Marfan syndrome: Getting to the root of the problem
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Citation for published version (APA):

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Adapted from:

Clinical features differ substantially between a Caucasian and Asian Marfan population

*Circ J.* 2013;25;77:2793-8

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Abstract

**Background:** Prevention of aortic dissection and sudden death in Marfan syndrome (MFS) requires accurate diagnosis. MFS is diagnosed by the Ghent criteria primarily based on clinical features of Caucasian MFS populations. We determined whether the Ghent criteria apply to Asian MFS populations.

**Methods and Results:** In this multicentre study, we included 255 adult MFS patients according to the Ghent criteria of 2010. Patients were excluded if their race was not Caucasian or Asian. The Asian MFS population (n=49) had a smaller body surface area (BSA: 1.8 m² versus 2.0 m², p<0.001), a more severely affected aortic root (absolute aortic diameter: 42.9 mm versus 43.3 mm, p=0.802; corrected for BSA: 24.9 mm versus 21.7 mm, p<0.001; Z-score: 4.5 versus 3.6, p=0.013), and more often a positive systemic score (75.5% versus 60.0%, p=0.045), but less frequently ectopia lentis (24.5% versus 48.1%, p=0.004) compared to the Caucasian population (n=206).

**Conclusion:** The Ghent criteria do not necessarily apply to Asian MFS populations, resulting in a more severely affected cardiovascular system. This may be due to under diagnosis of MFS by multiple factors, including the use of Z-score, and genetic and racial differences. The Ghent criteria should be adapted for Asian populations in order to accurately diagnose MFS.
Chapter 2: Caucasian versus Asian Marfan populations

Introduction

Marfan syndrome (MFS) is a monogenic connective tissue disorder, mainly caused by mutations in the gene encoding for fibrillin-1 (FBN1),¹ which leads to increased release of transforming growth factor-β (TGF-β).² ³ ⁴ Patients with Marfan syndrome (MFS) suffer from an increased risk of cardiovascular manifestations such as aortic root dilation, mitral valve prolapse, impaired biventricular function, and aortic dissection, the latter being the main cause of sudden death.⁵ ⁶ ⁷ ⁸ ⁹ Pregnant women need particular attention, because of the high risk for aortic dilation or dissection during and/or after pregnancy.¹⁰ ¹¹ ¹² Prevention of these cardiovascular complications requires accurate diagnosis,¹³ ¹⁴ which is currently guided by the Ghent criteria.¹⁵ In the Ghent criteria, MFS is diagnosed by genetic testing and more than 20 different clinical features, predominantly based on the Caucasian race.¹⁵ However, MFS is equally prevalent all over the world,¹⁷ without specific diagnostic criteria for races other than the Caucasian.

Currently, the general Asian population accounts for more than one-fifth of the total world population.¹⁸ Previous research has shown that some clinical features of MFS, such as myopia and scoliosis are more frequently present in the general Asian population.¹⁹ ²⁰ In addition, a study including Korean and Japanese MFS patients revealed differences in clinical features compared to Caucasian MFS populations.²¹ ²² Furthermore, genetic testing is not performed on routine basis in some Asian countries such as Singapore, adding even more weight to the accuracy of the Ghent criteria with regards to the clinical features in order to establish a reliable MFS diagnosis.

If the clinical MFS features differ between Asian and Caucasian MFS populations, the Ghent criteria may need adjustment in order to prevent delayed diagnosis and thereby to prevent cardiovascular complications. The aim of our study was to systematically compare the clinical features between a Caucasian and an Asian MFS population.

In this study we addressed the following research questions: (1) Which of the cardiovascular, ocular and skeletal features differ between a Caucasian and an Asian MFS population? (2) Do the observed differences between the Caucasian and Asian MFS population reveal that the Ghent criteria need adjustment for Asian populations?

