Familial Arteriopathies

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The Human Aorta

- Longest and largest blood vessel
- Anatomical segments differ in physiologic function, embryonic origins and biochemical composition
The Human Aorta

- Three layers of the aortic wall
- Media composed of
  - Smooth muscle
  - Elastic fibers
Aortic Pathology

- The human aorta can
  - Enlarge (dilate) ➔ aneurysm
  - Dissect (separation of the layers of the wall)
  - Rupture
  - Develop atherosclerosis
  - Develop inflammation
  - Become infected
Thoracic Aortic Pathology

- Aortic dilatation
Thoracic Aortic Pathology

- Aortic dissection
  - Type A
  - Type B Dissection
Abdominal Aortic Pathology

Aneurysm (AAA)  AAA Rupture
Abdominal Aortic Aneurysm Pathology

• Most are due to inflammation
  – Associated with male gender, age, smoking
  – Family history suggests a complex trait (offspring of affected mothers have higher risk)

• Some are associated with thoracic aortopathies
Aortic Dissection: First Description

George II (1683-1760)

Died suddenly 17 Oct while sitting in the WC

Autopsy showed a tear in the wall of the dilated ascending aorta

Nicholls F. Observations concerning the body of His Late Majesty. *Philos Trans Lond* 1761;52:265-74.
Thoracic Aortic Dissection: Epidemiology

- In US, 2-3.5 cases/100,000/year
- Risk factors:
  - Caucasian
  - Male
  - Increased age
  - Hypertension
Aortic Dissection: High Mortality

• Without treatment, 50% die in first 48 hours
• 90% die in first month
Aortic Dissection: High Mortality

Richard Holbrooke 1941-2010

Michael DeBakey, MD 1908-2008
Aortic Dissection: Familial in 25%

Tex Ritter
1905-1974

John Ritter
1948-2003
Autosomal dominant traits

- Familial aortic aneurysm (with dissection typically at a diameter > 5 cm)
- Familial aortic dissection (at normal or only slightly increased diameter)
- Differentiating between the 2 imprecise
Aortic Aneurysm

Other Associations

• Bicuspid aortic valve, coarctation, aortic aneurysm
  – Bicuspid aortic valve occurs in 1-1.5% of all humans
Marfan Syndrome

Cardiovascular features

- aortic root dilatation
- aortic dissection
- aortic regurgitation
- mitral valve prolapse
Marfan Syndrome

Understanding Natural History: Aortic Root Dilatation

- Progressive
  - May be congenital
  - Rate of dilatation variable
- Rarely extends beyond mid-ascending aorta
Marfan Syndrome

Aortic Root Dilatation: *Complications*

- Aortic regurgitation
  - CHF
  - Sudden death
- Aortic dissection
  - Sudden death
  - MI
  - Organ ischemia
    - Stroke
  - Late rupture
Marfan Syndrome

CV Surgical Therapy: *The Bentall Revolution*

The Composite Graft

## Marfan Syndrome

### CV Surgery: *Long-term Results*

<table>
<thead>
<tr>
<th>Timing of surgery</th>
<th>10-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective repair</td>
<td>455 pts 84%</td>
</tr>
<tr>
<td>Urgent (1-7 d)</td>
<td>117 74%</td>
</tr>
<tr>
<td>Emergency (&lt;24h)</td>
<td>103 66%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>75%</strong></td>
</tr>
</tbody>
</table>

Marfan Syndrome
Complex Aortic Surgery

E. Stanley Crawford
Aortic Root Dilatation
Medical Therapy

β-adrenergic blockade in 1978
Studies in turkeys
Experience in abdominal aortic aneurysm in humans
Anecdotes in Marfan syndrome, +/-
Marfan Syndrome

β-adrenergic Blockade: Effectiveness

Medical Therapy Involves Trade-offs
Applicable to All Aortopathies

• Medication
  – Benefits vs. being tied to a pill & side effects

• Exercise modification
  – Relevant to Athletics & Occupation
    • Benefits vs. loss of enjoyment & esteem
    • Occasionally, loss of income
  – Loss of job or limitations on using skills
Marfan Syndrome
Life Expectancy in the mid-90’s

- Increased awareness → Earlier diagnosis
- Regular follow-up
- Exercise modulation
- β-adrenergic blockade
- Prophylactic surgery
- Counseling about pregnancy

Silverman et al. *AJC* 1995;75:157-60
35 y/o man with sudden, severe chest pain.
No PCP. No health insurance.
1st ER: dx’d viral syndrome
2nd ER: dx’d food poisoning
On the 3rd day, still feeling unwell went to the theater. The next morning, found dead.
Autopsy: Aortic root aneurysm with ruptured type A dissection
Marfan Syndrome
Failure to Diagnose

THE WRONG CALL
Two ERs failed to save Rent playwright Jonathan Larson's life. How did it happen?

In the year since the opening of the first Broadway musical Rent, a father holding onto his son's final legacy has seen his dream of dreams come true. It was on the eve of the show's debut just over a year ago that Jonathan Larson, its 30-year-old creator, died of an aortic aneurysm, a blood-filled balloon in the artery that carries blood from the heart to the lungs. For the older Larson, everything that has happened since—two tours, the Pulitzer Prize, the critical acclaim—have merely served as reminders of one thing: "Jonathan," he says, "I wish I were here."

For all the irony of Jonathan Larson's death on the eve of meteoric success, more ironic is the possibility that his life might have been saved. In the final four days of his life, Larson had been rushed to two New York City emergency rooms complaining of chest pain, only to be

This X ray, taken a day before his death last year, may have signaled an ominous heart problem, yet Larson, with Lucy in '79, was told he had a virus.

