Marfan syndrome and related connective tissue disorders

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CHAPTER 2

Diagnostic yield in adults screened at the Marfan outpatient clinic using the 1996 and the 2010 Ghent nosologies

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ABSTRACT

Introduction

Marfan syndrome (MFS) is diagnosed according to the Ghent nosology, which has recently been revised. In the Netherlands, evaluation for possible MFS is usually performed in specialized Marfan outpatient clinics. We investigated the diagnostic yield in our clinic and the impact of the revised 2010 nosology.

Methods

All adult patients (n=343; 174 men/169 women) who visited our clinic between 1998-2008 were included. We analyzed their reasons for referral, characteristics and established diagnoses. In addition, we applied the 2010 nosology to all patients and compared the outcomes to those obtained with the 1996 nosology.

Results

In 41% of the patients a diagnosis could be made at initial evaluation: 13% MFS, 6% familial thoracic aortic aneurysm and/or dissection, 1% Loeys-Dietz syndrome, and 1% familial mitral valve prolapse syndrome (MVPS). Applying the 2010 nosology led to a significant increase in the number of diagnoses made (48% vs. 41%, $p<0.001$): 4 additional cases of MFS were identified (only 1 patient was 'lost' who no longer fulfilled the criteria) and 23 additional cases of MVPS. The diagnostic yield of patients with aortic root dilatation was high both at initial evaluation and after applying the 2010 Ghent nosology (65% and 70%, respectively).

Conclusion

The diagnostic yield in our specialized clinic was high in particular in patients with aortic root dilatation. The 2010 Ghent nosology led to a significant increase in the number of diagnoses made, mainly due to the lowering of the diagnostic threshold for MVPS.

INTRODUCTION

Marfan syndrome (MFS) is an autosomal, dominantly inherited, connective tissue disorder with an estimated prevalence of approximately 1-3 in 5,000 and it is usually caused by a mutation in the fibrillin-1 gene *(FBN1)*.[1,2] Manifestations of MFS occur in the ocular system, skeletal system, pulmonary system, skin and integument, central nervous system (CNS; dural ectasia) and, most importantly, in the cardiovascular system. Characteristic features of MFS include ectopia lentis (subluxation and luxation of the lens), thin body habitus and long extremities, pectus deformities and aortic root dilatation. Evaluation of possible MFS patients is usually performed in specialized Marfan outpatient clinics (MOC) and the diagnosis is established according to the Ghent nosology, which has recently been revised.[3,4] The main purpose of evaluation is to confirm or exclude MFS in a patient, but it may also lead to many other, clinically relevant diagnoses, such as Loeys-Dietz syndrome (LDS), familial thoracic aortic aneurysm and/or dissection (FTAAD), familial mitral valve prolapse syndrome (MVPS), mitral valve, aorta, skeleton and skin (MASS) phenotype and Ehlers-Danlos syndrome (EDS). Establishing the correct diagnosis is important as it provides prognostic information, has implications for treatment, and also guides (genetic) counseling of family members. So far, only two studies have reported on the outcome (diagnosis) in adult patients analyzed for possible MFS.[5,6] In order to establish the diagnostic yield of our clinic we determined the final diagnosis of all the patients referred for evaluation of MFS in a ten-year period. We were particularly interested in the diagnostic yield in patients with cardiovascular manifestations, since these carry important prognostic implications. Finally, we used the opportunity to analyze what the diagnostic yield would have been using the 2010 Ghent criteria.[3,4]

