Fibromuscular Dysplasia
Diagnosis, Treatment and Surveillance

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40 year-old woman referred for arm and leg weakness with exertion and chronic fatigue. Is this PAD or FMD?


This is not FMD!

FMD mimic:
Standing waves - vasospasm vs. artifact


Disclosures

• Advisor: Innovein, inc
Plan: Review Relevant Concepts in FMD Management

- Approach FMD with emphasis on contemporary data from the FMD Registry
  - Presentation
  - Suggested Surveillance
  - Treatment
- Address misconceptions

Misconception #1

All coronary, carotid, and renal artery disease is caused by atherosclerosis.

FMD can cause renal, visceral, cerebrovascular, extremity, and coronary disease.

Many patients have few or no atherosclerotic risk factors.

Whereas atherosclerosis occurs at the origin or proximal portion of the vessel, FMD occurs in the mid and distal part of the artery.

Fibromuscular Dysplasia is...

- Non-atherosclerotic, non-inflammatory arterial disease (not veins)
- Affects medium-sized vessels
  - Also described in almost every vascular bed
- First described by Leadbetter and Burkland in 1938
  - 5 yo boy with severe HTN 2ry to an occluded renal artery (intra-arterial mass of smooth muscle)
- Arterial stenosis, beading, dissection and aneurysm
Epidemiology

- Rare disease (National Organization for Rare Diseases)
  - <200,000 in US residents
  - Meta-analysis ~4% of potential kidney donor population
  - Consecutive cerebral angiograms: 0.3-3.2%
- Disease of women [9:1]
  - Women present with classic signs and symptoms
  - Men more likely present with visceral involvement
  - Men have a 2-fold increase in prevalence of arterial aneurysm and dissection

Prevalence

- Initially thought that renal FMD >> carotid FMD
- Currently a paradigm shift prompted from US Registry for FMD
- Most common: renal arteries = carotid (+/- vertebral arteries)

<table>
<thead>
<tr>
<th>Vascular Bed Involved</th>
<th>No. of Patients</th>
<th>WRS Imaging</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal artery</td>
<td>385</td>
<td>389</td>
<td>79.7</td>
</tr>
<tr>
<td>Extranodal carotid artery</td>
<td>326</td>
<td>338</td>
<td>74.8</td>
</tr>
<tr>
<td>Vertebrobasilar artery</td>
<td>82</td>
<td>221</td>
<td>58.6</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>73</td>
<td>60.0</td>
</tr>
<tr>
<td>Infrarenal carotid artery</td>
<td>35</td>
<td>106</td>
<td>17.0</td>
</tr>
<tr>
<td>Upper-extremity arteries*</td>
<td>16</td>
<td>63</td>
<td>15.9</td>
</tr>
<tr>
<td>Aorta</td>
<td>8</td>
<td>145</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Etiology... Theory but uncertainty remains

- No etiologic genes identified
- 60% of cases are thought familial
- Overlapping features with CTD
  - Loeys-Dietz syndrome
  - Ehlers-Danlos (vascular type)
- Likely gene-environment interactions
  - Smoking
  - Estrogen

Etiology

- Congenital
- Injury
- Hormonal
- CTD

Nomenclature is changing

- Historically, classified histopathologically into categories based on the dominant arterial layer
  - Media, intima, adventitia
- And the composition of the arterial lesion
  - Collagen deposition: fibroplasia
  - Hyperplasia of smooth muscle cells

Medial fibroplasia -> “string of bead”
Intimal and adventitial fibroplasia -> tubular and focal stenosis
Nomenclature is changing

Table 1. Classification of Fibromuscular Dysplasia

<table>
<thead>
<tr>
<th>Pathological</th>
<th>Angiographic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial</td>
<td>Multifocal</td>
</tr>
<tr>
<td>Vascular Hypoplasia (60-70%)</td>
<td>Vascular Hypoplasia (15-25%)</td>
</tr>
<tr>
<td>Internal Hypoplasia (5-15%)</td>
<td>Internal Hypoplasia (5-15%)</td>
</tr>
<tr>
<td>Atypical</td>
<td>-</td>
</tr>
</tbody>
</table>

**Note:** There may be multiple areas of focal disease (eg, renal artery and carotid artery in the same patient). Focal and multifocal disease can occur in the same patient.

European Consensus (2012)

- Multifocal, tubular and unifocal FMD

American Heart Association (2014)

- Multifocal (Medial Fibroplasia)
  - Collagen deposition in vessel media
  - Internal elastic lamina and adventitia generally spared
  - Sequential areas of stenosis (webs) followed by dilatation

  **Types:**
  - “String of beads”
  - “String of pearls”
  - “Stack of coins”
  - “Sausage links”

**Unifocal (Intimal Fibroplasia)**

- < 10% of cases
- Vascular intima involved
  - Collagen deposits in the intima
  - Internal elastic lamina is abnormal
- Variable angiographic appearance
  - Focal, severe concentric stenosis
  - Longer, tubular lesions; can mimic large vessel vasculitis (Takayasu arteritis)
- Much more common in pediatric FMD cases
- May present with aggressive, multi-vessel syndrome

