Novel diagnostic and therapeutic targets in Marfan syndrome
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Critical appraisal of the revised Ghent criteria for diagnosis of Marfan syndrome

Clinical Genetics, 2011; Feb 17.
ABSTRACT

Marfan syndrome (MFS) is a connective tissue disorder with major features in cardiovascular, ocular and skeletal systems. Recently, diagnostic criteria were revised where more weight was given to the aortic root dilatation. We applied the revised Marfan nosology in an established adult Marfan population to define practical repercussions of novel criteria for clinical practice and individual patients. Out of 180 MFS patients, in 91% (n=164) the diagnosis of MFS remained. Out of 16 patients with rejected diagnosis, four patients were diagnosed as MASS phenotype, three as ectopia lentis syndrome and in nine patients no alternative diagnosis was established. In 13 patients the diagnosis was rejected because the Z-score of the aortic root was <2, although the aortic diameter was larger than 40 mm in six of them. In three other patients the diagnosis of MFS was rejected because dural ectasia was given less weight in the revised nosology. Following the revised Marfan nosology, the diagnosis of MFS was rejected in 9% of patients, mostly due to absence of aortic root dilatation defined as Z-score ≥2. Currently used Z-scores seem to underestimate aortic root dilatation, especially in patients with large BSA. We recommend re-evaluation of criteria for aortic root involvement in adult patients with a suspected diagnosis of MFS.
INTRODUCTION

Marfan syndrome (MFS) is an autosomal-dominant connective tissue disorder with systemic involvement. Major features of MFS are progressive aortic root dilatation (1-3), ectopia lentis (EL) and skeletal features resulting from overgrowth of long bones. Other features are dilatation and aneurysms in other parts of aorta, mitral valve prolapse (4;5), progressive myopia, mild myopathy and osteopenia, dural ectasia and skin striae. (6) In 1991 heterozygous mutations in the FBN-1 gene coding for fibrillin-1 were reported to cause MFS. Nowadays, a FBN1 mutation is found in 90-95 % of Marfan patients. (7;8) However, because of the large clinical variability (both within and between families) and genetic heterogeneity (9;10), MFS remained a clinical diagnosis. Other connective tissue disorders, a relatively large group of syndromes with comparable clinical pictures, make the differential diagnosis challenging. Lately, novel syndromes of the connective tissue like Loeys-Dietz syndrome (LDS) and arterial tortuosity syndrome (ATS) emerged (11;12). To a large extent, these diseases share a similar pathophysiology and clinical features with MFS (13). Most features of MFS are age dependent, which often postpones the diagnosis in children and sometimes even in adults with a positive family history. This may lead to an anticipatory diagnosis in order to avoid uncertainty. Both situations raise anxiety in the family and possibly lead to unnecessary stigmatizing (14), restriction of insurance and career opportunities and reproductive choices. Therefore, there is a need for accurate diagnostic criteria in order to standardize the diagnosis of MFS, delineate it from similar syndromes, and put the diagnosis in the perspective of clinical relevance for the patient.

In 1996 the Ghent criteria were defined. (15) These original Ghent criteria made use of classification of different features into major and minor criteria. Presence of 2 major criteria in different organ systems and involvement of a third system were sufficient to establish the diagnosis. Major criteria were aortic root dilatation or dissection, EL, a combination of at least four out of eight major skeletal features, dural ectasia and a FBN1 mutation or a first degree family member fulfilling the same criteria for diagnosis. Minor criteria included some less specific features in different organ systems. These criteria had an
excellent specificity as a mutation in the FBN1 gene could be found in up to 97% of patients fulfilling them (16). However, the sensitivity was lower as the “target population” was not defined easily and some features, like dural ectasia, had rather subjective thresholds or no clinical relevance.