Study population and diagnostic evaluations

All adult patients (age >18 years) referred for evaluation for possible MFS to our clinic between 1998-2008 were included in our study. Every physician who suspected MFS in a certain patient was allowed to refer this patient to our MOC and there were no specific criteria patients had to meet to allow evaluation. The reason(s) for referral for all patients was routinely recorded. Evaluation of the patients was performed by a team of dedicated specialists, consisting of a clinical geneticist (JPvT), a cardiologist (MPvdB), an ophthalmologist (BAEvdP), and an orthopaedic surgeon. Inherent to this period of referral (i.e. up to 2008), the patient characteristics were collected according to the 1996 Ghent nosology.[3] Not all the Ghent criteria were evaluated in each patient, only when clinically relevant, i.e. when necessary to confirm or exclude MFS. All patient data, including echocardiographic data, were routinely fed into a clinical database. Mitral valve prolapse was defined as echocardiographic single or bileaflet prolapse of at least 2 mm beyond the long-axis annular plane, with or without leaflet thickening.[7] Finally, it is important to note that patients with a bicuspid aortic valve were not evaluated at this specific clinic.

Definitions of MFS and other relevant diagnoses

The diagnoses were established using the 1996 Ghent nosology but, as part of this study, we also retrospectively applied the 2010 Ghent nosology to all patients based on their characteristics as collected at the time of referral. Other diagnoses that could be made but are not mentioned in (one) of the Ghent nosologies were also established.

The 1996 nosology for MFS distinguished major and minor criteria in different (organ) systems. MFS was present if two major (organ) systems were involved and if a third (organ) system was involved in a minor way.[3] In the 2010 nosology, there is no differentiation between major and minor criteria. Aortic root dilatation (Z-score >2) combined with one of the following characteristics establishes a diagnosis of MFS (see also Table I): ectopia lentis, *FBN1* mutation, family history of MFS or a systemic score >7. A family history of MFS combined with ectopia lentis or a systemic score >7 also establishes a diagnosis of MFS.[4] Besides defining MFS, the Ghent nosology (in particular the 2010 nosology) also considers disorders that need to be differentiated from MFS. These include MASS phenotype, MVPS (familial or incidental), FTAAD, EDS, LDS and ectopia lentis syndrome.[3,4,7-9] Some of these disorders have not been summarized in the 1996 Ghent nosology but were added to the 2010 Ghent nosology, such as FTAAD, LDS and ectopia lentis syndrome. In addition, the definitions

Table I. Diagnostic criteria for MFS in adults according to the 2010 Ghent nosology

In the absence of a family history of MFS:

1. Aortic root Z-score ≥2 AND ectopia lentis
2. Aortic root Z-score ≥2 AND an *FBN1* mutation
3. Aortic root Z-score ≥2 AND a systemic score* ≥7 points
4. Ectopia lentis AND an *FBN1* mutation with known aortic pathology

In the presence of a family history of MFS (as defined above):

1. Ectopia lentis
2. Systemic score* ≥7
3. Aortic root Z-score ≥2

* Points for systemic score

- 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)
- Dural ectasia = 2
- Protrusio acetabula = 2
- Reduced upper segment/lower segment ratio 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 = 1

MFS; Marfan syndrome.

of some of these disorders differ between the 1996 and the 2010 Ghent nosologies. First, in the 1996 nosology, a MASS phenotype is defined as the presence of three of the following manifestations: myopia, mitral valve prolapse, borderline aortic root dilatation, striae and minor skeletal criteria. In the 2010 nosology, a MASS phenotype is defined as borderline aortic root dilatation and a systemic score >5 with at least one skeletal feature. Second, in the 1996 nosology, (familial) MVPS is defined as an autosomal, dominantly inherited trait, whereas in the revised nosology, the familial occurrence is no longer required, a prolapse of the mitral valve and a systemic score <5 is sufficient for the diagnosis MVPS. Benign hypermobility syndrome (BHMS) was defined according to Simpson et al.[10] An aneurysm of the thoracic aorta of unknown origin (UO) was defined here as: dilatation of the thoracic aorta (Z score >2) without evidence for a systemic or familial disorder.

Statistical analysis

Continuous data are reported as mean ± SD and categorical data as percentages unless stated otherwise. Differences between groups were tested using parametric or non-parametric tests, as appropriate. A p-value <0.05 was considered to indicate statistical significance. The analyses were performed using SPSS 16.0 software (SPSS, Chicago, Ill).