Methods

Patient population

In this retrospective multicentre study, we collected all relevant clinical and genetic data of patients from a Dutch and Singaporean MFS cohort. The Dutch patients were participants of the COMPARE study. In short, the COMPARE study is a multi-centre randomized clinical trial, investigating the effects of losartan on aortic dimensions.²³ They all were
enrolled through Marfan screening clinics of the four university hospitals in the Netherlands. Inclusion criteria are MFS according to the Ghent criteria of 1996 and adults aged 18 years or more. Patients were ineligible if they either were already using ACE inhibitors or ARB, had renal dysfunction, had an aortic root diameter > 50 mm, had a history of aortic dissection, or were planned for aortic surgery within six months of inclusion.

The Singaporean patients were collected from the Marfan screening clinic of the National University Hospital of Singapore. In the Marfan screening clinic in Singapore, absolute aortic diameters were used for diagnosis of MFS, we retrospectively calculated the Z-scores for these patients. Furthermore, we retrospectively excluded Singaporean patients not fulfilling the in- and exclusion criteria at the start of the COMPARE study (year 2008). For this study we also excluded all patients not fulfilling the Ghent criteria of 2010. Furthermore, we excluded patients if they were not Caucasian or Asian (Figure 1). Since genetic screening was not available for the Singaporean MFS population, an additional subgroup-analysis was performed, with only Caucasian patients who did not depend on presence of a \( FBN1 \) mutation to fulfil the Ghent criteria.

Clinical features
The available data include cardiovascular, ocular and skeletal features of MFS, which were determined by medical specialists of the attended hospital. Extended physical examination was performed by the clinical genetics departments. The aortic root diameter was measured by means of echocardiography by cardiologists in end-diastole at the level of the sinus of Valsalva at inclusion date by using the leading edge to leading edge technique.\(^{24,25}\) Eye examination was performed by ophthalmologists. The specialists of both countries identified the clinical features in the same manner following the Ghent criteria of 2010.

Statistical analysis
Data are presented as mean value ± standard deviation or as number of patients (percent) where appropriate. To determine the significant differences of clinical features between the Caucasian and Asian MFS population, we used the Student’s t-test, Mann-Whitney test or Fisher’s exact test, where appropriate. Similar analyses were performed for the subgroup analysis. All statistical tests were two-sided and differences were considered statistically significant at p < 0.05. Data analysis was performed using the SPSS statistical package (19.0 for windows; SPSS Inc., Chicago, Illinois, USA).
After exclusion of 15 patients because they were of a race other than the Caucasian or Asian race and 20 patients because they did not fulfil the Ghent criteria of 2010, a total of 255 MFS patients were enrolled in this study: mean age was 40 years (range 19-73 years) with 46% female (Figure 1). The Asian population (n=49) comprised 42 Chinese patients (85.7%), 5 Malay patients (10.2%) and 2 Indian patients (4.1%). The Caucasian population (n=206) was significantly older (41 years versus 35 years; p=0.008), taller (188 cm versus 178 cm; p<0.001) and heavier (79 kg versus 63 kg; p<0.001) compared to the Asian population (n=49). Table 1 shows the clinical characteristics of the Caucasian and Asian MFS population at the time the diagnosis was established. MFS diagnosis was differently distributed in both populations. In the Caucasian population MFS diagnosis mostly comprised aortic root dilation together with ectopia lentis (40%, Figure 2A), whereas in the Asian population MFS diagnosis was mostly established by aortic root dilation together with a positive skeletal score (47%, Figure 2B). Of all 255 patients 73% used a β-blocker on regular basis, with no significant difference of β-blocker use in both groups.

Figure 1. Flow chart of inclusion of adult Marfan patients from a Dutch and Singaporean population for main and subgroup analyses.
Clinical features of the cardiovascular system in MFS comprised aortic root dilation, aortic dissection (type A and B), descending aorta dilation and aortic surgery. Asian MFS patients had overall a more severely affected cardiovascular system compared to Caucasian MFS patients. There was no difference in absolute aortic root diameter between the Caucasian and Asian population (43.3 mm ± 4.7 versus 42.9 mm ± 8.5, respectively, p=0.802). However, when aortic root diameter was corrected for body surface area (BSA) or when Z-score was used, the aortic root was significantly larger among the Asian population compared to the Caucasian (24.9 mm/m² ± 5.8 versus 21.7 mm/m² ± 2.7, p<0.001 and 4.5 ± 3.2 versus 3.6 ± 1.7, respectively, p=0.013). No significant differences were found between both groups for type B dissections, descending aorta dilation or distal graft surgery (Figure 3A).

