Diseases of the aorta: Pediatric and adult clinical presentation of the main syndromes

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Short, up-to-date and comprehensive summary of the main syndromes....
Pubmed Results >10,000 publications/10 yrs

Thousands of Mutations

Logys-Dietz sy 1-4

Signalling

MRI – CT
When and how

heterogenities
Clinical
Which kind of aortic diseases are relevant for pediatric **AND** adult cardiologists?

Braunwald Heart Disease, 2014  
Dormand J CV MR 2013
What are the main syndromes? My Agenda for today....

- Familial thoracic aortic aneurysm and dissection syndrome (TAAD)

- Marfan Syndrome
  - What has changed with the new Ghent criteria?

- Loeys Dietz Syndrome
- Vascular Ehlers Danlos Syndrome
  - As differential diagnosis due to clinical overlap

- Bicuspid aortic valve aortopathy and Turner Syndrome
Starting with a Quiz: which vessel belongs to which person?

Morris et al. Circulation 2011
Loeys et al. NEJM 2006
Clinical presentation of the main syndromes ..... 

Family history counts
Awareness for suspicious (family) history to detect patients at risk is crucial

Familial thoracic aortic aneurysm and dissection syndrome (FTAAD)

20% of pts referred for surgery with thoracic aortic aneurysms or dissection have
- 1st degree relative with same problem (*Coady et al. 1999*)
- No clinical signs for Marfan, Loeys-Dietz syndrome etc.
- Mutations in genes TGFBR1/2, TGFB2, SMAD3 ......
- Often autosomal dominant – incomplete penetrance and high clinical variability even in one family

Pedigree in family with mutations in TGFBR3

*Loeys et al., J Am Coll Cardiol 2015*
Clinical manifestation of Marfan-syndrome –

what changed with the revised Ghent criteria, 2010?

Loeys et al. J Med Genet 2010
Criteria for Marfan-syndrome (revised Ghent-criteria 2010)

No family history

Dilatation of Sinus valsalva aortae (z-score ≥2) and one of the following criteria

- FBN1-gene mutation
- Ectopia lentis
- Systemic features (≥ 7 points)

Ectopia lentis

FBN1-gene mutation (with known aortic involvement)

Positive family history

One of the following criteria

- Dilatation of Sinus valsalva aortae
- Ectopia lentis
- Systemic features (≥ 7 points, no typical signs for DD)
Revised Ghent criteria – *discussion*...

**No family history**
- Dilatation of Sinus valsalva aortae (z-score ≥2) and one of the following criteria
- Ectopia lentis

**FBN1-gene mutation**
- Ectopia lentis
- Systemic features (≥ 7 points)

**Diagnostic gaps**
- No family history and FBN1-gene mutation and systemic features
  - check data base if mutation is known for aortic dilatation
- Ectopia lentis and FBN1-gene mutation as isolated entity

**Earlier diagnosis**, if cardiac involvement

**Mutation analysis**, if clinical signs typical for one of the differential dx
Criteria for Marfan-syndrome
(revised Ghent-criteria 2010)

-> Emphasis on two major criteria and genetics
### Systemic features

Maximum 20 pts, systemic involvement ≥7 pts

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist and thumb sign</td>
<td>3</td>
</tr>
<tr>
<td>Wrist or thumb sign</td>
<td>2</td>
</tr>
<tr>
<td>Pectus carinatum</td>
<td>2</td>
</tr>
<tr>
<td>Pectus excavatum/chest asymmetry</td>
<td>1</td>
</tr>
<tr>
<td>Hindfoot valgus</td>
<td>1</td>
</tr>
<tr>
<td>Pes planus</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>2</td>
</tr>
<tr>
<td>Protrusio acetabuli</td>
<td>2</td>
</tr>
<tr>
<td>Reduced US/LS and increased arm/height and no severe scoliosis</td>
<td>1</td>
</tr>
<tr>
<td>Scoliosis and thorakolumbar kyphosis</td>
<td>1</td>
</tr>
<tr>
<td>Reduced elbow extension</td>
<td>1</td>
</tr>
<tr>
<td>Skin stretch marks</td>
<td>1</td>
</tr>
<tr>
<td>Myopia &gt; 3 diopters</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
</tr>
<tr>
<td>Facial features (3/5)</td>
<td>1</td>
</tr>
<tr>
<td>(dolichocephalus, enophthalmus, malar hypoplasia, retrognathia, downslanting palpebral fissures)</td>
<td>1</td>
</tr>
</tbody>
</table>