In order to address these issues, the original Ghent criteria were recently revised (17). An international panel of experts aimed to improve the diagnostic criteria by using a practical patient-centric approach and maximal evidence based decision making. More weight was given to two cardinal features – aortic dilatation and EL, which was considered sufficient for making the diagnosis. FBN1 mutations were assigned a more prominent role, as well as mutations in the genes of related disorders (eg. TGFBR1 and 2) for differential diagnostic purposes. Less specific features were considered less valuable and some were removed from the revised nosology. Besides, the new nosology formalized a need to exclude features of related disorders even if the patient had sufficient findings to fulfill the criteria for diagnosis of MFS. In the case of findings suspicious for related disorders, additional diagnostics (often genetic or molecular testing) are now needed. It is important to differentiate these diseases as there are differences in health risks and needed clinical care. For example, aortic dissection in LDS may occur without substantial aortic dilatation and requires surgery at smaller aortic diameters than in MFS (18).

According to the revised Marfan nosology, a diagnosis of MFS in a proband can be established in presence of:

- Aortic root dilatation (Z score ≥2) and ectopia lentis.

- Aortic root dilatation (Z≥2) and FBN1 mutation

- Aortic dilatation (Z≥2) and systemic score ≥ 7 points (Table 1).

- Ectopia lentis and FBN1 mutation known to be associated with aortic dilatation in family members or the literature.
### Table 1. Scoring of systemic features following the new revised 2010 nosology

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thumb and wrist sign –</td>
<td>3</td>
</tr>
<tr>
<td>Wrist or thumb –</td>
<td>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>Hind foot deformity –</td>
<td>2</td>
</tr>
<tr>
<td>Plain 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 upper segment/lower segment and increased arm/length ratio and no severe scoliosis</td>
<td>1</td>
</tr>
<tr>
<td>Scoliosis or thoracolumbal kyphosis –</td>
<td>1</td>
</tr>
<tr>
<td>Reduced elbow extension –</td>
<td>1</td>
</tr>
<tr>
<td>Facial features (3/5) - (dolichocephaly, enophthalmos, downsloacting palpebral fissures, malar hypoplasia, retrognathia)</td>
<td>1</td>
</tr>
<tr>
<td>Skin striae –</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>
</tbody>
</table>

In a first degree relative of a MFS patient, diagnosis can now be made in the presence of either aortic dilatation ($Z \geq 2$), ectopia lentis or systemic score $\geq 7$. Special considerations were given to a diagnosis of MFS in children which we will not discuss in this paper. The authors anticipated that the criteria might postpone the diagnosis and defined criteria for 3 alternative diagnoses: ectopia lentis syndrome, MASS phenotype (myopia, mitral valve prolapse, borderline non-progressive aortic root dilatation, skeletal findings and striae) and MVPS (mitral valve prolapse) syndrome.

In this paper we applied the revised Ghent criteria to an established cohort of 180 adult Marfan patients in order to evaluate the practical repercussions of the novel criteria for clinical practice and individual patients. In addition, we assessed the relation between BSA and aortic root diameter in a group of 38
healthy volunteers with a relatively large BSA to evaluate the reliability of the Z-score in patients with a large BSA.

MATERIALS AND METHODS

Patients

Patients included in this analysis are the participants of the COMPARE study (19) in whom sufficient data were available. All patients fulfilled the original Ghent criteria and were diagnosed with MFS in one of four specialized Marfan outpatient clinics of the Netherlands. In all patients a physical examination was performed at inclusion in the COMPARE study and all clinical features of the MFS were reevaluated. Data about ectopia lentis, ocular minor criteria and myopia, dural ectasia, protrusio acetabuli and pneumothorax were derived from patients’ charts. Genotyping was performed if necessary to confirm or rule out the diagnosis. If no FBN1 mutation was found, TGFBR1, TGFBR2 and in several patients ACTA2 mutations were also screened. Data on the family history of MFS were derived from the patients’ charts and family history was assumed positive when a first-degree family member fulfilled the revised criteria. If data were missing or inconclusive, no family history in the proband was assumed. In patients with a pathogenic FBN1 mutation and no family history of MFS, published data and databases were searched in order to determine whether the mutation is associated with aortic dilatation.

