Thoracic Aortic Aneurysms with a Genetic Basis

Aws Hamid¹, Elizabeth Lee¹, Maryam Ghadimi Mahani¹, Brian Smiley¹, Jimmy C Lu¹,², Adam L Dorfman¹,², Prachi P Agarwal¹

Department of Radiology, University of Michigan¹
Department of Pediatrics, University of Michigan²
Disclosures

None
Goals and Objectives

• To familiarize imagers with the spectrum of syndromic and non-syndromic familial thoracic aortic aneurysms.

• To describe the role of CT and MR imaging.

• To outline the recommendations for detection, monitoring and management.

• To highlight recent advances and emerging concepts.
Introduction

- Aortic aneurysms with a genetic basis include syndromic and non-syndromic familial aortopathies.
- Aortic dilatation occurs at an earlier age and predisposes to fatal aortic complications like dissection and rupture.
- Effective screening and surveillance allows for early diagnosis.
- Management guidelines are more aggressive for genetic aortopathies compared to sporadic thoracic aneurysms.
Spectrum of Aortic Aneurysms

- **Syndromic**
  - e.g. Marfan, Loeys-Dietz, Ehlers-Danlos, Turner

- **Non-syndromic**
  - Familial (Positive Family History)
  - Sporadic (Negative Family History)

Compared to sporadic forms, patients with familial aneurysms are younger, have a faster annual growth rate and stronger genetic predisposition.
Genetic Landscape of Thoracic Aortic Aneurysms

- The genetic basis of thoracic aortic aneurysms (TAAs) is highly heterogeneous.

- A variety of genes are implicated.

- There are three main pathophysiologic mechanisms leading to aneurysm formation.

Genes encoding for extracellular matrix (e.g. FBN1)

TGF beta signaling (e.g. TGFBR1)

Smooth muscle cell contractile apparatus (e.g. PRKG1)

Major categories of genes associated with syndromic and non syndromic aortic aneurysms.

Key syndromes to consider include:

- **Marfan syndrome**
  - Characterized by a variety of skeletal (joint laxity and overgrowth), ocular (ectopia lentis and myopia), skin (striae), and cardiovascular (aortic root aneurysm or dissection and mitral valve prolapse) abnormalities.
  - Typical associated with hypertelorism, bifid uvula or cleft palate, and arterial tortuosity with widespread aortic aneurysms.
  - Autosomal recessive disease with variable expression.
  - Mutation involving several genes such as TGFBR1, TGFBR2, and SMAD3.
  - Rapidly progressive aortic aneurysm is a distinct feature.
  - Aortic root aneurysms occur early in life.

- **Loeys-Dietz syndrome (LDS)**
  - Vascular form is a rare autosomal dominant disease.
  - Thin skin, easy bruising, tissue fragility (vascular and intestinal rupture).
  - Involves mutation in the COL3A1 gene encoding for type III collagen synthesis.

- **Ehlers-Danlos syndrome**
  - Cardiovascular manifestations include bicuspid aortic valve, aortic coarctation and dilatation, and anomalous pulmonary veins.

- **Turner syndrome**
  - Characterized by a variety of skeletal (joint laxity and overgrowth), ocular (ectopia lentis and myopia), skin (striae), and cardiovascular (aortic root aneurysm or dissection and mitral valve prolapse) abnormalities.
  - 45, X = complete or partial absence of sex chromosome.
  - Phenotypically female.
  - Mutation in gene coding for fibrillin-1.
Other Syndromes

- A few other rare syndromes are associated with aortic aneurysms including:
  - Shprintzen-Goldberg syndrome
  - FBN2-related Beal's syndrome (congenital contractural arachnodactyly)
  - Arterial tortuosity syndrome
  - Polycystic kidney disease

The above rare syndromes are not the focus of this exhibit.
Marfan Syndrome

• Commonest connective tissue disorder with aortic aneurysms.

• Autosomal dominant inheritance

• Clinical diagnosis established by revised Ghent criteria.

• Mutation in gene fibrillin-1 (FBN1) leads to loss of elastin and aortic wall integrity.
Marfan Syndrome: Cardiovascular Manifestations

- Aortic Aneurysms: Predominantly involve the aortic root.

- Classic appearance of annuloaortic ectasia: Dilatation of the annulus and sinuses with effaced sinotubular junction.

- Thoracoabdominal and peripheral arterial dilatation occurs in 10-20%.

- Mitral and tricuspid valve prolapse and regurgitation.
### Marfan Syndrome: Indications for Surgery

| External diameter of the aortic root/ascending aorta of 5.0 cm | Family history of aortic dissection at a diameter <5.0 cm or the presence of significant aortic regurgitation | Rapid growth of >0.5 cm /y | Prophylactic replacement of aortic root/ascending aorta if diameter exceeds 4 cm in female planning for pregnancy* |

* Increased risk of dissection at lower diameters in pregnancy.