*Highest diagnostic yield*
Systemic involvement

Thumb OR wrist sign 2 pts

Thumb AND wrist sign 3 pts
Skeletal manifestations

- Pectus excavatum
- Pectus carinatum
- Arachnodactyly
- Hindfoot valgus
Facial features

Dolichocephaly – down slanting palpebral fissures – malar hypoplasia – enophthalmus

High arched palate and dental crowding

Sponseller et al. 2010, Utreja and Evans 2009
Newborn with arachnodactyly, arthrogryposis and dilatation of aortic sinus

Langenbach et al. 2012

Gupta, Oman

Langenbach et al. 2012

Left atrium
Clinical course with 9 months

-> Splice acceptor mutation in Fibrillin-1 gene
Diagnosis:
Early manifestation of Marfan syndrome

- Mutations more often in certain exons (25/26)

- 50% mortality in first year of life due to cardiac complications

- Pharmacological therapy (Beta-Blocker, AT1-Antagonist, ACE-inhibitor) often no significant effects

- Revised Ghent criteria -> early diagnosis because of cardiac involvement
Loeys-Dietz Syndrome (Typ I) – a clinical triad

- Aortic aneurysms and arterial tortuosity
- Orbital hypertelorism, Craniosynostosis
- Bifid uvula or cleft palate

- Autosomal-dominant, mutations in TGFBR1, TGFBR2, TGFB2, SMAD3
...clinical signs of Loeys-Dietz syndrome at different ages

- Blue sclera
- Hypertelorism
- Exophthalmus
- Malar flattening
- Camptodactyly
- Arachnodactyly

Clinical spectrum in the largest cohort of Loeys-Dietz-Sy patients (Loeys et al. NEJM 2006)

- 98% aortic (root) aneurysms with risk for
  - thoracic aortic dissection > abdominal aortic dissection > intracerebral bleeding

- Dissection at low aortic diameters
- High incidence of pregnancy related complications
## Clinical overlap of main syndromes

<table>
<thead>
<tr>
<th>Marfan Syndrome</th>
<th>Loeys Dietz Syndrome Typ 1/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:10,000</td>
<td>&lt;1:100,000</td>
</tr>
<tr>
<td>Fibrillin gene</td>
<td>TGFBR1/2 gene, TGFB2 gene</td>
</tr>
<tr>
<td>Aortic dilatation</td>
<td>Aortic dilatation</td>
</tr>
<tr>
<td>Skeletal abnormalities</td>
<td>Skeletal abnormalities</td>
</tr>
<tr>
<td>Ectasia dura</td>
<td>Ectasia dura</td>
</tr>
<tr>
<td>Ectopia lentis</td>
<td>NO Ectopia lentis</td>
</tr>
<tr>
<td></td>
<td>Arterial tortuosity</td>
</tr>
<tr>
<td></td>
<td>Hypertelorism, craniosynostosis</td>
</tr>
<tr>
<td></td>
<td>Uvula bifida, cleft palate</td>
</tr>
<tr>
<td></td>
<td>Mental retardation (possible)</td>
</tr>
</tbody>
</table>
Loeys-Dietz Syndrome Type 2

Visible veins

Distended scars

Translucency of skin

Loeys et al, NEJM, 2005

Vascular Ehlers Danlos Syndrome

Visible veins

Distended scars

Easy bruising and bleeding

Sobey, Arch Dis Child 2015, Germain, Orphanet J Rare Dis 2007
Clinical overlap of main syndromes