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**When to consider the diagnosis**

- Classic Symptoms:
  - Hypertension
  - Headache, usually migraine type
  - Pulsatile tinnitus ("swoosh")
  - Dizziness
  - Cervical bruit
  - Neck pain
- The signs and symptoms are broader

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**Symptoms US Registry 2012 (447 patients)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>64%</td>
</tr>
<tr>
<td>Headache</td>
<td>52%</td>
</tr>
<tr>
<td>Pulsatile tinnitus</td>
<td>28%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>26%</td>
</tr>
<tr>
<td>Cervical bruit</td>
<td>22%</td>
</tr>
<tr>
<td>Neck pain</td>
<td>22%</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>19%</td>
</tr>
<tr>
<td>Chest Pain/SOB</td>
<td>16%</td>
</tr>
<tr>
<td>Flank/abdo pain</td>
<td>16%</td>
</tr>
<tr>
<td>Aneurysms</td>
<td>14%</td>
</tr>
<tr>
<td>Cervical artery dissection</td>
<td>12%</td>
</tr>
<tr>
<td>Epigastric bruit</td>
<td>9%</td>
</tr>
<tr>
<td>Hemispheric TIA</td>
<td>9%</td>
</tr>
<tr>
<td>Post-prandial abdo pain</td>
<td>9%</td>
</tr>
<tr>
<td>Stroke</td>
<td>8%</td>
</tr>
<tr>
<td>Claudication</td>
<td>7%</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>5%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>5%</td>
</tr>
<tr>
<td>Horner syndrome</td>
<td>5%</td>
</tr>
<tr>
<td>Renal artery dissection</td>
<td>3%</td>
</tr>
<tr>
<td>Azotemia</td>
<td>2%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2%</td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>1%</td>
</tr>
<tr>
<td>No signs/symptoms</td>
<td>6%</td>
</tr>
</tbody>
</table>

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**Misconception #2**

The most common presentation for carotid FMD is TIA or stroke.
Misconception #2

The most common presentation for carotid FMD is TIA or stroke.

- Although TIA, stroke, and cervical dissection can occur with carotid FMD, the most common presentations represent nonspecific symptoms.
  - Headaches, dizziness, light-headedness, and pulsatile tinnitus
- Carotid FMD can also be asymptomatic and detected incidentally via imaging for another reason or when a cervical bruit is appreciated.

Differential Diagnosis to Consider

- Standing Waves or Stationary Waves
- Atherosclerosis
- Vasculitis
- Segmental Arterial Mediolysis
- Ehlers-Danlos syndrome
- Neurofibromatosis type I
- Williams syndrome
- Reversible cerebral vasoconstriction syndrome
- Median arcuate ligament syndrome

Aneurysms and Dissections in FMD

<table>
<thead>
<tr>
<th>Aneurysms</th>
<th>% in Registry (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid</td>
<td>94 (71)</td>
</tr>
<tr>
<td>Cervical</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Aortic</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Renal</td>
<td>6 (4.5)</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>9 (6.5)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (1.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissections</th>
<th>% in Registry (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid</td>
<td>66 (71)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>33 (36)</td>
</tr>
</tbody>
</table>

Summary for Presentation: Who is the Typical FMD Patient?

- 91% of patients are female
- Average age of diagnosis 52 years
- 1st FMD related symptom @ age 47
- 3 year delay in diagnosis
- Most common symptoms/signs:
  - Hypertension
  - Headache, usually migraine type
  - Pulsatile tinnitus ("swoosh")
  - Dizziness
  - Cervical bruit
  - Neck pain
- 20% of FMD patients have had an arterial dissection; 17% have had an aneurysm
- FMD disease location:
  - Most common: renal arteries = carotid +/- vertebral arteries
  - Less common: mesenteric, external iliac arteries
  - Uncommon: brachial arteries, intracranial FMD, coronary arteries
  - More than 1/3 patients have more than 1 vascular bed involved
Surveillance and Screening

- Gold standard remains catheter-based angiography
- Less invasive modalities are increasingly used
- Optimal diagnostic imaging for surveillance unknown
- Recommended screening algorithm

**SCREENING:**
Once diagnosis is established in a vascular bed, consider performing a 1-time brain-to-pelvis imaging study (US Registry)
~17% positive for aneurysm in ≥1 vascular bed

Renal artery FMD

- Renal u/s features
  - Increased velocities
  - Color and spectral turbulence
    - Severe lesions characterized by delayed systolic upstroke in the spectral doppler waveform of arterial segments distal to the stenosis
  - It is not possible to get an accurate % stenosis in multifocal FMD
  - A high-quality duplex u/s is highly accurate for the diagnosis of renal FMD in the main renal artery (less sensitive in the branch arteries)

Carotid artery FMD

- Carotid duplex first
- Findings (mid to distal cervical ICA and vertebral arteries)
  - Velocity shifts
  - Spectral broadening
  - Turbulent color doppler flow
  - Tortuosity and redundancy of carotid artery in an “S-curve” configuration
- Findings contrast atherosclerosis but both may coexist
- Limitation: Not possible to show accurate % stenosis because of the complex nature of the tandem lesions

Non-invasive imaging increasingly useful

CTA and MRA
Catheter-Based Angiogram—Gold Standard

- Multifocal lesion - renal artery
- Focal lesion — renal artery

Misconception #3
Duplex ultrasound velocities predict degree of carotid or renal FMD severity or both.

