Fibromusculaire dysplasie, een ondergediagnosticeerde oorzaak van hypertensie

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Nefrologie & Hypertensie
UZ Brussel

Symposium Belgische Cardiologische Liga
Brussel, 13 mei 2017

Outline

- Introductie
  - Secundaire oorzaken van HT
  - Definitie en Klassificatie van FMD
- Renale FMD
  - Epidemiologie
    - Prevalentie
    - Risicofactoren
  - Screening
  - Diagnose & DD
  - Behandeling & FU
    - Medisch
    - Interventioneel
Hypertensie: Etiologie

- >90% essentieel
- <10% secundair
  - Renale hypertensie
    - Primaire nierziekte
    - Progressieve nierinsufficiëntie
  - Renovasculaire hypertensie
  - Endocriene oorsprong
    - Primair hyperaldosteronisme (S van Conn)
    - Feochromocytoom
    - Cushing syndroom en ziekte, ...
  - Obstructief SlaapApnoe S, ...
  - .....

Cave BD verhogende geneesmiddelen e.a.

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**Revisiting Fibromuscular Dysplasia: Rationale of the European Fibromuscular Dysplasia Initiative**

Alexandre Persu, Patricia Van der Niepen, Emmanuel Touzé, Sofie Gevaert, Elena Berra, Pamela Mace, Pierre-François Plouin and Xavier Jeunemaître on behalf of the Working Group Hypertension and the Kidney of the European Society of Hypertension and the European Fibromuscular Dysplasia Initiative

_Hypertension_. 2016;68:832-839; originally published online August 8, 2016; doi: 10.1161/HYPERTENSIONAHA.116.07543
Introduction
Definition & Classification of FMD

- 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.

- Histopathological classification: three main types:
  1. Intimal FMD (5%)
  2. Medial FMD (>85%)
  3. Perimedial FMD (10%)

~ Harrison & McCormack (1971)
- Intimal Fibroplasia (1 - 2%)
- Medial FMD (>85%)
  - Medial fibroplasia (60 – 70%)
  - Perimedial fibroplasia (15 – 25%)
  - Medial hyperplasia (5 – 15%)
- Adventitial FMD (<1%)

Introduction
Angiographic Classification: 3/ 2 angiographic types

- Multifocal (‘string-of-beads’ appearance), unifocal (solitary stenosis <1 cm in length), and tubular (stenosis ≥1 cm in length) (Kincaid OW et al. Am J Roentgenol 1968;104:271-82).
- As the two last categories differ only by the length of the diseased segment, it was proposed to group them under the general term unifocal (Savard S, et al. Circulation 2012; 126:3062–69).
Introduction

Angiographic Classification: 3/2 angiographic types

- **Multifocal** ('string-of-beads' appearance), **unifocal** (solitary stenosis <1 cm in length), and **tubular** (stenosis ≥1 cm in length) (Kincaid OW et al. Am J Roentgenol 1968;104:271-82).

- As the two last categories differ only by the length of the diseased segment, it was proposed to group them under the general term **unifocal** (Savard S, et al. Circulation 2012; 126:3062–69).

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**Medial FMD**

80%

Lower female prevalence, more severe and early presentation, higher hypertension cure rate after revascularization.

**Intimal FMD**

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Introduction

Definition & Classification of FMD

- The diagnosis of **multifocal FMD** can be established when a “string-of-beads” appearance is observed in a medium-sized artery, in the absence of aortic involvement or exposure to vasoconstrictor agents.

- The diagnosis of **unifocal FMD** can be established in young patients (usually <40 y), in the absence of atherosclerotic plaque, multiple vascular risk factors, inflammatory syndrome or vascular thickening, and familial or syndromic disease.
Differential diagnosis
The diagnosis of FMD requires exclusion of

- Arterial dis. of monogenic origin
- Vasospasm
- Elastorhexis (Ehlers Danlos)
- Atherosclerosis
- Segmental arterial mediolysis
- Vasculitis (Takayasu)
- Inflammatory arterial disease


Screening for renal FMD (patients with HTN)

- Age <30 years, especially in women (no family history, no other CV risk factors)
- Grade 3 (180/110 mmHg), accelerated or malignant HTN
- True Resistant HTN (BP target not achieved despite triple therapy at optimal doses including a diuretic)
- Small kidney without history of uropathy
- Abdominal bruit without apparent atherosclerosis
- FMD in at least another vascular territory

In individuals aged less than 50 years, screening for FMD may also be considered in milder HTN cases.

Renal artery FMD - Epidemiology
FMD is not so rare!

