (17%)</td>
<td>19 (31%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>49 [42, 58]</td>
<td>30 [25, 39]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bilateral stenoses</td>
<td>171 (62%)</td>
<td>13 (21%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Small kidney</td>
<td>19 (10%)</td>
<td>16 (33%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Interventions*</td>
<td>50 (35%)</td>
<td>28 (90%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Among patients with a FU ≥1 year  Savard S et al, Circulation 2012;126:30
Screening in a hypertensive patient

Incidental finding
Screening in a hypertensive patient

Incidental finding
The prevalence of current smoking is greater in patients with FMD than in matched controls. Current smoking is associated with more severe and more rapidly progressing disease in patients with multifocal FMD. This study highlights the critical importance of encouraging patients with FMD to quit smoking.

Smoking cessation should be strongly encouraged in patients with FMD
FMD-related renal artery stenosis

Indications of revascularisation

• HTN of recent onset
• Medical treatment failure
• Renal function degradation
  (especially after administration of a RAS inhibitor)
• Renal size reduction

Renal FMD is not always a curable disease

Meta-analysis: HTN cure rate following PTA

Relationship with age

FMD-related renal artery stenosis
PTA vs. surgery

- Renal PTA is the first-line revascularisation technique.
- Stenting is usually not recommended (risk of kinking or stent fracture)
- Surgery should be considered in the following cases:
  - Stenosis associated with complex aneurysms
  - Restenosis despite two attempts of PTA
  - Complex lesions of arterial bifurcation or branches

Screening in a hypertensive patient

Incidental finding
FMD a systemic vascular disease?

- Multiple vascular beds may be affected
- Multisite FMD is frequent
- SCAD
- FMD patients may share features with systemic diseases
- Underlying subclinical vascular abnormalities
FMD: a disease affecting multiple vascular beds


Courtesy of P. Chenu
Table 4. Distribution of Vascular Bed Involvement in FMD

<table>
<thead>
<tr>
<th>Vascular Bed Involved</th>
<th>n</th>
<th>No. of Patients With Imaging</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal artery</td>
<td>294</td>
<td>369</td>
<td>79.7</td>
</tr>
<tr>
<td>Extracranial carotid artery</td>
<td>251</td>
<td>338</td>
<td>74.3</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>82</td>
<td>224</td>
<td>36.6</td>
</tr>
<tr>
<td>Mesenteric arteries</td>
<td>52</td>
<td>198</td>
<td>26.3</td>
</tr>
<tr>
<td>Lower-extremity arteries*</td>
<td>42</td>
<td>70</td>
<td>60.0</td>
</tr>
<tr>
<td>Intracranial carotid arteries†</td>
<td>35</td>
<td>206</td>
<td>17.0</td>
</tr>
<tr>
<td>Upper-extremity arteries*</td>
<td>10</td>
<td>63</td>
<td>15.9</td>
</tr>
<tr>
<td>Aorta‡</td>
<td>0</td>
<td>145</td>
<td>0</td>
</tr>
</tbody>
</table>

28% multisite FMD

Lüscher TF. et al. Nephron, 1986; 44 (suppl.1): 109-114

<table>
<thead>
<tr>
<th>N° vascular beds imaged</th>
<th>N° of patients</th>
<th>N° of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>357</td>
<td>35% FMD of 2 vb</td>
</tr>
<tr>
<td>3 or more</td>
<td>292</td>
<td>22% FMD of 3 vb</td>
</tr>
<tr>
<td>4 or more</td>
<td>232</td>
<td>9% FMD of 4 vb</td>
</tr>
</tbody>
</table>

Renal arteries

Extracranial carotid/vertebral arteries

65%

Is FMD a systemic disease?
Results from the ARCADIA registry

PF Plouin for the French-Belgium ARCADIA (Assessment of Renal and Cervical Artery Dysplasia) Registry Investigators
Bordeaux, Brussels, Caen, Clermont, Grenoble, Lille, Marseille, Nancy, Paris, Toulouse and Versailles
Results from the ARCADIA registry

Patients giving informed consent, n=499

Excluded, n=30
- FMD diagnosis rejected, 14
- Angiographic imaging of abdominal and cervico-cephalic arteries not available, 9
- Miscellaneous, 7

Population available for analysis, n=469

Single-site, n=244
- Multifocal, 212
- Focal, 32

Multisite, n=225
- Multifocal, 217
- Focal, 8

48.0% of FMD patients had multisite lesions (50.1% of those with multifocal FMD)

Courtesy of PF Plouin
Screening for cervico-cephalic FMD

- Retinal or cerebral ischemic events
- Intracranial aneurysms
- Subarachnoid hemorrhage
- Cervical or intracranial dissection
- Pulsatile tinnitus

Screening for carotid FMD: echography is not enough

CT- and MR-angiography are likely to perform better than Doppler in detecting lesions involving the medium and distal thirds of carotid and vertebral arteries.