RESULTS

Patients

Between 1998 and 2008, 349 adult patients were referred to our clinic for evaluation of possible MFS. Six patients were excluded from analysis because of incomplete data, leaving a study group of 343 patients. Men (n=174) and women (n=169) were equally represented (p=0.829) and the average age was 40 ± 14 years. Reasons for referral are given in Figure 1, the most common being aortic pathology (aortic dilatation or aortic dissection). More than one reason for referral was present in 113 patients.

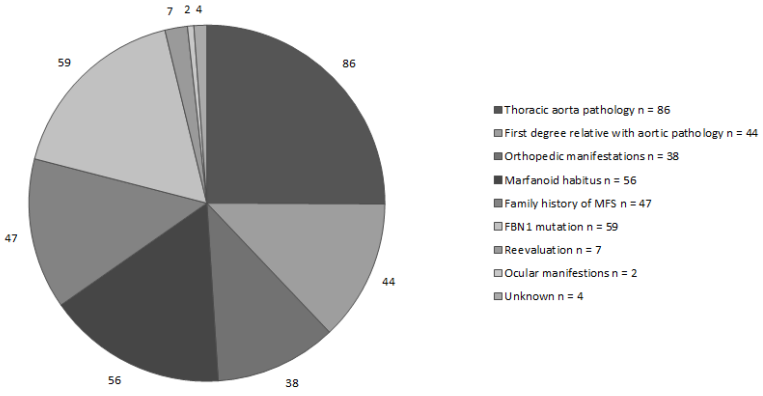

Figure 1 Reasons for patients being referred to our Marfan outpatient clinic (*n*=343).
MFS, Marfan syndrome.

Patient characteristics

In Table II and Figure 2 the characteristics of the patients according to the 1996 nosology are presented. Major cardiovascular involvement (aortic root dilatation/type A aortic dissection) was present in 28% of the patients. Ectopia lentis was present in 8% of patients and 40% of the patients had a family history of MFS and/or an *FBN1* mutation in the family. Dural ectasia was evaluated in 88/343 patients and was detected in 31 of them (35%). Major skeletal involvement was rare; it was present in only two patients.

Table II Prevalence of characteristics in 343 patients evaluated at our clinic according to the 1996 Ghent nosology

System	Major	Minor	None	Not evaluated
Cardiovascular	95 (28%)	42 (12%)	192 (56%)	14[a] (4%)
Skeletal	2 (0.6%)	66 (19%)	246 (72%)	29[b] (8%)
Ocular	29 (8%)	7 (2%)	274 (80%)	33[b] (10%)
Familial/genetic	136 (40%)	n.a.	207 (60%)	-
Pulmonary	n.a.	11 (3%)	296(86%)	36[b] (10%)
Skin	n.a.	114 (33%)	197 (57%)	32[b] (9%)
CNS	31 (10%)	n.a.	57 (17%)	255[b] (74%)

n.a.,not applicable; CNS, central nervous system.

[a] in these 14 cases only DNA analysis was performed because of familial MFS with a pathogenic *FBN1* mutation.

[b] in these cases evaluation was deemed not relevant, since regardless of the outcome this would not have had any clinical consequences.