Aortic diameters were measured at the time of inclusion in the COMPARE study by means of standard echocardiography and Magnetic Resonance Imaging (MRI), in end-diastole from leading edge to leading edge. Normative data for aortic root diameter used were published before by Roman et al.(20) and Z-scores were calculated using the following formulas: $Z_{\text{age}<40\ year} = (\text{measured aortic root diameter} - (0.97 + 1.12 \times \text{BSA})) / 0.24$ ; $Z_{\text{age}>40\ year} = (\text{measured aortic root diameter} - (1.92 + 0.74 \times \text{BSA})) / 0.37$. Dural ectasia were evaluated by means of MRI and dural sac ratios were calculated as described before.(21) Protrusio acetabuli involvement was excluded from the analysis due to a high frequency of missing data
as X-rays of the hips were not routinely used for diagnostic purposes. In all patients bifid uvula, mental retardation, cranisynostosis and hypertelorism were excluded.

For the evaluation of the relation between BSA and aortic root dimensions healthy volunteers with a relatively large BSA were asked to participate. After exclusion of cardiac disease, connective tissue disorders and hypertension, echocardiography was performed. Aortic root diameters were measured during end-diastole from leading edge to leading edge, according to the guidelines. (22)

Statistics

Data are shown as percentages and mean (standard deviation). SPSS version 18 statistical package was used for statistical analysis.

RESULTS

We applied the proposed revised Marfan nosology in 180 adult Marfan patients (53% male, mean age 37 (range 18-62)). Frequencies of features according to original Ghent criteria and the revised Marfan nosology in the patient population are shown in tables 2 and 3.

Table 2. Characteristics of 180 patients according to the original Ghent criteria

<table>
<thead>
<tr>
<th>Original Ghent criteria</th>
<th>Major criteria</th>
<th>Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>86% (154/180)</td>
<td>56% (86/151)</td>
</tr>
<tr>
<td>Eyes</td>
<td>47% (84/180)</td>
<td>31% (28/89)</td>
</tr>
<tr>
<td>Skeletal system</td>
<td>13% (24/180)</td>
<td>53% (96/180)</td>
</tr>
<tr>
<td>Dura</td>
<td>76% (66/87)</td>
<td></td>
</tr>
<tr>
<td>Family history/FBN1mutation</td>
<td>88% (129/146)</td>
<td></td>
</tr>
<tr>
<td>Skin/integmentum</td>
<td>64% (114/177)</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>14% (25/180)</td>
<td></td>
</tr>
</tbody>
</table>
In 91% (164) of patients the diagnosis of Marfan syndrome was confirmed when the revised criteria were applied. Of these patients 80% had aortic root dilatation in combination with ectopia lentis, systemic involvement or a FBN1 mutation/family history. Another 20% were diagnosed based on family history of MFS/FBN1 mutation in combination with either ectopia lentis or systemic involvement. Out of 16 patients in whom the diagnosis of MFS was rejected according to the revised nosology, four received the diagnosis of MASS phenotype, three patients were diagnosed with ectopia lentis syndrome and in nine patients no alternative diagnosis could be established (figure 1).

Data of the 16 patients with a rejected diagnosis of MFS are shown in table 4. In three of these patients the Z-score was >2 but they lacked ectopia lentis, a systemic score >7 or a FBN1 mutation. These patients fulfilled the original Ghent criteria because they had dural ectasia, a major criterion in the original Ghent criteria. The other 13 patients with a rejected diagnosis of MFS in the revised criteria had a Z-score <2, of whom six patients with an absolute aortic diameter of 40 mm or more and seven patients with an aortic diameter less than 40 mm. In the latter group, the aortic root commonly had a shape typical for Marfan syndrome (Figure 2), whereas the absolute diameters and Z-scores of these patients were normal. One patient with an aortic root diameter of 44 mm had a Z-score <2 due to a large BSA.
Figure 1: Flow diagram of the application of the new criteria on 180 adult Marfan patients