- The degree of “stenosis” cannot be determined by Doppler velocity shift
- No diagnostic velocity criteria exist for cerebrovascular or renal FMD
- Example of statement:
  - “There is an increased velocity (PSV, 450 cm/s), turbulence and tortuosity in the mid and distal renal (or carotid) artery consistent with FMD”

Misconception #4
The severity of multifocal FMD (medial fibroplasia) can be accurately ascertained by visual inspection of the angiogram.
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- There is no accurate way to determine the degree of stenosis by visual inspection of an arteriogram or other imaging studies.
- IVUS or measurement of pressure gradient should be obtained in the renal arteries before and after angioplasty in patients with FMD.

Medical Management
- Cerebrovascular FMD
  - Antiplatelet 81-325 mg of ASA for patients
- Carotid/vertebral Dissection
  - Historically: Heparin (or LMWH) followed by warfarin for 3-6 months, followed by antiplatelet therapy
  - Antiplatelet may be sufficient (CADISS Trial)
- Renal/mesenteric/external iliac FMD
  - Antiplatelet reasonable
- Renal FMD Hypertension
  - ACE inhibitor or ARB, monitoring renal function
- CV risk factors and lifestyle modification general wellness
- Statins (may be at increased risk of premature atherosclerosis)

Data from the US FMD Patient Registry
- 50% of FMD patients have undergone a vascular procedure
- Renal arteries and endovascular procedures predominate

Surgical Management: Renal Artery
- Indications for Revascularization:
  - Renal artery stenose, restenosis, or dissection
  - Renal artery aneurysm
  - Renal artery hypertension
  - Pre-existing chronic renal disease
  - PTA first-line therapy
  - Surgery for lesions not amenable to PTA, aneurysms or lesions that have not responded to prior intervention
PTA for Renal FMD

- Technical success rate generally high
- Technical success does not always = cure of hypertension (clinical success)
- Gradient pre-post or IVUS
- Stenting is generally reserved for dissection or poor PTA result
  - Goal of PTA is to improve flow to kidney
  - Do not aim for angiographic perfection or to "straighten out the beads"

Results of PTA in Renal Artery FMD and Hypertension

Technical success does not always = cure of hypertension (clinical success)

Gradient pre-post or IVUS

Stenting is generally reserved for dissection or poor PTA result

- Goal of PTA is to improve flow to kidney
- Do not aim for angiographic perfection or to "straighten out the beads"

Results of Open Revascularization in Renal Artery FMD and Hypertension

Those most likely to benefit clinically (HTN cured or improved):
- Shorter duration of hypertension (< 8 years)
- Normal creatinine
- Normal size of ipsilateral kidney
- No evidence of metabolic syndrome (lipid, glucose abnormalities)
- Medial type FMD
- Age (i.e., > 50 years) controversial as an independent predictor
  - Duration of hypertension may be more than age

Results of Renal Revascularization

- Those most likely to benefit clinically (HTN cured or improved):
  - Shorter duration of hypertension (< 8 years)
  - Normal creatinine
  - Normal size of ipsilateral kidney
  - No evidence of metabolic syndrome (lipid, glucose abnormalities)
  - Medial type FMD
  - Age (i.e., > 50 years) controversial as an independent predictor
    - Duration of hypertension may be more than age

References:
Carotid Artery FMD

- Endo or Surgical Treatment is infrequently required
  - Symptomatic patients
    - Recurrent cerebral ischemic events despite optimal medical therapy (often in setting of dissection)
    - Antiplatelet/anticoagulation contra-indicated
  - Intracranial aneurysms
  - Pseudoaneurysm 2ry to dissection
  - Not Asymptomatic patients
    - Natural history of cerebrovascular FMD is different from that of atherosclerotic disease
- Typically PTA performed with the use of stent reserved for recalcitrant lesions or post-angioplasty flow-limiting lesions

Misconception #5
Patients with renal or carotid artery FMD undergoing intervention should receive a stent.

- There is no indication for stent placement in FMD under most circumstances.
- Angioplasty alone is all that is needed to resolve the pressure gradient and to normalize the appearance on IVUS.
- The only indications for stent implantation are failure to achieve a desirable result with PTA alone (rare) and dissection during the procedure.

Top Priorities Identified by the AHA

- True prevalence of FMD
- Biological and genetic determinants of FMD
- Role of sex hormones/pregnancy
- Creation of rational and cost-effective method for screening
- Development of doppler criteria for carotid and renal FMD
- Natural history of FMD
- RTC
  - Optimal primary/secondary prevention of stroke/TIA
  - Treatment of HTN (endo vs medical) in renal FMD
Conclusions/Take-Home

- Uncommon, non-inflammatory arterial disorder of unclear pathophysiology

- Diagnosis remains challenging to make but once done, allows proper screening and treatment

- Future efforts and research priorities have been outlined by the AHA