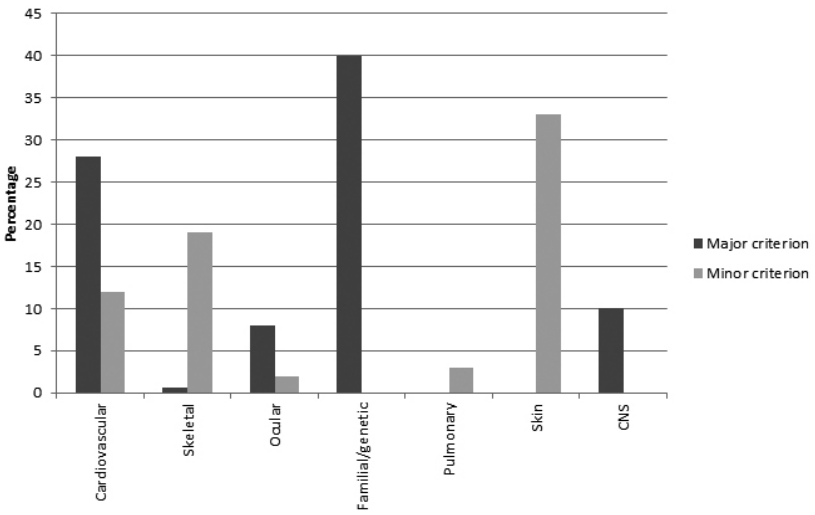

Figure 2 Prevalence of the characteristics according to the 1996 Ghent nosology of the 343 patients evaluated at our Marfan outpatient clinic.
CNS, central nervous system.

Diagnoses

In Table III the diagnoses of all patients are presented, both at initial evaluation using the 1996 nosology and after reevaluation applying the 2010 nosology. The patients were not clinically reevaluated, but the 2010 nosology was applied to the already established characteristics of the patients. In addition diagnoses that were established but not mentioned in (one) of the Ghent nosologies are also presented. At initial evaluation, a diagnosis could be made in 41% (n=140) of the patients. MFS was the most common diagnosis (13%), followed by a thoracic aortic aneurysm of unknown origin (9%), FTAAD (6%) and BHMS (6%). MVPS was found in 1%. Other diagnoses are listed in Table III. No specific diagnosis could be made in 59% (n=203) of the patients. Thirteen of these patients without a specific diagnosis had a high likelihood of MFS but did not (yet) fulfill the 1996 diagnostic criteria. They fulfilled one of the following profiles: 1. aortic root dilatation/ type A aortic dissection combined with ectopia lentis OR an *FBN1* mutation, 2. (suspected) family history of MFS AND an *FBN1* mutation 3. ectopia lentis AND an *FBN1* mutation. Age did not differ

Table III Diagnoses of the 343 patients evaluated at our clinic according to the 1996 and 2010 Ghent nosologies

	Initial evaluation		Reevaluation	
	Other[†]	1996 nosology	2010 nosology	Other[‡]
Diagnosis				
MFS		44 (13%)	47 (14%)	
MVPS		5 (1%)	28 (8%)	
MASS phenotype		6 (2%)	3 (1%)	
EDS hypermobile type		5 (1%)	5 (1%)	
BHMS		19 (6%)	19 (6%)	
FTAAD	22 (6%)		22 (6%)	
LDS	4 (1%)		4 (1%)	
Ectopia lentis syndrome			1 (0.3%)	
Thoracic aortic aneurysm UO	30 (9%)			31 (9%)
Remaining diagnoses[d]	5 (1%)			5 (1%)
No diagnoses	203 (59%)		178 (52%)	
Total	343 (100%)		343 (100%)	

BHMS, benign hypermobility syndrome; EDS, Ehlers-Danlos syndrome; FTAAD, familial thoracic aortic aneurysm and/or dissection; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; MVPS, mitral valve prolapse syndrome; UO, unknown origin.

[†] Diagnoses not mentioned in the 1996 Ghent nosology.

[‡] Diagnoses not mentioned in the 2010 Ghent nosology.

[d] Duane syndrome, Lujan-Fryns syndrome, XYY-karyotype, dilated cardiomyopathy, congenital cataract.

significantly between patients with or without a diagnosis (38±14 years vs. 41±14 years; p=0.123) and distribution of gender was equal (p=0.274).