Dysplasie fibromusculaire rénale et anévrisme cérébral chez une patiente hypertendue avec histoire familiale d'accidents vasculaires cérébraux

A. Persu, C. Dubois, Y. Pirson, J.F. de Plaen
In case of hypertension

In case of suggestive symptoms or if likely to alter management

Screen for cerebral aneurysms if likely to modify management

If suggestive symptoms
Spontaneous coronary artery dissection (SCAD) and FMD of extra-coronary vascular beds

<table>
<thead>
<tr>
<th>Table 4. Involvement With Noncoronary FMD Among These Patients With SCAD (N = 50)</th>
<th>51.0 ± 9.6 y, 98% of females</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD in ≥1 noncoronary territories</td>
<td>86.0% (43)</td>
</tr>
<tr>
<td>FMD in ≥2 noncoronary territories</td>
<td>42.0% (21)</td>
</tr>
<tr>
<td>FMD not observed</td>
<td>14.0% (7)</td>
</tr>
<tr>
<td>Incomplete screening</td>
<td>10.0% (5)</td>
</tr>
<tr>
<td>Screened cerebral, renal, iliac</td>
<td>4.0% (2)</td>
</tr>
<tr>
<td>FMD vascular involvement (n = 43)</td>
<td>58.1% (25)</td>
</tr>
<tr>
<td>Renal arteries</td>
<td>48.8% (21)</td>
</tr>
<tr>
<td>Iliac arteries</td>
<td>46.5% (19)</td>
</tr>
<tr>
<td>Cerebrovasculature</td>
<td>16.3% (7)</td>
</tr>
</tbody>
</table>

Spontaneous coronary artery dissection

Look for renal, iliac and cervical FMD

Tortuosity

Figure 1. Tortuosity definition. **Left:** Example of tortuosity of the left anterior descending coronary artery. **Right:** Example of severe tortuosity of the left circumflex coronary artery.
Carotid triple signal in FMD patients

Control

Right CCA

FMD

Right CCA

Boutouyrie P. et al. *J Hypertens.* 2003; 2287-2295
High carotid score in FMD patients and relatives

Perdu et al. 2007

- **Familial FMD cases** (N = 13): 4.81 ± 0.28
- **FMD first degree relatives** (N = 47): 4.17 ± 1.23
- **Sporadic FMD cases** (N = 125): 4.02 ± 1.11
- **Controls** (N = 47): 2.52 ± 0.09
Clinical and biochemical profiles suggest fibromuscular dysplasia is a systemic disease with altered TGF-β expression and connective tissue features.

**TABLE 3.** Spine magnetic resonance imaging features

<table>
<thead>
<tr>
<th>Feature</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative disc disease at any location in the spine</td>
<td>45</td>
<td>95.7</td>
</tr>
<tr>
<td>Degenerative disc disease noted in cervical spine</td>
<td>39</td>
<td>83.0</td>
</tr>
<tr>
<td>Degenerative disc disease noted in thoracic spine</td>
<td>21</td>
<td>44.7</td>
</tr>
<tr>
<td>Degenerative disc disease noted in lumbar spine</td>
<td>39</td>
<td>83.0</td>
</tr>
<tr>
<td>Facet changes noted at any location</td>
<td>35</td>
<td>74.5</td>
</tr>
<tr>
<td>Facet changes at cervical spine</td>
<td>6</td>
<td>12.8</td>
</tr>
<tr>
<td>Facet changes at thoracic spine</td>
<td>5</td>
<td>10.6</td>
</tr>
<tr>
<td>Facet changes at lumbar spine</td>
<td>34</td>
<td>72.3</td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>20</td>
<td>42.6</td>
</tr>
<tr>
<td>Chiari I malformation</td>
<td>3</td>
<td>6.4</td>
</tr>
<tr>
<td>Tonsillar ectopia</td>
<td>7</td>
<td>14.9</td>
</tr>
<tr>
<td>Scoliosis on magnetic resonance imaging</td>
<td>14</td>
<td>29.8</td>
</tr>
<tr>
<td>Spinal stenosis at any location in the spine</td>
<td>31</td>
<td>66.0</td>
</tr>
<tr>
<td>Spinal stenosis at cervical spine</td>
<td>22</td>
<td>46.8</td>
</tr>
<tr>
<td>Spinal stenosis at thoracic spine</td>
<td>5</td>
<td>10.6</td>
</tr>
<tr>
<td>Spinal stenosis at lumbar spine</td>
<td>17</td>
<td>36.2</td>
</tr>
</tbody>
</table>

