Update on aortopathy

RCP meeting
October 2017

Dr Paul Clift
Queen Elizabeth Hospital Birmingham
Aortic dissection

- Type A
- Type B

Hereditary aortopathy

- Who to suspect
- What to do
- management
Aortic dissection

- Type A
- Type B

<table>
<thead>
<tr>
<th>Percentage</th>
<th>60%</th>
<th>10–15%</th>
<th>25–30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>DeBakey I</td>
<td>DeBakey II</td>
<td>DeBakey III</td>
</tr>
<tr>
<td></td>
<td>Stanford A (Proximal)</td>
<td>Stanford B (Distal)</td>
<td></td>
</tr>
</tbody>
</table>
Aortic dissection

• Type A

• Type B

Cheung et al 2012
Aortic dissection

- Type A

- Type B
• Type A Dissection

Clinical suspicion as part of any chest pain presentation

Ripping pain through to the back

High index of suspicion in pregnancy, any known connective tissue disease or any family history

Contrast CT scan is diagnostic

Surgical management within first 24 hours is mandated

Surgery is life-saving and usually carried out in most cardiothoracic units
• Type B Dissection
US trends

Fig. 3. Rates of total thoracic and thoracoabdominal aortic aneurysm repair (diamonds), open repair (squares) and endovascular repair (triangles) in Medicare patients, 1998–2007. CI, Confidence interval.

Scali et al. J Vasc Surg. Author manuscript; available in PMC 2012 March 27.

Total Repair Rate Ratio 1.7
(95% CI 1.5-1.8)

Open Repair Rate Ratio 1.1
(95% CI 0.9-1.3)

Endo Repair Rate Ratio 29.3
(95% CI 22.9-36.6)
US outcomes

Survival Following Thoracic Aneurysm Repair

- **Intact**
  - Log rank p<0.001

- **Ruptured**
  - Log rank p=0.01

**Adjusted analyses representing male, non-black patients under age 75, with Charlson score < 2, performed after 2009**

- **Open**
- **TEVAR**

Years Following Repair:
- 0
- 1
- 2
- 3
- 4
- 5

Proportion Surviving:
- 1.00
- 0.75
- 0.50
- 0.25
- 0.00

NB: Standard Errors: all <0.10 at 5 years: Intact Open=0.008, Intact TEVAR=0.02, Ruptured Open=0.01, Ruptured TEVAR=0.05

Goodney et al Circulation. 2011
TEVAR v medical therapy in chronic Type B dissection (INSTEAD trial)

A Cumulative survival within 24 months after randomization

B Freedom from aorta-related mortality within 24 months after randomization

C INSTEAD: Freedom from progressive aortic disease

Nienaber et al Circulation 2009
Can we define who will require a TEVAR?

combined end point of progression and adverse events (aorta-related death, conversion, and ancillary interventions, including the second stent graft procedure, access revision, peripheral interventions)

INSTEAD XL trial

Nienaber et al 2013
Can we define who will require a TEVAR?

post-dissection resistant hypertension

large (≥10 mm) or single entry tears

EARTLY INTERVENTION (<14 days)
is associated with a poor outcome

ongoing tissue inflammation assessed on PET

total diameter of dissected aorta at presentation of >35 mm

false lumen diameter of >20 mm

Nienaber et al 2016
Surgical options – chronic dissection

• Indications
  • >55mm diameter descending aorta
  • >4mm growth in 12 months
  • Malperfusion
Surgical options – chronic dissection

The trunk evolution

1982
Birth of ET
H. Borst

1992
ET modified
distal suture
crawford-
svensson

2004
Branched ET
neri

2003
Birth of FET
chavan-haverich

2007
FET hybrid graft

2012
Branched FET
Surgical options – chronic dissection
Thoraco-abdominal aneurysm
Thoraco-abdominal aneurysm
Volume to outcome relationship

especially during the chronic phases of the disease. Indeed, for most aortic surgeries, a hospital volume–outcome relationship can be demonstrated. Regarding the thoracic aorta, in a prospective cardio-thoracic surgery-specific clinical database including over 13,000 patients undergoing elective aortic root and aortic valve-ascending (EVAR).\(^\text{19}\) Overall, these data support the need to establish centres of excellence, so-called ‘aortic teams’, throughout Europe; however, in emergency cases (e.g. Type A AD or ruptured AAA) the transfer of a patient should be avoided, if sufficient medical and surgical facilities and expertise are available locally.
Key points

• Type A dissection is a surgical emergency

• Type B dissection has better prognosis but high risk patients may benefit from endovascular repair

• All patients should ideally be referred for discussion at a relevant MDT to form long term management strategy
Familial Aortopathies
Presentation

• Index case usually less than 60 years of age

  • Aortic dissection
  • Unexpected finding on routine investigation
  • Complication of congenital heart defect/syndrome

• Family history
Age at presentation
Birmingham aortic dissection data

<table>
<thead>
<tr>
<th>Age Group</th>
<th>1. Died Within 3 Days</th>
<th>2. Died 3 - 30 days</th>
<th>3. Died 1 Month - 1 Year</th>
<th>4. Died After A Year</th>
<th>Total Died</th>
<th>Total Dissections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 0-20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2. 20-40</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>3. 40-60</td>
<td>9</td>
<td>2</td>
<td>6</td>
<td>14</td>
<td>31</td>
<td>97</td>
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<td>4. 60-80</td>
<td>11</td>
<td>8</td>
<td>12</td>
<td>25</td>
<td>56</td>
<td>159</td>
</tr>
<tr>
<td>5. Over 80</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26</strong></td>
<td><strong>16</strong></td>
<td><strong>24</strong></td>
<td><strong>48</strong></td>
<td><strong>114</strong></td>
<td><strong>323</strong></td>
</tr>
</tbody>
</table>

Aortic Dissection
Mortality By Age Group and Time Period

- 1. Died Within 3 Days
- 2. Died 3 - 30 days
- 3. Died 1 Month - 1 Year
- 4. Died After A Year
- 5. Over 80
Features suggestive of hereditary aortopathy

- Features suggestive of connective tissue disease
  - Joint abnormalities
  - Chest wall deformities
  - Kyphoscoliosis
  - Lens dislocation

- Early onset arthritis

- History of death following childbirth in family
Diagnosis of Marfan Syndrome

Aortic root aneurysm (AA) and ectopia lentis (EL) are now cardinal features.