After applying the 2010 Ghent nosology, a diagnosis could be made in 48% (n=165) of the patients (vs. 41% using the 1996 nosology, p<0.001). There were several changes compared to the diagnoses made at initial evaluation. The diagnosis of 4 patients changed from no specific diagnosis to MFS. All 4 of these patients belonged to the group of 13 patients with a high likelihood of MFS at initial evaluation. Two of these patients had aortic root dilatation and an *FBN1* mutation. The other 2 patients had aortic root dilatation and ectopia lentis. Conversely, in one patient MFS could no longer be confirmed using the 2010 criteria (1/44 patients). This patient had a history of acute type A aortic dissection, dural ectasia, dolichocephaly, malar hypoplasia, striae and no *FBN1* mutation. According to the 2010 nosology this leads to a systemic score of 3, which together with the type A aortic dissection was insufficient for a "revised" diagnosis of MFS. In one patient in whom initially no specific diagnosis could be made because of ectopia lentis and an *FBN1* mutation, the diagnosis changed to ectopia lentis syndrome. There were further major changes for MVPS: according to the 1996 nosology MVPS was diagnosed in 5 patients (1%) but according to the 2010 nosology MVPS was present in as many as 28 patients (8%). In three patients the diagnosis changed from MASS phenotype to "no diagnosis". Age did not differ significantly between patients with or without a diagnosis when using the 2010 nosology (38±14 years vs. 39±14 years; p=0.205) and distribution of gender was equal (p=0.476).

***FBN1* mutations**

DNA analysis for *FBN1* mutations was performed in 140 patients.

Of the 44 MFS patients diagnosed using the 1996 nosology, 34 patients had an *FBN1* mutation (77%). In 11 other patients an *FBN1* mutation was also present. They all had a high likelihood of MFS but did not (yet) fulfill the diagnostic criteria (see previous paragraph for the definition of these patients).

Of the 47 MFS patients diagnosed using the 2010 nosology, 36 patients had an *FBN1* mutation (77%). In 9 other patients an *FBN1* mutation was also present. One had ELS and the other 8 all had a (suspected) family history of MFS and an *FBN1* mutation.

Aortic root dilatation

In 65% (n=52) of the patients with aortic root dilatation (n=80) a specific diagnosis could be established at initial evaluation, compared to 70% (n=56) after applying the 2010 nosology. Figure 3 summarizes the diagnoses of the patients with aortic root dilatation using both the 1996 and 2010 Ghent nosologies.