Jonathan Larson
Marfan Syndrome
Search for a Cause

Mutations in \textit{FBN1}
Dietz et al 1991
Marfan Syndrome
Search for a Cause

Mutations in \textit{FBN1}

Dietz et al. \textit{Nature}
1991;352:337-339
# Marfan Syndrome

## Utility of \textit{FBN1} Testing: Limitations

Mutations in \textit{FBN1} Associated with Phenotypes Other Than MFS

<table>
<thead>
<tr>
<th>Mutation</th>
<th>AA change</th>
<th>Exon &amp; type</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>(364)C→T</td>
<td>R122C</td>
<td>4 EGF(ncb)</td>
<td>atypical skeletal, no CV</td>
</tr>
<tr>
<td>(3379)G→A</td>
<td>G1127S</td>
<td>27 EGF(cb)</td>
<td>familial aortic aneurysm</td>
</tr>
<tr>
<td>(5138)ins4</td>
<td>frame shift</td>
<td>41 TGFßBP</td>
<td>MASS</td>
</tr>
<tr>
<td>(7339)G→A</td>
<td>E2447K</td>
<td>59 EGF(cb)</td>
<td>familial ectopia lentis</td>
</tr>
<tr>
<td>(8176)C→T</td>
<td>R2726W</td>
<td>64 CT</td>
<td>familial tall stature</td>
</tr>
<tr>
<td></td>
<td>G1796E</td>
<td>EGF(cb)</td>
<td>Scheuermann kyphosis</td>
</tr>
<tr>
<td>Genomic deletion</td>
<td></td>
<td>9-11</td>
<td>Weill-Marchesani syndrome</td>
</tr>
</tbody>
</table>
Phenotypes Associated with Mutations in *FBN1*

**Marfan syndrome**

**Weill-Marchesani syndrome**

**Gelophysic dysplasia**
Marfan Syndrome
Studies of Pathogenesis

Long-standing perceptions are incorrect
The microfibril is not simply a reinforcing rod in the extracellular matrix
Microfibrils connect cell membranes to the matrix; defective microfibrils alters the phenotype of the smooth muscle cell
Microfibrils are mediators of signaling pathways, especially transforming growth factor β1 (TGFβ1)
Marfan Syndrome
Studies of Pathogenesis

Binding the large latent complex (LLC) to fibrillin keeps TGFβ1 inactive
Mutations in fibrillin-1 lead to increased activity of TGFβ1, which can be crucial at early stages of development.
Disorders of TGFβ Receptors:
Loeys-Dietz Syndrome

- Pleiotropic features in
  - Cardiovascular
  - Craniofacial
  - Neurocognitive
  - Skeletal development

Genetic Determinants of Aortic Disease

*Genes Involved in TGF-β Signaling*

- *TGFBR1*
- *TGFBR2*
- *SMAD3*
- *TGFB2*

OMIM® classifies all phenotypes associated with these genes as Loeys-Dietz syndrome. This is inappropriate and detrimental! Reserve LDS for the phenotype originally described.
Genetic Determinants of Aortic Disease
Many are Vascular Smooth Muscle Genes

Annu. Rev. Genomics Hum. Genet. 9:283–302
Mutations in Cytoskeletal Proteins

- *ACTA2* Accounts for ~20% of HTAD
- *MYH11*
- *MYLK*
- *PRKG1*
Mutations in *ACTA2*

- Cause not just an aortopathy, but an arteriopathy
  - Dissection of medium-caliber arteries
    - Carotids & vertebrales
  - Arterial tortuosity
  - Moyamoya malformation
Mutations in \textit{ACTA2}

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Mutations in *ACTA2*

- 10 - 14% of familial TAAD
- Most genotype-phenotype correlation:
  - Stroke, early coronary artery disease, livedo reticularis and iris flocculi can be seen
Screening for Arteriopathy
Screening for Arteriopathy
Moyamoya malformation
Mutations in Proteins that Increase Oxidative Stress

• **MAT2A**
  – α subunit of methionine adenosyltransferase II
Molecular Genetic Testing for Arteriopathies

- Panels offered by many commercial labs
  - Number of genes on each lab’s panel increases almost monthly—now > 25
- Can target a suspected gene (or two), then reflex to the rest
- Can reflex to deletion/duplication testing if sequencing unrevealing
Molecular Genetic Testing for Arteriopathies

- Likelihood of a VUS (variant of uncertain significance) is high
  - A duty to re-contact when you are smarter
- $3-4k
- Covered by most insurance plans
- Once a mutation is found in the proband, cost of screening relatives is minimal
Heritable Thoracic Aortic Diseases
Genetic Aortopathies

ECM TGF-β Vasculopathies

- Risk for Aneurysms in the aorta, branch arteries off the aorta and cerebral arteries
- Aortic root aneurysms
- MFS-like skeletal and facial features, bifid or broad uvula, and thin skin may be present
- Other features of clinical spectrum are still to be discovered

FTAAD
SMC Contractile Vasculopathy

- Aneurysms may involve the root and/or ascending aorta
- PDA may be present with ACTA2 and MYH11
- Occlusive vascular disease, such as stroke and coronary artery, may occur with ACTA2
- Livedo reticularis and iris floculi may be present with ACTA2

* Mutations in these genes cause additional disorders that have a lower risk for thoracic aortic disease.
Thank You
Questions?