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Delphine Détaint[1]*, Laurence Faivre[2,3], Gwenaelle Collod-Beroud[4,5], Anne H. Child[6], Bart L. Loeys[7], Christine Binquet[3,8], Elodie Gautier[3,8], Eloisa Arbustini[9], Karin Mayer[10], Mine Arslan-Kirchner[11], Chantal Stheneur[12], Dorothy Halliday[13], Christophe Beroud[4,5,14], Claire Bonithon-Kopp[3,8], Mireille Claustres[4,5,14], Henri Plauchu[15], Peter N. Robinson[16], Anatoli Kiotsekoglou[6], Julie De Backer[7], Lesley Adès[17,18,19], Uta Francke[20,21], Anne De Paepe[7], Catherine Boileau[22,23], and Guillaume Jondeau[1,24]

[1]AP-HP, Hôpital Bichat, Consultation pluridisciplinaire Syndrome de Marfan et apparentés, Paris F-75018, France; [2]CHU Dijon, Centre de Génétique, Dijon F-21000, France; [3]CHU Dijon, Centre d'investigation clinique – épidémiologie clinique/essais cliniques, Dijon F-21000, France; [4]INSERM, U827, Montpellier F-34000, France; [5]Université Montpellier I, Montpellier F-34000, France; [6]Department of Cardic and vascular Sciences, St. George's Hospital, London, UK; [7]Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium; [8]INSERM, CIE1, Dijon F-21000, France; [9]Centre for Inherited Cardiovascular Diseases, Foundation IRCCS Policlinico San Matteo, Pavia, Italy; [10]Center for Human Genetics and Laboratory Medicine, Martinsried, Germany; [11]Institute of Human Genetics, Hannover Medical School, Hannover, Germany; [12]AP-HP, Hôpital Ambroise Paré, Service de Pédiatrie, Boulogne F-92000, France; [13]Department of Biochemistry, University of Oxford, Oxford, UK; [14]CHU Montpellier, Hôpital Arnaud de Villeneuve, Laboratoire de Génétique Moléculaire, Montpellier F-34000, France; [15]Hôtel Dieu, Service de Génétique, Lyon F-69, France; [16]Institut für Medizinische Genetik, Universitätsmedizin Charité, Berlin, Germany; [17]Marfan Research Group, The Children's Hospital at Westmead, Sydney, Australia; [18]Discipline of Paediatrics and Child Health, University of Sydney, Sydney, Australia; [19]Department of Clinical Genetics, The Children's Hospital at Westmead, Sydney, Australia; [20]Department of Genetics, Stanford University Medical Center, Stanford, CA, USA; [21]Department of Pediatrics, Stanford University Medical Center, Stanford, CA, USA; [22]AP-HP, Hôpital Ambroise Paré, Laboratoire de Génétique Moléculaire, Boulogne F-92000, France; [23]Université Versailles-Saint Quentin en Yvelines, UFR P.I.F.O, Garches F-92380, France; and [24]INSERM U698, Faculté Bichat, Paris VII, Paris, France

Aims In patients with Marfan syndrome and other type-1 fibrillinopathies, genetic testing is becoming more easily available, leading to the identification of mutations early in the course of the disease. This study evaluates the cardiovascular (CV) risk associated with the discovery of a fibrillin-1 (*FBN1*) mutation.

Methods and results A total of 1013 probands with pathogenic *FBN1* mutations were included, among whom 965 patients [median age: 22 years (11–34), male gender 53%] had data suitable for analysis. The percentage of patients with an ascending aortic (AA) dilatation increased steadily with increasing age and reached 96% (95% CI: 94–97%) by 60 years. The presence of aortic events (dissection or prophylactic surgery) was rare before 20 years and then increased progressively, reaching 74% (95% CI: 67–81%) by 60 years. Compared with women, men were at higher risk for AA dilatation [≤30 years: 57% (95% CI: 52–63) vs. 50% (95% CI: 45–55), $P = 0.0076$] and aortic events [≤30 years: 21% (95% CI: 17–26) vs. 11% (95% CI: 8–16), $P < 0.0001$; adjusted HR: 1.4 (1.1–1.8), $P = 0.005$]. The prevalence of mitral valve (MV) prolapse [≤60 years: 77% (95% CI: 72–82)] and MV regurgitation [≤60 years: 61% (95% CI: 53–69)] also increased steadily with age, but surgery limited to the MV remained rare [≤60 years: 13% (95% CI: 8–21)]. No difference between genders was observed (for all $P > 0.20$). From 1985 to 2005 the prevalence of AA dilatation remained stable (P for trend = 0.88), whereas the percentage of patients with AA dissection significantly decreased (P for trend = 0.01).

Conclusion The CV risk remains important in patients with an *FBN1* gene mutation and is present throughout life, justifying regular aortic monitoring. Aortic dilatation or dissection should always trigger suspicion of a genetic background leading to thorough examination for extra-aortic features and comprehensive pedigree investigation.