We found elevated plasma TGF-β1 (P=0.009), TGF-β2 (P=0.004) and additional inflammatory markers, and increased TGF-β1 (P=0.0009) and TGF-β2 (P=0.0001) secretion in dermal fibroblast cell lines from subjects with FMD compared to age- and gender-matched con-
Screening in a hypertensive patient

Incidental finding
Genetic predisposition to FMD


- Suggestion of an autosomic dominant transmission (Rushton 1980) - 20 pedigrees: in 12 of them one to eleven affected relatives (interview) - reduced penetrance for clinical signs

- Presence of angiographically-proven FMD in 11% of index cases with FMD (Pannier-Moreau, 1997)

- In the US registry, 7% of patients reported a ‘confirmed diagnosis’ of FMD among a family member (Olin, 2012)
PHACTR1 Is a Genetic Susceptibility Locus

rs9349379 (PHACTR1)

P Value (−log₁₀)

Chromosome Position

Kiando SR,.....Jeunemaitre X, Bouatia-Naji N.
More about PHACTR1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases</th>
<th>Controls</th>
<th>OR per G Allele</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary Heart Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nikpay M, et al. 2015</td>
<td>60801</td>
<td>123504</td>
<td>1.14 [1.12; 1.16]</td>
<td>1.81e−42</td>
</tr>
<tr>
<td>UK Biobank</td>
<td>4461</td>
<td>107877</td>
<td>1.16 [1.11; 1.22]</td>
<td>1.16e−11</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td></td>
<td></td>
<td>1.14 [1.12; 1.16]</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary Calcification</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>O'Donnell CJ, et al. 2011</td>
<td>NA</td>
<td>NA</td>
<td>1.22 [1.20; 1.25]</td>
<td>5.44e−80</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td></td>
<td></td>
<td>1.22 [1.20; 1.25]</td>
<td></td>
</tr>
<tr>
<td><strong>Migraine Headache</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anttila V, et al. 2013</td>
<td>4834</td>
<td>7232</td>
<td>0.86 [0.82; 0.90]</td>
<td>2.14e−10</td>
</tr>
<tr>
<td>UK Biobank</td>
<td>3161</td>
<td>109177</td>
<td>0.91 [0.87; 0.96]</td>
<td>0.000717</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td></td>
<td></td>
<td>0.88 [0.85; 0.92]</td>
<td></td>
</tr>
<tr>
<td><strong>Cervical Dissection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debette S, et al. 2014</td>
<td>2052</td>
<td>17064</td>
<td>0.75 [0.69; 0.82]</td>
<td>6.44e−11</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td></td>
<td></td>
<td>0.75 [0.69; 0.82]</td>
<td></td>
</tr>
<tr>
<td><strong>Fibromuscular Dysplasia</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kiando SR, et al. 2015</td>
<td>1154</td>
<td>3895</td>
<td>0.72 [0.65; 0.80]</td>
<td>7.4e−10</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td></td>
<td></td>
<td>0.72 [0.65; 0.80]</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK Biobank</td>
<td>62711</td>
<td>43521</td>
<td>0.97 [0.96; 0.99]</td>
<td>0.00685</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td></td>
<td></td>
<td>0.97 [0.96; 0.99]</td>
<td></td>
</tr>
</tbody>
</table>

PHACTR-1
A distal regulator of endothelin-1 Gene expression

Gupta et al.
The European FMD registry

Adapted from the French FMD registry (coord. P.-F. Plouin), created in 2010 to merge existing local FMD databases and to share data semantics with the US registry.