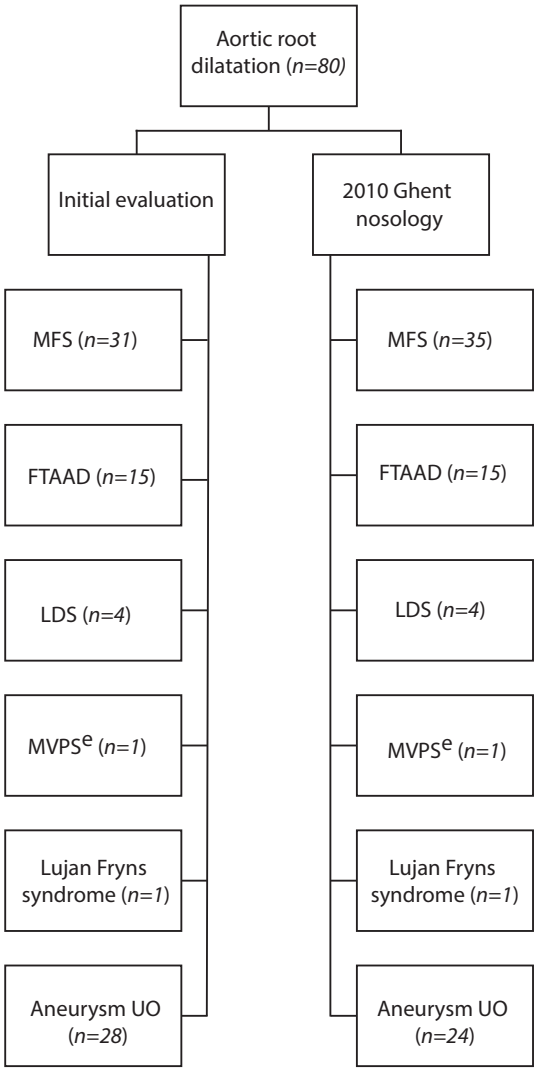

Figure 3 Diagnostic yield of aortic root dilatation using the 1996 and 2010 Ghent nosologies.
MFS, Marfan syndrome; FTAAD, familial thoracic aortic aneurysm and/or dissection; LDS, Loeys-Dietz syndrome; MVPS, mitral valve prolapse syndrome; UO, unknown origin.
[e]This patient had familial MVPS and aortic root dilatation caused by a previously described *FLNA* mutation.

DISCUSSION

Diagnostic yield

Here we have presented the diagnostic yield in our specialised MFS clinic between 1998-2008. We used the 1996 Ghent nosology and specific criteria for other disorders to evaluate the patients at that time. The overall diagnostic yield at initial evaluation in terms of establishing a specific

diagnosis was 41%. Besides MFS (13%) many other important diagnoses were made, including FTAAD in 6%, LDS in 1% and familial MVPS in 1% of the patients. Compared to a study by Rybczynski et al., who also evaluated the diagnostic yield of patients referred for a possible diagnosis of MFS, we diagnosed MFS less frequently (13%; n=44 vs. their 50%; n=138).[5] This might be due to the low threshold for referral to our center and a certain selection in the patients referred to their institution. They only evaluated 279 patients in 9 years from the Hamburg metropolitan area (approximately 4.3 million inhabitants), whereas we evaluated 343 patients in 10 years from three northern provinces in the Netherlands (approximately 1.7 million inhabitants). However, Rybczynski et al. diagnosed FTAAD in 3% and MVPS in 3% of their patients, which is comparable to our results (6% and 1%, respectively) and argue against a selection in the German study. Hamod et al. also reported on the diagnostic yield of patients referred for a possible diagnosis of MFS. In a relatively small study (n=75) they diagnosed MFS in 37% (n=28) of the patients. However, they did not report on other diagnoses that were made.[6]

The cardiovascular relevance of a timely diagnosis of MFS is obvious; MFS predisposes to aortic dissection and/or rupture causing significant morbidity and mortality. Lifelong follow-up of the aortic (root) dimensions, beta-blocker therapy, prophylactic aortic surgery (when thresholds are reached), and screening of family members is indicated as soon as MFS is established.[4,11]
Likewise, timely diagnosis of FTAAD and LDS is important as both are also characterized by aggressive aortic pathology. Family members of patients with these syndromes should also be screened.

Finally, it is also preferably if familial MVPS is recognized early since it can be accompanied by serious complications, such as significant mitral regurgitation, bacterial endocarditis, thromboembolism and even sudden cardiac death.[12-14]

Aortic root dilatation

The diagnostic yield in patients with aortic root dilatation was high: 65% at initial evaluation and 70% after applying the 2010 criteria. Diagnoses that we made in this patient category were: MFS, FTAAD, LDS, familial MVPS and Lujan-Fryns syndrome. As a practical implication, we believe it would be reasonable to evaluate all patients younger than 50 years with unexplained aortic root dilatation, established by whatever imaging technique, for a possible connective tissue disorder.

Implications of the revised Ghent nosology

In addition to establishing the diagnostic yield of our clinic, we were also able to evaluate the implications of the recent revision of the MFS Ghent nosology. Although the 1996 nosology had a high specificity for detecting patients with *FBN1* mutations and was clinically useful, there were points of criticism, stimulating the development of the revised nosology.[15] In the 2010 nosology more emphasis is placed on cardiovascular manifestations, ectopia lentis and genetic evaluation. More attention is also paid to the differential diagnosis. Using the revised nosology for our study population led to several changes compared to the outcome of the 1996 nosology. A diagnosis