→ In general population: 0.4% (Plouin et al. Orphanet J Rare Dis 2007; 2:28)

<table>
<thead>
<tr>
<th>First author</th>
<th>Source</th>
<th>Potential donors</th>
<th>FMD Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cragg, 1989</td>
<td>Universities of Iowa, Minnesota, California San Francisco and Los Angeles, Mayo Clinic 1964-86</td>
<td>1862</td>
<td>71 (3.8%)</td>
</tr>
<tr>
<td>Neymark, 2000</td>
<td>University of California San Francisco, 1988-98</td>
<td>716</td>
<td>47 (6.6%)</td>
</tr>
<tr>
<td>Andreoni, 2002</td>
<td>University of North Carolina, 1995-2001</td>
<td>159</td>
<td>7 (4.4%)</td>
</tr>
<tr>
<td>Kolettis, 2004</td>
<td>University of Alabama, 1995-2001</td>
<td>1176</td>
<td>66 (5.6%)</td>
</tr>
<tr>
<td>Blondin, 2010</td>
<td>University of Duesseldorf, 2004 - 2008</td>
<td>101</td>
<td>4 (3.9%)</td>
</tr>
<tr>
<td>McKenzie, 2013</td>
<td>Mayo Clinic, 2000-2011</td>
<td>2640</td>
<td>68 (2.6%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>6654</td>
<td>263 (4.0%)</td>
</tr>
</tbody>
</table>

→ In CORAL trial participants: 5.8% (Hendricks et al. Vasc Med 2014; 19:363-7)

Fibromuscular dysplasia – results of a multicentre study in Flanders

Marie De Groote1, Patricia Van der Niepen2, Dimitri Hemelsoet3, Bert Callewaert4, Frank Vormassen5, Jean-Marie Billiouw6, An De Vriese7, Jan Donck8, and Tine De Backer9

Table 1. Demographic data and cardiovascular risk factors of FMD patients at inclusion.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Flamish registry, n (%)</th>
<th>US registry 2012 [1], n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (±SD) (range) /y**</td>
<td>63.8 (±15.9) (24, 92)</td>
<td>65.7 (±13.1) (18, 86)</td>
</tr>
<tr>
<td>Age at diagnosis of FMD, mean (±SD) (range)</td>
<td>67.3 (±15.8) (19, 94)</td>
<td>61.9 (±13.4) (5, 83)</td>
</tr>
<tr>
<td>Female</td>
<td>103/123 (83.7)</td>
<td>406/447 (91)</td>
</tr>
</tbody>
</table>

Renal FMD in a 65 y man with Coronary Heart Disease

Renal artery FMD
Pathogenesis and Risk factors

- Genetic
  - Autosomal dominant with variable penetrance in 60% of cases based on “clinical symptoms”\(^1\)
  - 11% prevalence angiographically\(^2\)
  - PHACTR1 (phosphatase and actin regulator 1)\(^10\): a first confirmed FMD risk locus

- Hormonal
  - No difference in gravidity or parity rates, effect on disease progression\(^3\)
  - Oral contraceptive pill use?\(^4,5\)

- Mechanical
  - Ptosis of the right kidney\(^6\)
  - Repetitive trauma such as hyperextension and rotation of the neck\(^6\)

- Mural ischemia
  - Occlusion of the vasa vasorum\(^7\)
  - Vasospasm (ergotamines, methysergide)\(^8\)
  - Tobacco use\(^9\)

FMD, a familial disease?

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sporadic FMD</th>
<th>Familial FMD</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis of FMD</td>
<td>44.1 ± 13.6</td>
<td>43.5 ± 10.9</td>
<td>0.81</td>
</tr>
<tr>
<td>Multicellular fibroelastolysis</td>
<td>10/15</td>
<td>11/0</td>
<td>0.00</td>
</tr>
<tr>
<td>Solitary kidney</td>
<td>5 (5.7)</td>
<td>2 (2.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Blunted FMD</td>
<td>43 (48.3)</td>
<td>3 (28.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Maximum diameter &gt;70%</td>
<td>45 (51.1)</td>
<td>22 (12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ischemic renal failure</td>
<td>18 (20)</td>
<td>4 (4.0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Percentage: 10.6 %


Screening for hereditary FMD

- It is recommended to question a patient with FMD about:
  - precocious HTN,
  - history of dissection, aneurysm, or
  - history of cerebral haemorrhage among his/her first-degree relatives.

- In case of a positive answer to at least one of these questions, the patient may inform the respective relative(s) about the possibility of hereditary FMD.

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 progressinig disease in patients with multifocal FMD. This study highlights the critical importance of encouraging patients with FMD to quit smoking.