If the patient is not a candidate for surgery, imaging follow up is recommended:
- Baseline, 6 months then annually if stable
- Sizes > 4.5 cm or growing should be followed more frequently

2010 ACCF/AHA/AATS/ACR/ASA/SCAI/SIR/STS/SVM Guidelines for Diagnosis and Management of Patients With Thoracic Aortic Disease.
Loeys-Dietz Syndrome (LDS): Manifestations

- First described in 2005.
- Autosomal dominant inheritance.
- Mutations in TGFBR1/2.
- Additional genes identified recently are SMAD3, TGFB2/3.
- Several craniofacial abnormalities have been described.
  - Bifid uvula
  - Cleft palate
  - Hypertelorism
  - Blue sclera
  - Retrognathia

- Skeletal features
  - Similar to Marfan syndrome
  - Craniosynostosis
Loeys-Dietz Syndrome (LDS): Cardiovascular Manifestations

• Vascular
  - Aortic aneurysm
  - Tortuous vertebral arteries
  - Pulmonary arterial dilatation
# Loeys-Dietz syndrome: Indications for Surgery

<table>
<thead>
<tr>
<th>Adults:</th>
<th>Young children:</th>
<th>Pregnancy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic diameter &gt; 4.2 cm on echo or &gt; 4.4 to 4.6 cm on CTA/MRA</td>
<td>Aortic diameter over 99\textsuperscript{th} percentile for age and aortic valve annulus diameter between 1.8-2.0 cm</td>
<td>Prophylactic surgery is not indicated although risk is higher for dissection (10% if aortic dilatation &gt; 4 cm)</td>
</tr>
</tbody>
</table>

Imaging follow-up for non-surgical patients: 6 months, then annually from the head to pelvis.

---

2010 ACCF/AHA/AATS/ACR/ASA/SCAI/SIR/STS/SVM Guidelines for Diagnosis and Management of Patients With Thoracic Aortic Disease.
Ehlers-Danlos Syndrome (EDS): Manifestations

- Heterogeneous group of disorders
- Autosomal dominant
- Six subtypes.
  - The commonest subtypes are I and II which are characterized by transparent skin that bruises easily and fragile tissue.
    - Vascular manifestations are rare in these forms.
  - Vascular EDS is type IV.
    - Due to mutation in COL3A1 gene that encodes type III procollagen.
Ehlers-Danlos Syndrome (EDS): Cardiovascular Manifestations

- Effects medium and large arteries.
- Results in dilatation, dissection, and rupture.
- Prognosis is poor. Surgery and interventions can be challenging due to vascular fragility.

3D SSFP MRI demonstrates ascending aortic dilatation in a 22 year old male with EDS.

Axial contrast enhanced CT demonstrates ascending aortic dilatation in 45 year old male with EDS. Also note pulmonary artery dilatation.
Ehlers-Danlos Syndrome: Management

**Surgical repair**
- Limited by risk of rupture, bleeding tendency, tissue fragility, and poor wound healing.
- Careful handling of tissue and use of special sutures is recommended.

**Pregnancy**
- Poor outcome (rupture of vessels and uterus)
Turner Syndrome (TS)

- **45, X = complete or partial absence of sex chromosome.**
  - Phenotypically female

- **Characteristics**
  - Primary amenorrhea
  - Short stature
  - Broad chest
  - Webbed neck
  - Low hairline
  - Low-set ears
Turner Syndrome (TS): Cardiovascular Manifestations

- Cardiovascular disease
  - Bicuspid aortic valve (10% to 25%)
  - Aortic coarctation (8%)
  - Aortic dilation (33%)
  - Aortic dissection (1.4%)
  - Risk increases with bicuspid aortic valve, coarctation and hypertension

Bicuspid aortic valve in a patient with Turner syndrome.

Ascending aortic aneurysm (arrow) and coarctation (arrowhead) in Turner syndrome.
Turner Syndrome (TS) and Aortic Aneurysm: Special Considerations

- Normal ascending aortic diameters are related to body size and age.
- TS patients are small, hence their aortic diameter is smaller than the average for age-matched control females.
- Data on aortic diameters normalized to body surface area for adults with TS are available.

33 year old female with Turner syndrome, status post Dacron patch repair of coarctation and augmentation of hypoplastic aortic arch. Note the residual narrowing in the distal aortic arch (arrow) and ascending aortic aneurysm (*).
Turner Syndrome and Aortic Aneurysm: Special Considerations

• Available data suggests that unadjusted values greater than 28-32 mm will identify patients with diameters greater than 95% of controls.

• If aortic dilatation is defined as ascending-to-descending aortic diameter >1.5, then 33% of TS patients have aortic dilatation.

