Loeys-Dietz Syndrome
- an update -

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CXR and volume rendered CT in a 10 month old baby girl with LDS
Molina-Sánchez, Cardiol Young 2017
Faculty Disclosure

The presenter has advised that the following presentation will NOT include discussion on any commercial products or service and that there are NO financial interests or relationships with any of the Commercial Supporters of this years Conference.
Loeys-Dietz syndrome

- First described 2005, letter to Nature Genetics
- “New aortic aneurysm syndrome”
  - Characterised by:
    - hypertelorism
    - bifid uvula +/- cleft palate
    - generalised arterial tortuosity
    - additionally: craniosynostosis, structural brain abnormalities, mental retardation, congenital heart disease
  - TGFβR 1 and 2 mutations
    - Increased TGFβ signaling
  - Phenotypic overlap with MFS (and SGS*), but
    - don’t meet criteria
    - manifestations in organs ‘beyond’ MFS
    - aneurysms tend to be “particularly aggressive and rupture at an early age”

(SGS = Shprintzen- Goldberg syndrome)
Vascular tortuosity in a 7 year old with LDS

Craniosynostosis
Hypertelorism
Bifid uvula
Scoliosis
Osteoarthritis
Arterial tortuosity
Extra aortic vascular involvement
Camptodactyly
Club foot
Blue sclerae
Thin skin with atrophic scars
Easy bruising
Joint hypermobility

(Loeys, NEJM 2006; Uike, BMC Research Notes 2013)
Update – How far have we come?

1. Always syndromic?
2. Diagnostic criteria?
3. Other genes? Genotype-phenotype relationship?
4. Is the vascular disease always aggressive?
5. Therapeutic consequences?
6. Different surgical approach?
7. Why does a specific diagnosis matter?
8. Conclusion
1. LDS is characterised as a syndromic aortopathy

• BUT patients are not all syndromic
  – Syndromic phenotype can vary within families
  – Modulators of genotype-phenotype relationship…..
    • Environmental?
    • Additional genetic?
    • Epigenetic factors?

Syndromic features understood to overlap particularly with Marfan syndrome and vascular EDS

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(Schepers, Human Mutation 2018)
Cautionary tale

- Type A dissection 40 treated surgically
- Ruptured brain aneurysm late 40’s, deceased
- Syndromic (Translucent skin, OA, carotid tortuosity)
- Type B dissection stent 31
- Prox extension requiring arch surgery cx stroke

UPDATE: contacted, offered testing re ?LDS… SMAD3 mutation confirmed in Father and Son
SAME mutation, MRA normal…. type B dissection 3/12 later
2. Diagnostic criteria?

**MFS**

- ✓ Family history
- ✓ Family history

- + EL
- + Syst ≥7
- + Ao Z ≥ 2 > 20; ≥ 3 <20

- Ao Z ≥ 2 + EL
- Ao Z ≥ 2 + FBN1
- Ao Z ≥ 2 + Syst ≥7
- EL + FBN1 + Ao

**MFS = Marfan syndrome**

**EL = ectopia lentis score**

**Syst = systemic features**

**Ao = aortic dilatation or dissection; z = z score**

- Vascular dissection or rupture only mentioned in vEDS/EDS IV EDS
- Ascending aortic aneurysm; only mentioned in spondylophydysplastic EDS (AR, rare)
  - updated nosology (2017)

LDS diagnostic criteria

• Proposed:
  – Proband:
    • Heterozygous pathogenic mutation in relevant gene + either
      • AoR enlargement (z score ≥ 2) or type A dissection OR
      • Characteristic craniofacial, skeletal, cutaneous and/or vascular manifestations
  – With a family history:
    • Diagnosis can be made in at risk relatives if they have the mutation (“even if vascular involvement or other features not yet apparent”)

(MacCarrick, Genet Med 2014; Schepers Human Mutation 2018)
3. Are there other genes identified?

- YES: LDS now recognised to be caused by:
  - $TGF\beta R\ 1\ and\ 2$ (as in original report) and also
  - $SMAD2, SMAD\ 3, TGF\beta 2, TGF\beta 3$

Most clinical genetic services offer aortopathy panel approach
Genotype – Phenotype relationship?

Relationships are generalisations, don’t always hold true….