**Cardiovascular system**

Clinical features of the cardiovascular system in MFS comprised aortic root dilation, aortic dissection (type A and B), descending aorta dilation and aortic surgery. Asian MFS patients had overall a more severely affected cardiovascular system compared to Caucasian MFS patients. There was no difference in absolute aortic root diameter between the Caucasian and Asian population (43.3 mm ± 4.7 versus 42.9 mm ± 8.5, respectively, p=0.802). However, when aortic root diameter was corrected for body surface area (BSA) or when Z-score was used, the aortic root was significantly larger among the Asian population compared to the Caucasian (24.9 mm/m² ± 5.8 versus 21.7 mm/m² ± 2.7, p<0.001 and 4.5 ± 3.2 versus 3.6 ± 1.7, respectively, p=0.013). No significant differences were found between both groups for type B dissections, descending aorta dilation or distal graft surgery (Figure 3A).

**Ectopia Lentis and a positive Family History for Marfan syndrome**

Besides aortic root dilation with a Z-score ≥ 2, ectopia lentis and a positive family history with proven MFS are major features of the Ghent criteria. Ectopia lentis was more prevalent in the Caucasian population (48.1% versus 24.5%, p=0.004) compared to the Asian population (Table 1). There was no difference in family history with proven MFS between both groups.

**Systemic score**

Most skeletal features were more prevalent in the Asian population, with the exception of pectus abnormalities. A positive wrist and thumb sign was seen in 80% of the
Asian MFS population and 48% of the Caucasian MFS population (Figure 3B, p < 0.001). In addition, an arm length/height ratio of more than 1.05 was more present in Asians (53% versus 18%, p < 0.001) compared to the Caucasian MFS population. Furthermore, in the Asian MFS population prevalence of dural ectasia was higher (69% versus 47%, p=0.008), scoliosis of more than 20% (53% versus 27%, p < 0.001), reduced extension of the elbows (27% versus 13%, p=0.029), myopia more than 3 dioptres (47% versus 22%, p < 0.001) and mitral valve prolapse (MVP: 80% versus 57%, respectively p=0.005) compared to the Caucasian MFS population (Figure 3A).

The pectus abnormalities were more prevalent in the Caucasian population with more often pectus carinatum (39% versus 22%, p=0.032) and pectus excavatum, which required surgery (14% versus 2%, p=0.022).

Subgroup-analysis

Subgroup-analysis was performed in Asian MFS patients and Caucasian MFS patients who were not dependent on their FBN1 mutation to fulfil the Ghent criteria of 2010. For the subgroup-analysis we excluded one patient from the Asian population and 16 patients from the Caucasian population. The subgroup analysis rendered similar results as the main analysis, regarding the cardiovascular complications and differences between clinical features (data not shown).
Discussion

This study demonstrated significant differences in clinical features of the cardiovascular, ocular and skeletal system between a Caucasian and Asian MFS population. Especially the cardiovascular system seemed to be more severely affected in the Asian population, with larger aortic root dimensions corrected for BSA or when Z-scores are used and more frequently MVP, while there was similar use of β-blocker therapy.

In line with previously described Caucasian and Asian Marfan populations, we confirmed that Asian Marfan populations have a higher prevalence of aortic root dilation compared to Caucasian Marfan populations (Table 2). A possible explanation for the more severely affected cardiovascular system in the Asian population may be due to under diagnosis of MFS by three factors. The first factor may involve “true” racial differences between Caucasian and Asian populations in general. Some clinical features, such as myopia and scoliosis, are much more common in the general Asian population compared to the Caucasian population. Therefore, these features are less likely to be noticed, resulting in reduced MFS screening and under diagnosis. In our study we also found a high prevalence of myopia and scoliosis in the Asian MFS population. Furthermore, our study confirmed that the Asian population has a lower prevalence of ectopia lentis and less pectus deformities.