160 MFS patients
original Ghent criteria

164 MFS patients
Revised Marfan nosology

16 not MFS patients
Revised Marfan nosology

3 patients
Z score >2 and no alternative diagnosis

13 patients
Z score <2

3 patients
MASS phenotype

1 patient
EL syndrome

2 patients
no alternative diagnosis

6 patients
AoR >= 40 mm

7 patients
AoR <40 mm

1 patient
MASS phenotype

2 patients
EL syndrome

4 patients
no alternative diagnosis

**Figure 1: Differential diagnosis proposed in Revised Ghent nosology**

EL syndrome – ectopia lentis syndrome - is diagnosed in presence of ectopia lentis with or without systemic score, with or without a FBN1 mutation not associated with aortic root dilatation (AoR); MASS phenotype -myopia, mitral valve prolapse, borderline non-progressive aortic root dilatation, skeletal findings and striae. Diagnosis of MASS is made in individuals with an aortic root size below Z=2, at least one skeletal feature and a systemic score ≥5. The presence of ectopia lentis precludes this diagnosis. When mitral valve prolapse is present in association with limited systemic features (systemic score < 5), the term mitral valve prolapse syndrome (MVPS) was suggested. In patients presented in this paper no MVPS patients were found.
Table 4. Overview of 17 patients with a rejected diagnosis of MFS

### Three patients with Z-score > 2 and no alternative diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>BSA</th>
<th>AoR</th>
<th>Z score</th>
<th>EL</th>
<th>SS</th>
<th>Specification SS*</th>
<th>FBN1</th>
<th>FH</th>
<th>DE</th>
<th>DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>m</td>
<td>2.00</td>
<td>90</td>
<td>2.24</td>
<td>4.4</td>
<td>2.23</td>
<td>-</td>
<td>3</td>
<td>DE, facial features</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>m</td>
<td>1.80</td>
<td>95</td>
<td>2.18</td>
<td>4.4</td>
<td>4.12</td>
<td>-</td>
<td>5</td>
<td>Pectus carinatum, hindfoot,DE</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>m</td>
<td>1.78</td>
<td>70</td>
<td>1.86</td>
<td>4.6</td>
<td>3.52</td>
<td>-</td>
<td>2</td>
<td>DE</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

### Seven patients with normal Z-score and aortic root diameter >=40 mm

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>BSA</th>
<th>AoR</th>
<th>Z score</th>
<th>EL</th>
<th>SS</th>
<th>Specification SS</th>
<th>FBN1</th>
<th>FH</th>
<th>DE</th>
<th>DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>f</td>
<td>1.83</td>
<td>86</td>
<td>2.09</td>
<td>4.1</td>
<td>1.71</td>
<td>-</td>
<td>6</td>
<td>wrist and thumb sign; hindfoot; reduced US/LS and increased arm/height</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>MASS</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>m</td>
<td>1.92</td>
<td>105</td>
<td>2.38</td>
<td>4.4</td>
<td>1.94</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>c.6884 G&gt;A (p.Cys2295Tyr)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>f</td>
<td>1.83</td>
<td>89</td>
<td>2.13</td>
<td>4</td>
<td>1.36</td>
<td>-</td>
<td>6</td>
<td>wrist sign; hindfoot; DE</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>MASS</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>f</td>
<td>1.91</td>
<td>75</td>
<td>1.99</td>
<td>4</td>
<td>1.64</td>
<td>-</td>
<td>9</td>
<td>pectus carinatum, hindfoot deformity;DE; striae</td>
<td>np</td>
<td>-</td>
<td>+</td>
<td>MASS</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>f</td>
<td>1.83</td>
<td>75</td>
<td>1.95</td>
<td>4</td>
<td>1.72</td>
<td>+</td>
<td>9</td>
<td>wrist and thumb sign; hindfoot;DE; scoliosis; facial features</td>
<td>np</td>
<td>-</td>
<td>+</td>
<td>EL sy</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>f</td>
<td>1.81</td>
<td>86</td>
<td>2.08</td>
<td>4.1</td>
<td>1.73</td>
<td>-</td>
<td>1</td>
<td>thumb sign</td>
<td>c.2147G&gt;C (p.Gly716Ala)</td>
<td>-</td>
<td>np</td>
<td>-</td>
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</table>
Seven patients with normal Z-score and aortic root diameter < 40 mm