- OA-Aneurysm syndrome = LDS3 BUT not all SMAD3+ LDS have osteoarthritis
- Said to have similar severity of aortic disease, and lesser disease severity down the table (*but how much does that reflect the far smaller # cases with other genes identified?*)

- HOWEVER very significant intrafamilial and interfamilial variation accepted, so not a straight genotype=phenotype story

<table>
<thead>
<tr>
<th>LDS subtype</th>
<th>Gene</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDS type 1</td>
<td>TGFBRI1</td>
<td>20–25%</td>
</tr>
<tr>
<td>LDS type 2</td>
<td>TGFBRI2</td>
<td>55–60%</td>
</tr>
<tr>
<td>LDS type 3</td>
<td>SMAD3</td>
<td>5–10%</td>
</tr>
<tr>
<td>LDS type 4</td>
<td>TGFB2</td>
<td>5–10%</td>
</tr>
<tr>
<td>LDS type 5</td>
<td>TGFB3</td>
<td>1–5%</td>
</tr>
<tr>
<td>LDS type 6</td>
<td>SMAD2</td>
<td>1–5%</td>
</tr>
</tbody>
</table>
4. Is the vascular disease *always* more aggressive?

• May be too early to truly know........
  – Ascertainment bias with ‘new’ conditions means that we identify most severely affected individuals ..... 
  – Many LDS have been ‘re-diagnosed’ from MFS
    • LDS account for the worst end of the spectrum clinically?

“In an ironic turn of events, the family that Victor introduced to me my first day at Johns Hopkins, has done very well, being followed as having MFS. However, when molecular genetic analysis was performed recently, their mutation is in SMAD3.”

(Pyeritz, one of the co discoverers of FBN1 as the genetic basis for MFS, Ann Cardiothorac Surg 2017)
Life expectancy – change over time

- **MFS:**
  - Average age death: 32 years, aortic cx 80% (n = 257)
  - Old data (1939–1970, 1 individual died 1903)
  - Clinical dx: “Full picture… arachnodactyly, chest deformity, kyphosis, lens dislocation, aortic dilatation or dissecting aneurysm” or “less than full picture” but members of affected family (Murdoch, NEJM 1972)
  - ‘Life expectancy now near normal’ thanks to the emergence of prophylactic aortic surgery (Pyeritz, Trends in CVS Med 2016)

- **LDS?**
  - TGFBR1: average age death 23 (n = 64)
  - TGFBR2: average age death 32 (n = 26) (Loeys, NEJM 2006)
  - TGFB R2 more often presented with aortic dilatation/ dissection/ death cf MFS BUT if diagnosed, very similar incidence of dissection and age as MFS (Attias, Circ 2009)
  - ‘Observed survival’ much better than initially reported (Jondeau, Circ CVS Genet 2016)
Literature: dissection earlier and in smaller vessels

Limited data:

- GenTAC - multicenter prospective registry of participants with genetically associated TAA. N = 1991, BUT only 38 had LDS and none dissected (Weinsaft, JACC 2016)
- 33 mutation+ and 25 deceased individuals (7 obligate carriers, 18 presumed, TGFBR1 and 2): median age 1st CVS event 50 (Teixido-Tura, Heart 2016)
- Surgical series 68 patients with 115 interventions, all operated on with a clinical +/- genetic dx of MFS, subsequently 17% reclassified to LDS: no difference in frequency of dissection, age at dissection or subsequent need for intervention (used aortic root of 45 – 50 mm as threshold for intervention) (Shoenhoff, Eur J Cardiotorac Surg 2014)
Largest publication gene\(^+\) LDS

- Montalcino Aortic Consortium
  - 15 centres worldwide
  - \(n = 441\) (228 families) - 176 \(TGFBR1\), 265 \(TGFBR2\)
    - \(TGF\beta R1\) males increased aortic risk
    - \(TGF\beta R2\) no gender associated aortic risk, BUT females at lower diameters
  - In 31 type A dissections (44% of all Type A): pre dissection AoR measure available:
    - 68.3 (± 23) mm \(TGFBR1\) vs
    - 51.8 (± 13.4) mm \(TGFBR2\) (\(p = 0.06\)).
    - In 7, it was ≤ 45 mm, of whom 6 were women with \(TGFBR2\)
  - Logistic regression – association with systemic features
  - 122 women had 316 pregnancies, diagnosis not made in 84% women at time; dissection in 5 preg (1.6%)

First aortic event

<table>
<thead>
<tr>
<th>Dissection</th>
<th>(TGFBR1)</th>
<th>(TGFBR2)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>18%</td>
<td>15%</td>
<td>ns</td>
</tr>
<tr>
<td>Type B</td>
<td>1.7%</td>
<td>6%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 5. Patients With Mutation Either in \(TGFBR1\) or \(TGFBR2\): Prognostic Value of Aortic Tortuosity and Extra-Aortic Features on Aortic Risk (Preventive Surgery or Dissection)