The second factor for under diagnosis of MFS may be that genetic testing for a FBN1 mutation is not routine practice in Singapore, as a consequence of insurance regulations. Since MFS is a progressive disease, genetic testing to reveal MFS is important in patients who do not yet meet the Ghent criteria, such as mildly affected and young patients. They may develop MFS and cardiovascular complications over time. As a result,
patients will be diagnosed at a later stage of disease and therefore present with more severe features. Therefore, especially in countries where genetic testing is not routinely available, accurate applicability of the Ghent criteria to different races is a necessity to prevent cardiovascular complications.

The third factor for under diagnosis of MFS is the use of absolute aortic diameters in Singapore instead of Z-scores. Although the Asian and Caucasian MFS population had
similar absolute aortic root diameters, the aortic root corrected with use of the Z-score was significantly more dilated in the Asian compared to the Caucasian MFS population. In populations with a large BSA, Z-scores seem to underestimate aortic root dilation, because the relationship between aortic root diameter and BSA is not linear but has an absolute threshold in individuals with a large BSA of about 38 mm. However, in populations with much smaller BSA, such as the Asian population, the Z-score seems to be more accurate in prediction of severity of aortic root dilation. Furthermore, the Z-score is currently calculated following formulas using aortic root diameters and BSA of the Caucasian population (See Appendix).

**Appendix - Z-score and mean dependent on age and body surface area**

The Haycock formula:

\[
BSA \ (m^2) = 0.024265 \times \text{Height}\ (cm)^{0.3964} \times \text{Weight}\ (kg)^{0.5378}
\]

Z-score for aortic root diameter:

\[
Z\text{-score} = \frac{\text{AoD} \ (mm) - \text{mean} \ (mm)}{\text{SD} \ (mm)}
\]

Mean aortic root diameter:
- Age < 18 years: mean = 1.02 x (0.98 x BSA (m²))
- Age < 40 years: mean = 0.97 x (1.12 x BSA (m²))
- Age > 40 years: mean = 1.92 x (0.74 x BSA (m²))

BSA = body surface area (m²), Z = Z-score, AoD = aortic root diameter (mm), mean = mean aortic root diameter in general population dependent on age and body surface area (mm), SD = standard deviation (mm)

Adjustment of these formulas for Asian populations with mean BSA measurements of the general Asian population is recommended.

Although we confirmed several differences between the clinical features of an Asian and Caucasian MFS population in comparison with some smaller studies, discrepancies exist. Akutsu et al. and Yoo et al. found less involvement of the skeletal system in their Japanese and Korean MFS population, respectively, compared to our Asian cohort.²¹,²² The studies of Akutsu et al. and Yoo et al. had some selection bias, since most of their patients came to the hospital with an indication for aortic surgery or acute aortic dissection, whereas our patients were enrolled from Marfan screening clinics. Another explanation may be the lack of genetic testing in our Singaporean cohort. However, we propose this as a minor factor, because when we excluded MFS patients who were dependent on their FBN1 mutation to fulfil the Ghent criteria of 2010 in our study, differences in clinical features between the Asian and Caucasian population were essentially similar.
In conclusion, clinical features of the cardiovascular, ocular and skeletal system significantly differ between a Caucasian and Asian MFS population. Following the outcomes of our study, we recommend the use of Z-score for the indication of aortic root dilation in Asian populations. Furthermore, more information about the prevalence of MFS features in the general and MFS Asian population is needed in order to optimize the Ghent criteria for accurate diagnosis and prevention of cardiovascular complications of MFS for the Asian race. Finally, genetic testing in young and mildly affected patients is recommended in order to diagnose MFS before the onset of cardiovascular complications.

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