Less Classical presentations of FMD
Renal artery aneurysms/ vascular ectasia

- **US Registry (n, 447):**
  - 17% artery aneurysms
    - 33% in renal artery,
    - 21% in carotid artery

- Complications: rare
  - Rupture
  - Distal emboli
  - AV fistula with renal vein

- **Flemish Registry (n, 123):**
  - 20% artery aneurysms
    - 32% in renal artery
    - 44% in carotid artery

Abdominal angio-CT scan: renal artery FMD with RAAs:
Left artery: type 1 (saccular) aneurysm (2.5 cm diameter)
Right renal artery: type 2 (fusiform) aneurysm (1.3 cm)

Less Classical presentations of FMD
Renal artery dissection

- **US Registry** (n, 447): 19.7% arterial dissection (22% in renal artery, 75% in carotid artery)
- Flemish Registry (n, 123): 11.4% AD (14% RA, 50% CA)
- **Lacombe** (n, 22 isolated renal artery dissection): 45% FMD as cause
  - Occur esp. tubular stenosis
  - May cause renal infarction (total occlusion or distal emboli) → flank pain, hematuria a/o rapidly progressive HTN

Renal artery FMD
Clinical manifestations

- Hypertension is the most common clinical presentation (Renovascular HT)
  → Variable severity
  → Variable onset

- Epigastric or flank bruit on physical ex

- Flank pain < dissection, or aneurysm

- Renal insufficiency: uncommon
  → RA dissection and Renal infarction (→) CKD
  → Progression to ESRD: rare

### Renal artery FMD

**Diagnostic tools: non-invasive & invasive imaging studies**

<table>
<thead>
<tr>
<th></th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| **Duplex Ultrasound** | Widely available  
Less expensive  
Non-irradiating  
Extra information on:  
- Hemodynamic impact  
- Kidney size | Time-consuming  
Operator-dependent  
Less sensitive  
Technical problems (obesity, bowel gas) |
| **CT-angiography** | Good sensitivity & specificity  
CTA: better spatial resolution (0.5 mm; distal lesions) | Less accurate for quantification of degree of stenosis  
No info on hemodynamic impact  
CTA: irradiation, nephrotoxicity, allergic reactions  
MRA-Ga: nephrogenic systemic fibrosis |
| **Digital subtraction angiography** | Gold-standard for site & morphology  
Unsurpassed spatial resolution (<0.1 mm)  
Simultaneous PTA | Cave spontaneous dissection  
Irradiation, nephrotoxicity, allergic reactions |

### Renal artery FMD

**Diagnostic tools: CT-angiography**

- Specificity for detecting RAS due to FMD: 92%
- Sensitivity: 64%
  (branch vessels)

 Renal CTA with coronal plane Maximum Intensity Projection reconstruction, showing the typical “string-of-beads” aspect of the right renal artery

Renal artery FMD
Diagnostic tools: MR-angiography

FMD of right medial renal artery.
(a) Nonselective anteroposterior aortogram: long stenosis (arrow) in medial part of right RA.
(b) Coronal maximum intensity projection and (c) volume-rendered image, both of which were obtained at contrast-enhanced MRA (5.2/1.5, 40° flip angle, and 0.78x0.78x1.5-mm reconstructed voxel), show lesion with overestimation of stenosis.

Renal artery FMD
Casus 1:

- 22-yr female student – HTN since 18 mths (21/12 cm Hg)
- Treated with ≠ antihypertensive drugs – not controlled
- No fam. history
- Work out other hospital
  → Renal US: Nl
  → sCreat: 0.91 mg/dl
- Second Opinion

Geen MBV nierarteriën
sCreat → 1.13 mg/dl

→ Bitherapy (ACEI+BB)
→ BP: 135/88 mm Hg
→ MR angiography
→ IADSA renal aa (2013)
Renal artery FMD

Casus 1:

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- Work out other hospital
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  → MR angiography
  → IADSA renal aa (2013)
Renal artery FMD
Treatment: Medical vs Interventional (PTA vs surgical)

- Decision depends on
  - Nature & location of vascular lesions (stenosis/ dissection/ aneurysm)
  - Presence & severity of symptoms
  - Prior vascular events related to FMD
  - Comorbid conditions