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(Jondeau, Circ CVS Genet 2016)
5. Therapeutic consequences

• Most importantly: make the diagnosis
  – Easy, if the patient is syndromic
  – Otherwise: clinical vigilance
    • investigate unexpected aortic test result AND
    • pay attention to personal and family history
    • ask ‘why?’ with every dissection
  – The sequelae: extent and frequency screening, threshold for action

Genetic aortopathy dx n = 760
- 221 MFS, 311 ns TAA, 228 BAV
- Ao dissection presentation commonest: ns TAA
  (Sherrah, JACC 2016)
6. Surgical timing?

- 1st post LDS recognition driven by 1 publication (hence class IIa LOE: C)
- Surgical series:
  - Retrospective series: n = 71, 6 deaths pre surgery (2 were AoR dissection). Elective op: mean AoR 4cm kids, 5cm adults (Williams, Ann Thorac Surg 2007)
  - Retrospective: n =79 patients with LDS and surgery; 48.1% <18y; 6 presented acute Type A dissection; reported AoR op mean 4.17 ± 0.97 cm (operative mortality 2.5%) (Patel, J Thor CVS Surg 2017)
- Post dissection, tendency for other aortic dilatation, increased risk for further interventions; one study reported 25% req further surg at average 5 y (Iba, Ann Thorac Surg 2012; Williams, Ann Thorac Surg 2015; Patel, J Thor CVS Surg 2017)
- Latest ESC guideline: more nuanced regarding threshold

### AHA G'lines, Hiratzka 2010

1. It is reasonable to consider surgical repair of the aorta in all adult patients with Loey-Dietz syndrome or a confirmed TGFBR1 or TGFBR2 mutation and an aortic diameter of 4.2 cm or greater by transesophageal echocardiogram (internal diameter) or 4.4 to 4.6 cm or greater by computed tomographic imaging and/or magnetic resonance imaging (external diameter)" (Level of Evidence: C)

### ESC Guidelines, Erbel 2014

- “Observation, in both children and adults, of a wide- spread and aggressive arteriopathy led to the recommendation of early operative intervention at ascending aortic diameters of ≥42 mm” (same ref as above)...."however a definite threshold cannot be proposed...requires further investigation"
- Management is tailored according to extensive vascular imaging … and family history…"
7. Why does a specific diagnosis matter?

- Aortic size, in isolation, insufficient to guide decision making in genetic aortopathies
- Currently, specific diagnosis:
  - Identify and educate patients at risk
  - Appears to improve prognosis (MFS, LDS)
  - Guides wider vascular screening and earlier intervention (even if exact size unclear)
- Future: gene specific intervention thresholds?

(Patel, J Thor CVS Surg 2017)

(Weinsaft, JACC 2016)
In conclusion – in 2018….we describe LDS as

- An inherited aortopathy
  - syndromic: *usually*
  - phenotypically: *variable*
  - # of genes: all affect the TGFB *pathway*
  - extra-aortic vascular manifestations: *wider vascular screening*
  - gene type and specific mutation appears to influence outcome – but data is small, particularly in the rarer subtypes and the intrafamilial phenotypic variation suggests that other factors are at play!

- What do we need?
  - **BETTER PREDICTOR OF DISSECTION THAN SIZE**
  - Better diagnostic tools to diagnose acute dissection
  - Collaboration; ongoing Registry collation (such as MAC)
    - Explore effect of different gene mutations
    - Drug trials
    - Prospective data collection to guide future treatment

ClinicalTrials.Gov
- No pharmaceutical trials in LDS listed
- “Pathogenetic Basis of Aortopathy and Aortic Valve Disease” includes LDS, Univ. Indiana, (est. completion 2028)
Thank you
Chances of finding a mutation?