<table>
<thead>
<tr>
<th>Loeys Dietz Syndrome Typ 2</th>
<th>Vascular Ehlers-Danlos Sy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1:1.000 00</td>
<td>1:50.000</td>
</tr>
<tr>
<td>TGFB1/2 gene</td>
<td>Collagen COL3A1 gene</td>
</tr>
<tr>
<td>No craniofacial abnormalities</td>
<td></td>
</tr>
<tr>
<td>Aortic dissection without / mild dilatation</td>
<td>Aortic dissection without / mild dilatation</td>
</tr>
<tr>
<td></td>
<td>Very friable vascular tissue!</td>
</tr>
<tr>
<td></td>
<td>Bowel / uterine rupture</td>
</tr>
<tr>
<td></td>
<td>High bleeding risk in trauma/ surgery</td>
</tr>
</tbody>
</table>
Disease specific risk for dissection

- **Marfan Syndrome**
  - Risk for dissection: Aortic root > 50 mm

- **Loeys-Dietz / Vascular Ehlers Danlos Syndrome**
  - Dissection without marked arterial dilatation (aorta and cerebral)

- **Loeys-Dietz with craniofacial features**
  - Highest risk for arterial rupture at early age and small dimensions

- **Vascular Ehlers Danlos Syndrome**
  - Highest risk during or immediately after vascular surgery

Mean survival depends on syndrome

- **Marfan Syndrome**
  - Untreated 45 yrs, when treated up to 70 yrs

- **Loeys-Dietz Syndrome (first described 2005)**
  - 37 yrs

- **Vascular Ehlers Danlos Syndrome**
  - 48 yrs
„Valvuloaortopathie“: Bicuspid aortic valve and aortic dilatation

- Most common congenital heart defect (1-2 % worldwide)
- Responsible for more deaths and complications than the sum of all other congenital heart defects
- Ascending aorta aneurysm, dissection, aortic valve stenosis and regurgitation
New classification of bicuspid aortic valves (based on orientation of the fused bicuspid aortic valve)

- **BAV-AP**
  - Fusion of right and left coronary cusp (more often)

- **BAV-RL**
  - Fusion of right or left coronary cusp and Non-coronary cusp (more rare)

For more details, see Buchner et al. Heart 2010, Kang et al. JACC 2013
Fusion configuration of the bicuspid aortic valve influences pattern of aortopathy

A  Right–left fusion pattern
   Jet to right anterior wall

B  Right–noncoronary fusion pattern
   Jet to posterior wall

Potential higher risk for aortic aneurysms

Clinical variety of bicuspid aortopathy

Risk of life-threatening complications

- Incidence about 8 times higher than in general population (0.03%/yr)
- 0.5%/yr with aneurysms and > 50yrs
- Open questions: difference in pattern / rate of aortic dilatation between pediatrics and adults? Genotype-Phenotype correlation and risk assessment?

Kang et al. JACC CV Imaging 2013

Michelena et al. Circulation 2014
Turner Syndrome

- 1:2.500 live-born females

- Diagnosis requires XO-genotype and clinical features
  - **Endocrine system:** short stature, ovarian dysfunction, diabetes mellitus, hypothyroidism...
  - **Cardiovascular system:** Coarctatio of aorta (5-10%), bicuspid aortic valve (20-30%), hypertension

Lymphedema  Webbed neck  Pterygium colli  Low hairline
- 20-25% of all TS have aortic dilatation
- No rapid progression of dilatation of aorta ascendens
- Incidence of aortic dissection in TS is 100-fold increased compared to normal population
- Dissection in childhood → congenital heart defect
- Dissection in adulthood → abnormal aortic valve, dilated aorta ascendens, arch anomalies, arterial hypertension

Neck webbing and shield chest is a risk factor for aortic dilatation
Guideline for Cardiovascular Monitoring of the TS study group (Bondy et al., 2007)

- **At time of diagnosis** -> blood pressure, ECG and echocardiography
- **Reevaluation at transition to adult clinic** -> echocardiography and MRI

Hjerrild et al. J CV Magn Res 2010
What are the potential benefits of an (early) genetic and clinical diagnosis?

- Different natural course and risk of aortic dissection
- Life style modification and education
- **Pharmacotherapy** -> Francesca Bonassin
- **Surgical approach** at an optimal time point and dependent on the underlying disease (different values for Loeys Dietz, Marfan and bicuspid aortic valve) -> Florian Schönhoff
Thank you very much for your attention