With a family history of MFS:
- EL = MFS
- AA = MFS
- Systemic score >7 = MFS

With no family history:
- AA + EL = MFS
- AA and FBN1 = MFS
- AA and systemic score >7 = MFS
- EL and FBN1 = MFS

- Wrist AND thumb sign — 3 (wrist OR thumb sign — 1)
- Pectus carinatum deformity — 2 (pectus excavatum or chest asymmetry — 1)
- Hindfoot deformity — 2 (plain pes planus — 1)
- Pneumothorax — 2
- Dural ectasia — 2
- Protrusio acetabuli — 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis — 1
- Scoliosis or thoracolumbar kyphosis — 1
- Reduced elbow extension — 1
- Facial features (3/5) — 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae — 1
- Myopia > 3 diopters - 1
- Mitral valve prolapse (all types) — 1

Maximum total: 20 points; score ≥7 indicates systemic involvement; US/LS, upper segment/lower segment ratio.
Genetic basis of aortopathies/CTD

Van Laer Eur J Paed 2013
Aneurysm Syndromes Caused by Mutations in the TGF-β Receptor

Bart L. Loeys, M.D., Ph.D., Ulrike Schwarz, M.D., Tammy Holm, M.D., Bert L. Callewaert, M.D., George H. Thomas, Ph.D., Hariyadarshi Pannu, Ph.D., Julie F. De Backer, M.D., Gretchen L. Oswald, M.S., Sofie Symeens, B.S., Sylvie Manouvrier, M.D., Ph.D., Amy E. Roberts, M.D., Francesca Faravelli, M.D., M. Alba Greco, M.D., Reed E. Pyeritz, M.D., Ph.D., Dianna M. Milewicz, M.D., Ph.D., Paul J. Coucke, Ph.D., Duke E. Cameron, M.D., Alan C. Braverman, M.D., Peter H. Byers, M.D., Anne M. De Paepe, M.D., Ph.D., and Harry C. Dietz, M.D.
BGN COL1A2 COL3A1 COL5A1 COL5A2 EFEMP2
ELN EMILIN1 FBN1 FBN2 MFAP5 LOX
Extra-cellular Matrix genes

FLNA FOXE3 PRKG1 MAT2A MYH11 MYLK ACTA2
Smooth muscle genes

SK1 SLC2A10 SMAD2 SMAD3 SMAD4 TGFBR1 TGFBR2 TTGFBR2 TGFB3
Transforming growth factor Beta pathway

Less than 40% of families undergoing genetic testing
Features suggestive of hereditary aortopathy

Introduction
Loeys Dietz syndrome (LDS) was first described in 2005 as an AD connective tissue disorder caused by mutations in TGFBR2. LDS is characterised by aortic complications, craniofacial dysmorphism, and other systemic anomalies.

The key features of LDS are:
- Aortic complications, including aortic dissection and aneurysm
- Craniofacial dysmorphism
- Cardiovascular involvement
- Gastrointestinal anomalies
- Skin lesions
- Skeletal abnormalities

The genetic testing is performed by examining the TGFBR2 gene. The testing can be performed on blood samples from the patient and their family members.

What have we learnt?
- The incidence of LDS is estimated to be 1 in 500,000 live births.
- The incidence of LDS in the male population is higher than in the female population.
- The severity of the disease varies among individuals with LDS.
- The disease can be inherited in an autosomal dominant pattern.
- The disease can be diagnosed through genetic testing.

The diagnosis of LDS is based on the clinical presentation and genetic testing.

The family history shows a case series of LDS with typical clinical features.

B1: Age 44, Aortic dissection at age 42
B2: Aortic dissection at age 28 yrs postpartum
B3: RTA 48 yrs

Summary:
- Loeys Dietz Syndrome (LDS) is an inherited connective tissue disorder.
- The diagnosis is based on clinical presentation and genetic testing.
- The disease can be severe and requires careful management.
- Genetic testing is available to confirm the diagnosis and identify affected family members.
Features suggestive of hereditary aortopathy

Arterial tortuosity
Outcome of aortic surgery in patients with Loeys–Dietz syndrome primarily treated as having Marfan syndrome

Florian S. Schoenhoff, Christoph Mueller, Martin Czerny, Gabor Matyas, Alexander Kadner, Juerg Schmidli and Thierry Carrel

Retrospective review of 68 consecutive cases treated for TAA presumed to be MFS

Genotyping confirmed 30 MFS and 8 LD

12 years mean follow up

CONCLUSIONS Although early surgical intervention in LDS is warranted to avoid AAD, the current data suggest that once the diseased segment is repaired, there seems to be no additional burden in terms of mortality or reoperation rate compared with that in MFS patients, with or without confirmed FBN1 mutation.
Medical therapy

Science. 2006 April 7; 312(5770): 117–121.

Losartan, an AT1 Antagonist, Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome
Medical therapy
Key points

• Consider genetic causes in all and genetically test the young and those with a family history

• Basic science supports use of AII antagonists in hereditary aortopathy

• Lack of clinical trial basis

• Key role of aortic MDT in identification and management of all aortic patients
Thank you