33 year old female with Turner syndrome and ascending aortic aneurysm (*). Also note the unusual course of left innominate vein (coursing posterior to the carina) (arrow).
Partial anomalous pulmonary venous return seen in 13% of TS patients
- <1% in general population

Frequently involves the left upper pulmonary vein.

Clinical significance depends on degree of shunt.

Right superior pulmonary vein draining to SVC in Turner syndrome. This was missed on echocardiography. MRI has an advantage over echo in this regard.
### Turner Syndrome: Surveillance

| All patients require imaging evaluation. | MRI should be performed at least once when the patient is old enough to cooperate. | For patients with no risk factors such as bicuspid aortic valve, coarctation, dilated aorta, re-evaluation of the aorta is suggested every 5 to 10 years or if clinically indicated (e.g., attempting pregnancy or transition to an adult clinic). |
Familial Thoracic Aortic Aneurysms

- Mutations in genes encoding for smooth muscle contractile apparatus e.g. ACTA 2, MYH1, MYLK and PRKAG1 have been implicated.

- There is also some overlap with genes involved with syndromic aortopathies such as TGFBR2, FBN1, and SMAD3.

- Management depends on the specific gene mutation.

40 year old M with familial aortic aneurysm presenting with chest pain. Patient was known to have SMAD3 mutation. Note aortic rupture (arrow), hemothorax (*) and aortic dissection(arrowhead).
## Familial Thoracic Aortic Diseases: Management

<table>
<thead>
<tr>
<th>Identification of the underlying genetic mutation leading to familial thoracic aortic aneurysms and dissections provides critical clinical information for the family.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only family members who harbor mutations need to be routinely imaged for aortic disease.</td>
</tr>
<tr>
<td>Identification of the underlying mutation may lead to different management of the aortic disease.</td>
</tr>
</tbody>
</table>
Surveillance Aortic Imaging

- **Goals:**
  - Reproducible and accurate measurement of aneurysm size.
  - Evaluation of interval growth of aneurysm.

- CT and MRI provide 3D datasets.
- MR avoids cumulative radiation and is preferred for surveillance.
- MR can be degraded by artifacts from metallic devices.

Sagittal contrast enhanced CT

Sagittal Gad enhanced MRA showing artifact due to stent used for treating coarctation.
Aortic Measurements: Do’s and Don’t’s

DO:
- Measurements should be made at reproducible anatomic landmarks.
- External diameter (outer wall to outer wall) should be measured on CT and MRI.
- Measurements are made perpendicular to axis of flow.

DON’T:
- Measurements from straight axial images may not be representative depending on aortic tortuosity. True double oblique measurements should be obtained.
Aortic Root Measurement

- Can be challenging due to clover shape.
- Measurements can be done as cusp-commissure or cusp-cusp.
- Cusp-cusp measurements are 2-3 mm larger than cusp-commissure dimensions.
- Important to report the measurement technique used.
- This enables consistency and accurate comparisons on follow-up.

Cusp-commissure measurements are shown on this MR SSFP image oriented perpendicular to the aortic root.
Emerging Concepts

- Tortuosity indices (vertebral and aortic) have been described and linked to poor patient outcomes.
Vertebral Tortuosity Index (VTI)

• Some degree of “physiological” tortuosity of the vertebral arteries above the level of the C2 vertebral body is not unusual.

• The presence of corkscrew tortuosity is, however, most often pathologic.

• The degree of vertebral artery tortuosity can be quantified by vertebral tortuosity index (VTI).
  - $VTI = \left[\frac{\text{actual/straight length} - 1}{100}\right]$
Vertebral Tortuosity Index (VTI)

VTI = \[(\text{actual length}/\text{straight length})-1\] x 100

Actual length = 18 cm
Straight length = 10 cm
VTI = \[(18/10)-1\] x 100 = 80

- VTI > 50 is highly associated with Loeys-Dietz Syndrome compared to other aortopathies.
- VTI > 20 in combination with an elevated aortic root Z-score (>4.5) has been shown to be a strong predictor of adverse outcome (requirement for cardiac/aortic surgery, dissection and aneurysms)*

Aortic tortuosity index (ATI)

Marfan patients with ATI > 1.95 have been shown to have a 12-fold increased risk of aortic dissection.

Conclusions and Take Home Message

• Early diagnosis of genetic aortopathies is crucial for appropriate management.

• Loeys-Dietz syndrome has the lowest threshold among genetic aortopathies for surgical intervention.

• Aortic caliber should be interpreted in context of patient size and BSA. This becomes particularly important in Turner syndrome where patients have short stature.

• Knowledge of tortuosity indices has prognostic importance and should be included in vascular imaging reports.
References


Thank you

Presenting Author: *Aws Hamid*
Email address: awssshah@med.umich.edu