Diagnosis, follow up and treatment of children with Marfan syndrome

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Part 1: Diagnosis

Part 2: Follow up and treatment
Part 1: Diagnosis
1896
1st description: AB. Marfan

1955
V. McKusick

1986
Berlin nosology

1996
Ghent-1 nosology

2010
Ghent-2 nosology

2016

Gabrielle

Heritable disorders of the connective tissue

120 YEARS OF MARFAN SYNDROME
CURRENT DIAGNOSTIC CRITERIA: REVISED GHENT

More weight to the 2 main diagnostic criteria:

- Ectopia lentis
- Aortic dilation/dissection

More relevance to the molecular diagnosis: FBN1 mutation

Loeys et al. J Med Genet 2010
Removal of some minor features:
Systemic score

<table>
<thead>
<tr>
<th>Features</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aranodactilia: positive wrist and/or pols signs</td>
<td>3 or 1</td>
</tr>
<tr>
<td>Pectus carinatum</td>
<td>2</td>
</tr>
<tr>
<td>Pectus excavatum or chest asymmetry</td>
<td>1</td>
</tr>
<tr>
<td>Scoliosis (&gt;20°) or thoracolumbar kyphosis</td>
<td>1</td>
</tr>
<tr>
<td>Hindfoot deformity</td>
<td>2</td>
</tr>
<tr>
<td>Pes planus</td>
<td>1</td>
</tr>
<tr>
<td>Reduced US/LS ratio and increased armspan</td>
<td>1</td>
</tr>
<tr>
<td>Reduced elbow extension (&lt;170°)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>2</td>
</tr>
<tr>
<td>Protusio acetabuli</td>
<td>2</td>
</tr>
<tr>
<td>Facial abnormalities (at least 3/5)</td>
<td>1</td>
</tr>
<tr>
<td>Myopia (&gt;3 dioptries)</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolaps</td>
<td>1</td>
</tr>
</tbody>
</table>

Different normal values for children:
- 0-5jr < 1
- 6-7jr < 0,95
- 8-9jr < 0,90
- >10jr < 0,85

Contractures are more common in children, specially at young ages

Usually associated with amblyopia in children

CURRENT DIAGNOSTIC CRITERIA: REVISED GHENT
CURRENT DIAGNOSTIC CRITERIA: REVISED GHENT

In the absence of family history:
1. Ao (Z≥2) + EL = MFS
2. Ao (Z≥2) + FBN1 = MFS
3. Ao (Z≥2) + Syst (≥7pts) = MFS
4. EL + FBN1 with known Ao = MFS

In the presence of family history:
5. EL + FH of MFS (as defined above) = MFS
6. Syst (≥7 pts) + FH of MFS (as defined above) = MFS
7. Ao (Z≥2 in adults, Z≥3 in children) + FH of MFS (as defined above) = MFS

Special considerations for children (<20jr):
Systemic score < 7, borderline aortic z-score: “Non-specific connective tissue disorder”
FBN1 mutation identified but z-score <3: “Potential Marfan”

Loeys et al. J Med Genet 2010
SOME CONSIDERATIONS
MEASUREMENT OF THE AORTIC ROOT

Girl, 10jr
Weight: 44Kg
Length: 166cm
BSA: 1.41

Leading edge to leading edge in diastole

Inner to inner in systole
AORTIC ROOT Z-SCORE

Girl, 10jr
Weight: 44Kg
Length: 166cm
BSA: 1,41

Leading edge to leading edge in diastole

Gautier: 2,11
Colan: 3,57

Inner to inner in systole

Colan: 2,44
Gautier: 1,66

Colan et al JACC 2006
Gautier et al JACC 2010
82% of children in all age groups had AoR z-score >2

70% of children in all age groups had EL
CHILDREN HAVE AN EVOLVING PHENOTYPE

Specially noticeable in the skeletal features

Stheneur C et al. Gen Med 2014
## KID-SMS: A RISK SCORE FOR SUSPECTED MARFAN

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Level</th>
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</thead>
<tbody>
<tr>
<td>Ao dilation + EL</td>
<td>Very high risk</td>
</tr>
<tr>
<td>Ao dilation + MVP and TVP + PA + 3 skeletal features</td>
<td>High risk</td>
</tr>
<tr>
<td>EL + MVP and TVP + PA</td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Ao dilation</td>
<td></td>
</tr>
</tbody>
</table>