Includes over 50 items covering demographic and clinical characteristics of FMD, family history, type, localization, associated complications and interventions.

A flexible, user-friendly online version has been developed (L. Toubiana), allowing to add an indefinite number of new events.

Specific modules can be developed according to local interests.

Toubiana et al., Stud Health Technol Inform. 2015; 210:887-891
Belgian Multicentric Cohort of Fibromuscular Dysplasia (BEL-FMD)

Laurent TOUBIANA, PhD. Physique, Epidémiologiste

Directeur de l'IRSAN,
"Institut de recherche pour la valorisation des données de santé"
Responsable du SCEPID :
Systèmes Complexes et Epidémiologie
Laboratoire d'Informatique Médicale et d'Ingénierie des connaissances
INSERM UMR 1142 LIMICS, Paris, F-75006;
UPMC : Université Pierre et Marie Curie - Paris 6
Informed consents

Fill the data
http://etude-dfm-belgique.forxit.eu

For any information:
alexandre.persu@uclouvain.be

a. Collect 3 tubes

2 EDTA tubes 5ml

b. Label the tubes for Ex.: BEL-UCL-FMD1

c. Store them at 4°C for one week maximum

d. Stored at -80°C

Or

Send to us at room temperature
Before one week

+ IMAGES
Since October 2017
The European FMD registry

- Imaging
- Biomarkers
- Hemodynamics
- MicroRNAs
- Echotracking
- Proteomics
Persu et al., FMD revisited, Hypertension 2016; 68:832-9 update.
What is fibromuscular dysplasia (FMD)?

Fibromuscular dysplasia (FMD) is a disease of the artery wall, without a link to atherosclerosis (cholesterol deposits) or inflammation. Sometimes this can lead to an arterial stenosis (narrowing), a dilation (aneurysm) or a dissection (tear) of the affected artery. A stenosis or a dissection can be responsible for a reduction in arterial blood flow. The effect of this reduced blood flow depends on the location of the arteries involved. A ruptured aneurysm could be a cause of internal bleeding and would require urgent medical attention.

Many patients affected by FMD have no symptoms or detectable signs of the disease during medical examination. Often the disease is picked up during medical imaging (CT scan or MRI) carried out for another reason.

This site aims to provide scientifically valid and up to date information.

It has been realised by the patient association in conjunction with a scientific (medical) committee.

This information is not intended to replace that given to you by your doctor!
INTERNATIONAL SYMPOSIUM
REVISITING FIBROMUSCULAR DYSPLASIA & RELATED VASCULAR DISEASES

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

Thursday
Opening Ceremony
Opening Lecture
Welcome Cocktail

Friday
Session I
Fibromuscular Dysplasia (FMD): a multifaceted vascular disease

Session II
Registries, network and databases: what have we learnt?

Session III
Exploring the vascular structure and function of FMD patients

Session IV
Biomarkers and genetics

Saturday
Session I
Spontaneous Coronary Artery Dissection

Session II
Medium Size Artery Diseases and FMD mimics

For more information and for the registration to the Congress, visit the following website: www.fondazione-menarini.it
### Saturday, February 24th 2018 – Morning

**Session VI – Spontaneous coronary artery dissection**  
**AUDITORIUM ALBERT II - GROUND FLOOR**

<table>
<thead>
<tr>
<th>Time</th>
<th>Name</th>
<th>Location</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.30 a.m.</td>
<td>J. Saw (Vancouver, CA)</td>
<td>From coronary FMD to SCAD</td>
<td></td>
</tr>
<tr>
<td>09.50 a.m.</td>
<td>F. Alfonso (Madrid, SP)</td>
<td>Optimal management of SCAD</td>
<td></td>
</tr>
<tr>
<td>10.10 a.m.</td>
<td>S. Hayes (Rochester, US)</td>
<td>AHA scientific statement on SCAD</td>
<td></td>
</tr>
<tr>
<td>10.30 a.m.</td>
<td>D. Adlam (Leicester, UK)</td>
<td>The European SCAD consensus and registry</td>
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</tr>
<tr>
<td>10.50 a.m.</td>
<td></td>
<td>Coffee break</td>
<td></td>
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</tbody>
</table>

Contact  
alexandre.persu@uclouvain.be