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Certain (clinical or pathological)</td>
<td>2</td>
</tr>
<tr>
<td>High Risk Features</td>
<td></td>
</tr>
<tr>
<td>Any (Young, ECG, ECHO/MRI, multiple)</td>
<td>1</td>
</tr>
<tr>
<td>Pathology</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Any (syncope, arrhythmia, aborted cardiac arrest, sudden cardiac death, heart failure, AoD, other)</td>
<td>1</td>
</tr>
<tr>
<td>Multiple</td>
<td>1</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
</tr>
<tr>
<td>Any (FDR, SDR: same verified diagnosis OR same reported diagnosis plus other affected family members with same or related diagnosis or SUD)</td>
<td>1</td>
</tr>
<tr>
<td>Multiple relatives</td>
<td>1</td>
</tr>
<tr>
<td>Specific Diagnoses</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Arrhythmogenic cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Marfan syndrome</td>
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</tr>
</tbody>
</table>

**Score**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7th</th>
</tr>
</thead>
</table>

**Mutation Probability (%)**

<table>
<thead>
<tr>
<th></th>
<th>5</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
</tr>
</thead>
</table>

- **Clinical tool**
  - Derived from n = 125 (consecutive)
  - Validated in n = 40

- 23 had aortopathy, of whom 9 deceased
- AUC combined cohorts (n = 165): 0.88 for predicting positive mutation result

Relevant part of key reproduced below:
- Young < 50 y for thoracic aortic dissection or dilation
- Other high risk features = MFS phenotype with $\geq 7$ modified Ghent; Multiple aneurysms or vascular abnormalities
- AoD = aortic dilatation, dissection or surgery for either
Screening frequency

- “Computed tomography angiography or MRA of the entire vasculature (cerebral to pelvic) should be undertaken in the syndromic aortopathies where more widespread vascular involvement has been documented e.g. LDS, ATS. The interval has been suggested to be one year in the first instance and then at least two-yearly for LDS [25], though earlier recommendations had been for yearly MRA [23]. Abnormal results should translate into an increased screening frequency and referral as appropriate.

- (MacCarrick, Gen Med 2014; Hiratzka, Circ 2010)
Latest imaging guidelines

- Perpendicular to axis
- Largest diameter (as long as its perpendicular)
- Leading edge to leading edge* (includes 1 wall thickness)
- End diastole* (onset of QRS)

* Most literature

Multimodality Imaging of Diseases of the Thoracic Aorta in Adults: From the American Society of Echocardiography and the European Association of Cardiovascular Imaging
Endorsed by the Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance

(Goldstein, JASE 2015)
“Thus, for aortic measurements by CT and MRI, it is recommended to average the three sinus-to-sinus measurements in end-diastole in the sinus-of-Valsalva plane. When the sinuses are unusually asymmetric, it may be preferable to report the three measurements individually.”

“We emphasize that there is no standardized method for measuring the aorta across imaging modalities (echocardiography, CT, MRI, aortography). Although one of the major goals of this writing committee was to provide a uniform and universally accepted method to minimize differences among these various imaging modalities, no consensus could be reached”

(Davies, Nature Clin Med CVS Med 2007; Goldstein, JASE 2015)
Pharmacotherapy

Evolution in understanding over time

- FBN1: ‘Structural’ weakness of extracellular matrix (ECM)
- Early – mid 2000’s, appreciated that FBN1 regulator of TGFB signaling
- Discovery of LDS ‘cemented’ the new understanding
- Allows hope that pharmaceuticals might influence process

Altered TGFB signaling leading to increased TGFB

Mice data:
TGFB neutralising Ab’s
ARB’s

Human data:
Data has been less compelling (note trials in MFS)

(Loeys, Drug Disc Today 2015; Schepers, Hum Mut 2018)
Figure 20  95% confidence intervals for aortic root diameter at the sinuses of Valsalva based on body surface area in: children and adolescents (A), adults aged 20–39 years (B), and adults aged 40 years or more (C).\textsuperscript{132}
Diagnostic challenge relate to phenotypic overlap

There are few features that appear limited to a single diagnosis, and genetic testing has helped to differentiate between these conditions

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Marfan Syndrome</th>
<th>Loeys-Dietz Syndrome</th>
<th>Shprintzen-Goldberg Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FBN1</td>
<td>TGFBRI/TGFBRI2</td>
<td>SMAD3</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ectopia lentis</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cleft palate / bifid uvula</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Widely spaced eyes</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tall stature</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Arachnodactyly</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pectus deformity</td>
<td>++</td>
<td>+</td>
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<td>Clubfoot</td>
<td>-</td>
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<tr>
<td>Osteoarthritis</td>
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<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Aortic root aneurysm</td>
<td>+++</td>
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<td>Early dissection</td>
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<td>+++</td>
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<tr>
<td>Dural ectasia</td>
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<td>+</td>
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</tr>
</tbody>
</table>

(Loeys, Dietz; NCBI GeneReviews updated 2018)
Increasing voluntary contraction and increase in BP

*Danger of bodily collision

Increasing CO

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(Levine, JACC 2015)