- NO RCTs of revascularization vs medical therapy

Renal artery FMD
Treatment: Medical & Surveillance

- Limited knowledge of natural history & lack of RCTs
- Medical treatment if clinical asymptomatic
  - No HTN
  - RAS is not hemodynamically significant
  - No decrease in kidney function or size
- AntiHT therapy: first-line = RAAS blockers
- Antiplatelet & antithrombotic agents
  - Low dose ASA? No data in renal FMD: reasonable to ↓platelet adherence to intravascular webs; After PTRA: ASA 75 – 325 mg OD
  - If RA dissection: ASA alone or ASA + clopidogrel or anticoagulant (Heparin → coumarine 3 – 6 mths → ASA)
  - If RA thrombosis: systemic anticoagulation is appropriate
- Statins? unless other CVRF a/o atherosclerotic lesions

Renal artery FMD
Treatment: revascularization is recommended if

- HTN of recent onset (first-line treatment to normalize BP)
- Medical treatment failure (drug resistance or intolerance)
- Renal insufficiency or deterioration of renal function esp. after administration of a RAAS blocker, or after BP↓
- Renal size reduction downstream of the stenosis (≥1 cm during 2 successive exam’s)
- RA dissection (stent) or aneurysm (surgery, endovascular coiling, covered stent)

- HTN cure following revascularization of FMD-RAS:
  → 30 – 50%
  → Higher in younger pts, more recent HTN, unifocal FMD

Meta-analysis of HTN cure rates after PTRA.

Combined cure rate or BP improvement: 88.3% (95%CI, 83.2-92.6) – heterogeneity!

Meta-regression analyses assessing the relationship between the HTN cure rate after PTRA and mean age.

Renal artery FMD

Treatment: revascularization

Balloon PTA and surgical revascularization

- Stenting? Not indicated (risk of kinking or stent fracture), unless
  - Per-procedural artery dissection
  - PTA failure?
- Surgery? Should be considered
  - Complex lesions of arterial bifurcation or branches
  - Stenosis complicated with complex aneurysms
  - Following PTA failure (or complication): to prevent arterial trauma, 3rd PTA is not recommended
- Cutting balloons? Not recommended because of the risk of
  - Renal artery rupture and subsequent pseudoaneurysm formation


Renal artery FMD

Treatment & FU

- No optimal monitoring protocol, nor in case of medical treatment alone, nor post revascularization
- **No revascularization**
  - Optimal medical treatment
  - FU BP every 3 months once controlled
  - FU renal function: annually or earlier ~ kidney function
  - FU with renal ultrasound (kidney length)
    - Yearly if unifocal or bilateral FMD
    - Two-yearly
    - If BP increases or kidney function decreases

Renal artery FMD
Treatment & FU

- No optimal monitoring protocol, nor in case of medical treatment alone, nor post revascularization

- **After revascularization** (restenosis in ± 25%)
  - Clinical evaluation
    - at 1 mth: BP, antiHT Treatment and kidney function
    - 3-monthly: BP
  - Renal imaging
    - at 6 mth (cave restenosis) or before if BP↑ or KF↓
    - Annually (or 6-monthly first 24 mths, then yearly)
  - True Restenosis or Suboptimal initial PTRA?

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FMD is a systemic vascular disease
Different vascular beds and of multiple-site involvement

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By contrast, the % provided in the US registry correspond to the ratio of patients with FMD lesions of the corresponding vascular beds to the number of patients imaged for these vascular beds. This may lead to a substantial overestimation in some cases, as imaging of rarely involved vascular beds was targeted according to symptoms. In particular, imaging of lower limbs was performed only in a minority of patients (n=70), mostly in presence of claudication. In addition, for the US registry, the column ‘supra-aortic trunks’ refers to extracranial carotid artery involvement. The corresponding percentage for vertebral arteries was 36.6%.
Renal artery FMD
Casus 2:

- 48-yr young woman – HTN since >20 years (19/12 cm Hg)
- Treated with ≠ antihypertensive drugs – not controlled
- No fam. history
- Work out other hospital → PHA
- Second Opinion
  → BP: 162/112 mm Hg
  → Quadritherapy (ACEI + Diur + BB + spironolactone)
  → Renal function: NL
  → IVDSA renal aa (2003)
  → AIIA + CCB + BB: 118/74 mm Hg

- Chronic headache & Epilepsy, not controlled with anti-epileptic drugs
Visceral Fibromuscular Dysplasia

FMD of superior mesenteric artery: Tubular smooth stenosis, which spares orifice of artery.

FMD of superior mesenteric artery: Tubular smooth stenosis, which spares orifice of artery.