130 children of which 60 were finally diagnosed with Marfan
- Kid-SMS: 97% at least moderate risk
Table 1: Demographic characteristics at diagnosis: Carriers of FBN1 <25yr

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>40</td>
</tr>
<tr>
<td>Male (%)</td>
<td>27 (69.2%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>8.41 (3.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>147.64 (29.05)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>35.32 (16.01)</td>
</tr>
<tr>
<td>BSA</td>
<td>1.15 (0.37)</td>
</tr>
<tr>
<td>AoR dilation (%)</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td>AoR diameter (mm)</td>
<td>29.5 (4.82)</td>
</tr>
<tr>
<td>AoR z-score</td>
<td>3.29 (1.95)</td>
</tr>
</tbody>
</table>

Figure 1: Reason for evaluation

- Family screening: 50%
- Marfanoid habitus: 17.5%
- Ectopia lentis: 15%
- Orthopedic problems: 17.5%

Data not published
OUR OWN EXPERIENCE IN GHENT

Figure 2: Percentage of patients fulfilling the revised Ghent nosology

- No: 23.1%
- Yes: 76.9%

Figure 3: Reasons for diagnosis

- AOH: 43.6%
- AO+SS: 15.4%
- EL+FA: 2.6%
- A0+FA: 15.4%

Data not published
OUR OWN EXPERIENCE IN GHENT

Figure 2: Percentage of patients fullfilling the revised Ghent nosology

- 76.9% Yes
- 23.1% No

Figure 4: Evolution during follow-up

- 80% Fullfilling N=8
- 20% Not-fullfilling N=2

Mean FU: 4.63 ± 2.95 yr

Marfan syndrome
Potential Marfan

Data not published
1. Revised Ghent nosology is a good diagnostic tool for children with Marfan syndrome

2. Around 75-80% of children were diagnosed with Marfan at the moment of presentation

3. Those patients which are classified as “potential Marfan” or “non-specific connective tissue disorder” need further FU

4. An easy stratification scale, specially for non-specialized centers, is de Kid-SMS
Part 2: Follow-up and treatment
MULTIDISCIPLINARY APPROACH

(Paediatric) Cardiologist

Orthopedic surgeon

Physiotherapist

Paediatrician

Ophtalmologist

Geneticist
FOLLOW UP

Individualized!!

1. Echocardiography:
   - Yearly if aortic z-score stable
   - Every 6 months if rapid growth
   - Consider 2-yearly if no aortic dilation

2. MRI:
   - To be consider if no anaesthesia is necessary (usually >10yr)
   - If surgery is planned
   - Every 3-5yr depending on the findings
OTHER ASPECTS TO CONSIDER

Mitral valve prolapse with/without regurgitation

Aortic insufficiency

Myocardial dysfunction and arrhythmias
GLOBAL MEDICAL TREATMENT

Medical treatment

Lifestyle changes

Surgical techniques
1. Which medical treatment?

2. When to start medical treatment?
WHICH MEDICAL TREATMENT?
Different options in medical treatment:

- Beta-blocker alone
- Angiotensine receptor blocker (ARB) alone
- Beta-blocker and ARB
- Other therapy: ACE-inhibitors, Calcium antagonists, doxycycline
CARDIOVASCULAR MEDICAL TREATMENT

1970
Simpson et al

BB to prevent dissection

1971
Halpern et al

1971
Clinical use of BB

1994
Shores et al

Losartan: potential treatment

2006
Habashi et al

Losartan vs Atenolol

2014
Lacro et al

Prevent dissection
TREATMENT WITH BETA BLOCKER

Control Group (N = 38)

Mean slope: 0.084/yr

Treatment Group (N = 32)