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Height</th>
<th>Weight</th>
<th>BSA</th>
<th>AoR</th>
<th>Z score</th>
<th>EL</th>
<th>SS</th>
<th>Specification SS</th>
<th>FBN1</th>
<th>FH</th>
<th>DE</th>
<th>DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>f</td>
<td>1.87</td>
<td>72</td>
<td>1.93</td>
<td>3.5</td>
<td>0.41</td>
<td>+</td>
<td>9</td>
<td>wrist and thumb sign; pectus excavatum; hindfoot; scoliosis; striae</td>
<td>c.6113 G&gt;A</td>
<td>-</td>
<td>np</td>
<td>EL sy</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>m</td>
<td>1.86</td>
<td>85</td>
<td>2.10</td>
<td>3.5</td>
<td>0.07</td>
<td>-</td>
<td>9</td>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td>MASS</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>f</td>
<td>1.75</td>
<td>62</td>
<td>1.74</td>
<td>3.6</td>
<td>1.06</td>
<td>-</td>
<td>3</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>f</td>
<td>1.78</td>
<td>54</td>
<td>1.63</td>
<td>3.7</td>
<td>1.55</td>
<td>+</td>
<td>7</td>
<td>thumb sign; pectus carinatum; hindfoot; DE</td>
<td></td>
<td>-</td>
<td>+</td>
<td>EL sy</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>f</td>
<td>1.72</td>
<td>104</td>
<td>2.23</td>
<td>3.6</td>
<td>0.08</td>
<td>-</td>
<td>3</td>
<td>DE; striae</td>
<td>c.2860C&gt;T</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>f</td>
<td>1.84</td>
<td>87</td>
<td>2.11</td>
<td>3.8</td>
<td>1.94</td>
<td>-</td>
<td>3</td>
<td>DE; reduced US/LS and increased arm/height</td>
<td>c.2860C&gt;T</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>f</td>
<td>1.86</td>
<td>84</td>
<td>2.08</td>
<td>3.5</td>
<td>0.83</td>
<td>-</td>
<td>5</td>
<td>thumb sign; hindfoot; facial features; striae</td>
<td>c.2913delT</td>
<td>-</td>
<td>np</td>
<td>-</td>
</tr>
</tbody>
</table>

*Height and Weight are presented in m and kg respectively

AoR – Aortic root diameter in cm

EL-ectopia lentis

SS- systemic score

FH-Family hisory

DE- dural ectasia

DD –differential diagnosis according to the revised Marfan nosology

*- these patients fulfilled the original Ghent criteria due to two majors (aortic root dilatation and DE) an involvement of, respectively, ocular system, skeletal system and integumentum
Figure 2. Aortic roots of 7 patients with Z-score < 2 and the diameter < 40

Echocardiographic images of aortic roots in long axis of seven patients with normal Z-score and aortic root diameter < 40 mm chronologically from left to right Patient 1-Patient 7 as listed in Table 4

An echocardiogram was performed in 38 healthy volunteers (14 female, mean age 40 years, range 24-70). The mean BSA was 2.0 (range 1.5 – 2.7), and the mean aortic root diameter was 32 mm (range 24-38 mm). Correlation of aortic diameters with the BSA is shown in figure 3. No aortic diameters of 40 mm and larger were found.
DISCUSSION

Our retrospective analysis shows that, implementing the revised Marfan nosology, the diagnosis of MFS is not confirmed in 9% of patients with an established diagnosis of MFS according to the original Ghent criteria. The diagnosis was rejected mainly due to the use of the Z-score for the definition of aortic root dilatation. Currently used Z-scores seem to underestimate aortic root dilatation in patients with a large BSA. We recommend a re-evaluation of the criteria for aortic involvement in patients with a suspected diagnosis of MFS.

MFS remained a clinical diagnosis since it was described for the first time in the 19th century. Different classifications were meanwhile proposed in order to reach maximal sensitivity and specificity on the one hand and emphasize clinical relevance on the other hand. The field of heritable connective tissue disorders expanded with novel syndromes as causative genes emerged. Loeys, Dietz and colleagues provided an excellent revision of the Ghent nosology addressing these issues. The revised Marfan
nosology narrows the diagnosis of MFS to patients with fully expressed disease (aortic dilatation, EL and selected systemic features) and gives more weight to aortic dilatation, avoiding the unnecessary stigmatizing of a patient. In three patients with dilated aortic root and little or no other features of MFS except dural ectasia, the diagnosis was correctly rejected. In 20% of adult Marfan patients the diagnosis was made in absence of significant aortic dilatation (based on family history of MFS and/or FBN1 mutation associated with aortic root dilatation in combination with systemic score or ectopia lentis), which reflects a mild disease. These patients require regular follow-up of the aortic root (23) and can have an offspring with severe disease.