Aortogram (A) celiac axis: spontaneous celiac artery dissection with pseudoaneurysm

FMD - Multiple site involvement in one patient
Casus 3

62 y female patient – HTN/ asymptomatic – Ph Ex: no bruits → CTA → IADSA
Spontaneous coronary artery dissection (SCAD)

A. Type 1: a false lumen is visible,

B. Type 2a: a long narrowing with no visible false lumen and normal distal vessel,

C. Type 2b: no visible false lumen or distal vessel,

D. Type 3: similar to atherosclerotic,

E. Type 4: distal occlusion with subsequent confirmed healing and no identified embolic source.


Take Home Messages

- FMD is not a rare disease
- FMD is not only a disease of young women
- FMD is a systemic vascular disease:
  -> FMD can affect every arterial bed, but most commonly affects renal, extracranial carotid and vertebral arteries
  -> The coronary manifestations of FMD – spontaneous coronary artery dissection – are an emerging area of clinical research
  -> Multiple site involvement is frequent, and should be screened for
Take Home Messages (2)

- Pathogenesis remains unclear, but evidence supports a genetic basis for susceptibility to FMD
- Many signs and symptoms are non-specific. Hypertension is the most common clinical presentation
- A delay in diagnosis can lead to impaired quality of life and poor outcomes
- Conventional angiography is the gold standard
- Treatment includes optimal medical therapy a/o revascularization ~ specific indications
  - PTA does not always cure renal FMD
  - Stenting is not recommended

Good News

- INITIATIVES
  - European consensus
  - BEL-FMD project
  - European Registry
  - National Symposium
  - National/ European patient association: to improve the lives of FMD patients by
    - Building awareness
    - Raising funds to promote research towards new diagnostic tools and therapies
- RESEARCH ....

http://www.fmd-be.be/
BEL-FMD
a national project
nested within a European initiative

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Brussels, Belgium

Patricia Van der Niepen, MD, PhD
Nephrology & Hypertension Dept
Universitair Ziekenhuis Brussel
Free University of Brussels (VUB)
Brussels, Belgium
Second National Meeting on Fibromuscular Dysplasia

Saturday 10th December 2016
9h00-11h30
Auditorium Main (Auditorium centrale de la Fondation d’Hôpitaux de l’ULB)
Avenue Emmanuel Berbier 11 - 1200 Bruxelles
(more back cover for the map)

For information, contact
Prof. Alexandre Prinot (secretariat.versailles@chruversailles.fr) or
Prof. Patrick Van der Plaetsen
(Patrick.VanderPlaetsen@ulb.ac.be)

This meeting is supported by the Belgian Hypertension Community, the Belgian FMD patient association and the KU Leuven Institute of the Chinese University, Shantou Uni.

A registration has been requested.

Endorsed by the European Society of Hypertension

INTRODUCTION SYMPOSIUM

REVISING FIBROMUSCULAR DYSPLASIA & RELATED VASCULAR DISEASES

22-24 FEBRUARY 2018
BRUSSELS

Second National Meeting on Fibromuscular Dysplasia

PROGRAM

20h00-20h15
Bible Café
20h15-20h30
Introduction: Alexandre Prinot (ULB), Patrick Van der Plaetsen (ULB)
21h00-20h45
Clinical FMD from an epidemiologic already to see a recurring urological disease, not an enigmatic one. [Van der Plaetsen, ULB]
Discussion: D. Leclercq, Morscher
21h00-20h45
FMD as a cause of essential hypertension [De Winter, R. Ulm] Discussion: J. C. Mathoulin, EHS
21h00-20h45
21h00-20h45
Effect of 3D FMD - a new way of thinking? First results of the ANGIOHUB study [M. Pont, Paris] Discussion: J. C. Mathoulin, EHS
21h00-20h45
21h00-20h45
FMD - a rare disease, but not rare. Diagnosis and management of FMD [Faccini, P. De Simone] Discussion: T. De Weerdt, EHS
21h00-20h45
FMD patient associations: Beyond experience [C. Jackson, A. De Smedt, R. De Cuypere, S. Loos] Discussion: M. Brouns, F. van Engelen, EHS
21h00-20h45
Lunch
21h00-20h45
FMD - a heritable disease? [L. Safarova, Paris] Discussion: M. Brouns, F. van Engelen, EHS
21h00-20h45
FMD - a new treatment? [A. Arshad, D. Lalani] Discussion: M. Brouns, F. van Engelen, EHS
21h00-20h45
The European FMD registry [C. Wiel, A. Pescatore] Discussion: D. Klee, F. Heidelberg
21h00-20h45
The European FMD registry [A. Pescatore] Discussion: A. Brouns, EHS
21h00-20h45
Conclusions [M. Pont, Paris]

For more information and for the registration in the Congress, visit the following website: www.foaadazione-menarini.it