Mean slope: 0.023/yr

70 patients

Randomized

Propranolol
N=32
60% <18yr
Mean age 15.4yr

No treatment
N=38
68%<18yr
Mean age 14.5 yr

Follow up: 2.5-12.5yr

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Strategy</th>
<th>N</th>
<th>Age (yr)</th>
<th>FU-time (m)</th>
<th>AGR (mm/yr)</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tahernia 1994</td>
<td>Prospective</td>
<td>Propranolol</td>
<td>3</td>
<td>10±1, 8,3±4,9</td>
<td>40±18,3</td>
<td>0,28±0,25, 1,64±0,38</td>
<td></td>
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<tr>
<td></td>
<td>Randomized</td>
<td>No treatment</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not blinded</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Salim 1994</td>
<td>Prospective</td>
<td>Atenolol/prop</td>
<td>80</td>
<td>10,4±3,4, 10,2±4,6</td>
<td>66±32,4</td>
<td>1,1±1,1, 2,1±1,6 p=0,006</td>
<td>5 ARR</td>
</tr>
<tr>
<td></td>
<td>Not randomized</td>
<td>No treatment</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td>No events</td>
</tr>
<tr>
<td>Rossi-Foulkes 1999</td>
<td>Prospective</td>
<td>BB</td>
<td>15</td>
<td>11,2±5,3, 8,0±5,2</td>
<td>49±23</td>
<td>0,9±1,3, 1,8±0,9 p=0,020</td>
<td>3 ARR (ITAD B)</td>
</tr>
<tr>
<td></td>
<td>Not randomized</td>
<td>No treatment</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td>No events</td>
</tr>
<tr>
<td>Ladouceur 2007</td>
<td>Retrospective</td>
<td>Atenolol</td>
<td>77</td>
<td>6,1±3,2, 7,4±5,2</td>
<td>40±22</td>
<td>0,97±0,05, 1,09±0,06 p= 0,023</td>
<td>2 ARR, 1 death</td>
</tr>
<tr>
<td></td>
<td>Not randomized</td>
<td>No treatment</td>
<td>78</td>
<td></td>
<td></td>
<td></td>
<td>5 ARR, 3 death</td>
</tr>
<tr>
<td>Tierney 2007</td>
<td>Retrospective</td>
<td>Atenolol</td>
<td>29</td>
<td>9,2±4,0, 8,8±4,8</td>
<td>76,3±31</td>
<td>p=0,520</td>
<td>1 ARR (TAD A)</td>
</tr>
<tr>
<td></td>
<td>Not randomized</td>
<td>No treatment</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
<td>2 ARR, 1 death</td>
</tr>
</tbody>
</table>

Adapted from Gao et al. Acta Paediatrica 2011
EFFECT OF LOSARTAN IN A MOUSE MODEL FOR MARFAN

Habashi et al, Science 2006
### CLINICAL TRIALS WITH ARB ALONE

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Strategy</th>
<th>N</th>
<th>Age (yr)</th>
<th>FU-time (m)</th>
<th>Aortic growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brooke 2008</td>
<td>Retrospective Not randomized Not blinded</td>
<td>Losartan Irbesartan</td>
<td>18</td>
<td>1-16</td>
<td>12-47</td>
<td>Before: 3,54±2,87 After: 0,46±0,62 p&lt;0,001</td>
</tr>
<tr>
<td>Pees 2014</td>
<td>Prospective Not randomized Not blinded</td>
<td>Losartan</td>
<td>20</td>
<td>1,7-21,6</td>
<td>33±11</td>
<td>Ao growth: -3±2,8mm/m² p&lt;0,001</td>
</tr>
<tr>
<td>Mueller 2014</td>
<td>Retrospective Not randomized Not blinded</td>
<td>Valsartan Metoprolol</td>
<td>22</td>
<td>10,17±5,13</td>
<td>7,75±5,13</td>
<td>Z-score: -0,56±0,71 Z-score: -0,35±0,68 p&gt;0,05</td>
</tr>
<tr>
<td>Forteza 2015</td>
<td>Prospective Randomized Blinded</td>
<td>Losartan Atenolol</td>
<td>70</td>
<td>5-60</td>
<td>36</td>
<td>Ao growth: 1,4mm/3yr Ao growth: 1,1mm/3yr p=0,382</td>
</tr>
<tr>
<td>Mariucci 2015</td>
<td>Retrospective Not randomized Not blinded</td>
<td>Losartan</td>
<td>38</td>
<td>Paediatric</td>
<td>4,5±2,5</td>
<td>Ao growth: -0,1±0,4mm/yr</td>
</tr>
</tbody>
</table>