In the present study, in the 16 patients with a rejected diagnosis of MFS, the diagnoses of MASS phenotype, MVP syndrome and EL syndrome were proposed as alternatives according to the revised Marfan nosology. All three diagnoses were based on the absence of significant aortic root dilatation, defined as Z-score > 2, in combination with variable skeletal features or ectopia lentis. The stringent use of Z-scores for aortic involvement in the new criteria underestimates the actual aortic root dilatation in patients with large BSA and may not reflect the potential progressive nature of it. Superior definition of aortic root involvement, other than Z scores is therefore needed in adults with MFS as aortic root dilatation is made central in the Revised Marfan nosology. In the original Ghent criteria, aortic involvement was defined as “dilatation of the ascending aorta” and provided more flexibility for cardiologists to define aortic involvement. Revised Marfan nosology advises regular cardiovascular follow-up of all MASS phenotype, MVP and EL syndrome patients as they might still evolve in the MFS. This might be psychologically and unnecessary burdening for patients, certainly adults. Comprehensive research of the natural history of EL and MASS phenotypes is warranted in order to provide superior risk stratification for progressive aortic root dilatation and delineate these syndromes from MFS.

The Z-score quantifies the distance measured in standard deviations between the patient’s aortic root diameter and that of a healthy individual with the same BSA. Normative data which long since are used
as a golden standard are derived from a publication by Roman et al. These authors showed that BSA and aortic root diameters correlated significantly ($p<0.0005$). Regression line seemed to be linear up to the largest aortic diameter found (38 mm), but above that diameter linearity was merely assumed but not proven, and the linear relationship was only extrapolated. Moreover, Reed et al. demonstrated an only weak relationship between anthropometric measurements and aortic root dimensions in healthy controls with a large BSA (mean BSA $2.3 \text{ m}^2$) and height exceeding 95th percentile.$^{(24)}$ A screening study in over 1900 young competitive athletes also showed a nonlinear relation between BSA and aortic root dimensions, with an absolute threshold in individuals with a large BSA.$^{(25)}$ Recently, another study with over 2300 highly trained athletes found an upper normal limit (<99 percentile value) of the aortic root of 40 mm in men and 34 mm in women. Finally, in our group of 38 healthy individuals with a relatively large BSA, the largest aortic root was 38 mm. These data suggest that aortic roots with a diameter $\geq 40$ mm are all dilated. The diagnosis of MFS might be falsely rejected in patients with a Z-score <2 due to a large BSA.

In seven patients in our patient group with a Z-score <2 and an aortic root diameter <40 mm, the aortic root is nevertheless clearly affected, having a convex or pear shape. It is difficult to include subjective criteria in guidelines. Therefore, new parameters might be needed for aortic involvement which could objectivise these typical, not dilated but pear-shaped aortic roots, as they may still show progressive dilatation.$^{(26)}$ These patients received either no alternative diagnosis or the diagnosis of MASS and EL syndromes in absence of aortic root dilatation according to the revised Ghent criteria. The natural progression of aortic root involvement in these MASS and EL syndrome patients is still not well documented and both syndromes can evolve in MFS if aortic root dilatation occurs. Less frequent follow-up might be desirable.

In conclusion, according to the revised Ghent criteria the diagnosis of MFS can be established in presence of only cardinal features of MFS, aortic dilatation in particular, which prevents unnecessary
stigmatization of patients. The definition of aortic root dilatation in the revised nosology based on Z-scores alone, however, underestimates aortic involvement, especially in adult Marfan patients with large BSA. Appropriate definition of aortic root involvement in adult Marfan patients is therefore not ensured and may lead to inaccurate diagnosis of MFS. We recommend re-evaluation of the criteria for aortic involvement in adult patients with a suspected diagnosis of MFS.
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