of MFS could be established in 4 additional cases. All patients had aortic root dilatation combined with an *FBN1* mutation (2 cases) or ectopia lentis (2 cases). These cases nicely illustrate the hallmarks and the clinical consequences of the 2010 nosology for MFS. The diagnosis is more straightforward and specific characteristics of MFS are highlighted: aortic root dilatation, ectopia lentis and *FBN1* mutations. On the other hand, skeletal features, CNS involvement (dural ectasia), skin abnormalities, atypical cardiovascular and ocular manifestations are less relevant in the 2010 nosology. This is illustrated by the patient who no longer fulfilled the diagnostic criteria for MFS. Although this patient no longer has MFS, this does not have any clinical consequences. Due to the type A aortic dissection, regular imaging of the entire aorta is indicated to timely discover and treat a possible post-dissection aneurysm.

Furthermore, the use of the 2010 nosology led to a significant increase in the total number of diagnoses made. This was mainly due to an increase in the number of patients diagnosed with MVPS. Familial occurrence is no longer required in the 2010 nosology and therefore everyone with solely a mitral valve prolapse qualifies for MVPS. As mitral valve prolapse is a common valvular disorder (estimated prevalence 2-3%), mostly with a benign course (as opposed to certain familial forms), it is debatable whether it is useful to label all these patients as mitral valve prolapse syndrome.[12] It does not have clinical consequences as these patients are already well defined and guidelines for follow-up are available.[16] Instead, we believe the term mitral valve prolapse is sufficient in the large majority of patients with this valvular disorder.

At initial evaluation, a small number of patients (n=13) with no specific diagnosis had a high likelihood of MFS. The 2010 Ghent nosology established definite MFS in 4 of these patients and one of them could be diagnosed as ectopia lentis syndrome. The remaining 8 patients are all patients with a (suspected) family history of MFS and an *FBN1* mutation. In the 2010 nosology it is proposed to label children with a family history of MFS and an *FBN1* mutation as 'potential MFS'. We think it would be useful to also use this term in adults, as they also have a substantial risk for eventually developing definite MFS. They should at least have regular echocardiographic follow-up of aortic diameters. An age limit of 50 years for follow-up appears reasonable as the chances of developing MFS are not very large if aortic diameters at that age are still normal.

Finally, the revised criteria led to a less frequent diagnosis of MASS phenotype. The diagnostic criteria for this phenotype have been changed slightly, but remain rather subjective. In particular the criterion of borderline aortic root dilatation is unsatisfying.

Strengths and limitations

One strength of our study is that all the patients were seen by the same team of specialists. Another is that we determined the impact of the 2010 Ghent nosology by using it on patients suspected of MFS who were initially evaluated by the 1996 nosology, rather than applying the new nosology to patients with established MFS according to the old nosology, since this would introduce a bias. In addition, we did not evaluate patients with a bicuspid aortic valve at this particular clinic, since this

could introduce a bias in the outcome of the analysis. Our study is limited by the fact that not all the Ghent criteria were evaluated in each patient, although all the criteria necessary to establish a definite diagnosis were evaluated.

CONCLUSION AND PRACTICAL IMPLICATIONS

The general diagnostic yield of our specialised clinic was high: at initial evaluation, a diagnosis could be made in 41% of all referrals. Besides establishing or excluding MFS, our clinic's evaluation of a patient can lead to the diagnosis of other clinically relevant connective tissue disorders, like FTAAD, LDS and familial MVPS. Using the 2010 Ghent nosology led to a significant increase in the number of diagnoses that were made (diagnoses in 48% of the patients), which was mainly due to a lowering of the diagnostic threshold of MVPS. In addition, the 2010 nosology affords a more straightforward diagnosis of MFS in patients with aortic root dilatation, ectopia lentis and *FBN1* mutations. Finally, as the diagnostic yield in patients with aortic root dilatation was particularly high, all such patients (age <50 years) should be referred to a specialised MFS clinic to be evaluated for a possible connective tissue disorder.

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