Adapted from Ewans et al J Paeds & Child Health 2014 and Sigh et al Can J Cardiol 2016
THE PHN TRIAL: ATENOLOL VS LOSARTAN

608 patients, AoR z-score > 3

Losartan
N=305
Mean age 11± 6,2yr

Atenolol
N=303
Mean age 11,5± 0,5yr

- Both Atenolol and Losartan effectively reduced AoR z-score
- There was no difference between the 2 drugs

Lacro et al NEJM 2014
<table>
<thead>
<tr>
<th>Trial</th>
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<th>Strategy</th>
<th>N</th>
<th>Age (yr)</th>
<th>FU-time (m)</th>
<th>Aortic growth</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu 2013</td>
<td>Prospective Randomized</td>
<td>BB alone BB+Losartan</td>
<td>13</td>
<td>13,1± 6,3</td>
<td>35</td>
<td>0,89mm/yr 0,10mm/yr p= 0,02</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>Open label</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milleron 2015</td>
<td>Prospective Randomized</td>
<td>BB+Placebo BB+Losartan</td>
<td>150</td>
<td>&gt;10yr</td>
<td>42</td>
<td>0,51mm/yr 0,44mm/yr p= 0,36</td>
<td>13 AoRR, 2 TAD</td>
</tr>
<tr>
<td></td>
<td>Blinded</td>
<td></td>
<td>153</td>
<td></td>
<td></td>
<td></td>
<td>15 AoRR, 1 TAD</td>
</tr>
<tr>
<td>Mullen Ongoing</td>
<td>Prospective Randomized</td>
<td>Baseline+ Placebo Baseline +Irbesartan</td>
<td>490</td>
<td>6-40yr</td>
<td>36</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>Blinded</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gambarin Ongoing</td>
<td>Prospective Randomized</td>
<td>Nebivolol Losartan Combination</td>
<td>291</td>
<td>48</td>
<td></td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>Open-label</td>
<td></td>
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</tr>
</tbody>
</table>

Adapted from Ewans et al J Paeds & Child Health 2014 and Sigh et al Can J Cardiol 2016
1. Beta blockers seem effective for treatment of children with Marfan syndrome

2. Losartan seems to be a good alternative

3. Use of a combination therapy needs still more study
WHEN TO START TREATMENT?

- At diagnosis?
- When AoR is dilated?
  - When there is evidence of progressive dilation?
SOME ARGUMENTS TO CONSIDER EARLY START

Salim et al, JACC 1994
Retrospective study
Children<21yr
100 receiving BB vs 13 not treated

Max growth 6-14yr

“Treatment at a younger age blunted the rate of aortic growth to a greater extent”

Ladouceur et al, Am J Cardiol 2007
Retrospective study
Children<12yr
77 receiving BB vs 78 not treated

“Limitation in aortic dilation was more pronounced when the treatment duration was longer”

Lacro et al, NEJM, 2014

Although the rate of change in the aortic-root z score did not differ significantly between the two treatment groups, the aortic-root z score decreased significantly over time in each group, particularly in younger versus older participants, which suggests that there may be value in beginning therapy relatively early in the disease course. Without a placebo group, we are not able
Figure 5: Patients being treated after the 1st visit

N=40

- 46.5% No treatment
- 12.6% Beta-blocker (Atenolol)
- 22.5% No treatment
- 2.5% BB & Losartan
- 38.5% Beta-blocker

Mean FU: 4.63 ± 2.5 yr

Data not published
DATA FROM GHENT

N= 9 not treated

- 3 girls with z-score 2.5-3.5 intolerant for BB and losartan
- 1 boy age 6j with z-score 2.97 stable for 3yr
- 3 girls and 2 boys with Z-score <2.5
CURRENT RECOMMENDATIONS: TRIALIST PHN

Medical therapy for Marfan syndrome

- No aortic root dilation, z score < 2.5
  - Consider patient factors:
    - Family history of aneurysm
    - Family history of dissection
    - Vertebral artery tortuosity
    - Increased aortic stiffness

- Aortic root dilation, z score > 2.5
  - β-Blocker titrated to HR or angiotensin receptor blocker

- Severe or progressive aortic root dilation, z score > 5 or increasing z score
  - Consider combination therapy with β-blocker and angiotensin receptor blocker