Keywords Marfan syndrome • Cardiovascular risk • Aortic dilatation • Aortic dissection • FBN1 gene mutation

* Corresponding author: Centre de Référence Syndrome de Marfan et Apparentés, Cardiology Department, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France. Tel: +33 140256811, Fax: +33 140256854, Email: delphine.detaint@bch.aphp.fr

Introduction

The Marfan syndrome (MFS) was identified more than 100 years ago, and since then, diagnostic criteria have evolved.[1,2] Progress in cardiac imaging and the understanding of the genetic basis have modified the classification of patients, with increasing importance given to the primary genetic defect. Genetic testing is becoming easier and more readily available, leading to the identification of a fibrillin-1 (*FBN1*) mutation earlier in the evaluation of the patient, and is therefore increasingly used for familial screening in asymptomatic parents. The cardiac features are those responsible for the high mortality associated with the syndrome.[3] Thus, it is important to recognize the aortic and mitral risks associated with the discovery of a *FBN1* gene mutation, by far the most frequent genetic alteration for MFS fulfilling the international criteria,[4] but also for other rare disorders associated with *FBN1* gene mutations. These pathologies have been referred to as the fibrillinopathies, and include neonatal MFS,[5] isolated ectopia lentis,[6] isolated ascending aortic (AA) aneurysm,[7] isolated skeletal features,[8,9] and Weill–Marchesani syndrome.[10]

We present here the aortic and mitral valve (MV) features present in the largest population of patients with mutations in the *FBN1* gene and selected as such, collected through an international network.[11]

Methods

Population

The framework of the Universal Marfan Database (UMD)-*FBN1* and participating centres identified 1191 probands carrying an *FBN1* mutation between 1995 and 2005. For UMD database, see Supplementary material online. A total of 178 patients were excluded: there were insufficient data for 173, two different mutations on the same *FBN1* allele for 4, and compound heterozygousity for *FBN1* mutation was present in one patient. Forty-eight additional patients were excluded for the purpose of this study because they presented with neonatal MFS, the clinical course of which is known to be very different.[12] The remaining 965 patients were included in the study. They originated from 38 different countries located across 5 continents.

The clinical data were collected mainly from standardized questionnaires sent to the referring physician, and a minority of data were obtained from previous publications that included sufficient clinical data. All questionnaires were collected by one individual to avoid duplication of patients in the study (L.F.). Clinical information included a range of qualitative and quantitative parameters, including age at diagnosis and cardiovascular (CV), ophthalmological, skeletal, skin, lung, and dural manifestations as previously described.[13]

The diagnosis of type-1 fibrillinopathy included (i) MFS and (ii) other entities called 'other type-1 fibrillinopathies' which associate incomplete features for MFS with the presence of a *FBN1* gene mutation. Marfan syndrome was diagnosed according to international criteria when a patient presented with two major criteria and the involvement of at least one other body system, or one major criterion and the involvement of another body system, when another close family member had been independently diagnosed as having Marfan.[2]

Involvement of the cardiovascular system

Age at diagnosis was systematically noted for all CV features. We collected data about the presence of AA dilatation, the history of AA dissection, descending aorta dissection, and prophylactic referral for aortic root surgery. Indications for AA surgery relied on available guidelines and evolved with time (AA $\geq$ 50 mm or rapid diameter progression). Definition of AA dilatation was mainly based on echocardiography with calculation of *z*-score according to Roman's normograms.[14] However, depending on the year of diagnosis and the centre specificities, alternative methods (Angiography, CT scanning) could have been used to diagnose the aortic dilatation.

Aortic dissections were noted as either initially present at the time of diagnosis or as occurring once the diagnosis has been made. Both aortic surgery and aortic dissection were considered aortic events.

Data collected on MV features included presence of MV prolapse (MVP), significant mitral regurgitation (MR) (of at least moderate degree based on angiography or echocardiography) and surgery for MR. Diagnosis for MVP was made locally based upon available definitions at the time of inclusion.[15]

Statistical analysis

A time-to-event analysis technique was used to estimate a reliable cumulative probability of observing AA dilatation, AA dissection, AA dissection subsequent to the diagnosis, AA surgery (preventive surgery), MVP, MR, and surgery for MR. An aortic endpoint combining aortic dissection and preventive surgery was considered (aortic event). The baseline date (time zero) was the date of birth and the time to event diagnosis was defined as the interval between the date of birth and the date of the first manifestation of the event. The Kaplan–Meier method was used to estimate the cumulative probabilities of clinical manifestations. Comparisons between men and women were made by using the non-parametric log-rank test. Results are expressed with 95% confidence interval (CI).

As an adjunctive analysis, we calculated with Cox model the Hazard ratios (95% CI) of presenting a clinical aortic event (dissection or surgery) according to age of AA dilatation diagnosis and gender.

As the number of diagnoses of type-1 fibrillinopathy changed from one period to another, we normalized the number of aortic dilatation, aortic dissection, and preventive surgery by the number of diagnoses made during the same study period. Trends were examined in four time periods of 5 years from 1985 (approximate date of introduction of echocardiography in clinical practice) to 2005 and tested with linear regression. The effects of mutation type and localization on the occurrence of CV features were also studied.[13]

SAS software version 9.2 and Stata software version 8 were used for all statistical analyses. *P*-values of <0.05 were considered significant. The tests were two-sided.

Results

The study population consisted of 965 probands. The median age at diagnosis was 22 years (inter quartile range: 11–34). Fifty-three per cent ($n = 511$) of patients were male and 47% ($n = 454$) were female. Seventy-three per cent of the patients fulfilled the international criteria for MFS whereas 27% had incomplete feature for MFS.

The majority ($n = 854$) of patients demonstrated a cardiac manifestation, involving the AA only in 291 (34%), the MV only in 124 (15%), or both AA and MV in 439 (51%) cases. Occurrence of dissection of the descending aorta alone was rare, affecting 42 patients (4%). Their characteristics are described in *Table 1*.

Table 1 Characteristics of patients incurring an aortic dissection

	Ascending aorta, *n* = 144	Descending aorta only, *n* = 42
Age at diagnosis (inter quartile range)	33 (25–43)	33 (21–44)
Age of dissection (inter quartile range)	35 (29–44)	36 (26–45)
Gender, male %	61%	57%
Presence at the time of diagnosis, %	67%	62%
Family history of type-1fibrillinopathy, %	67%	64%

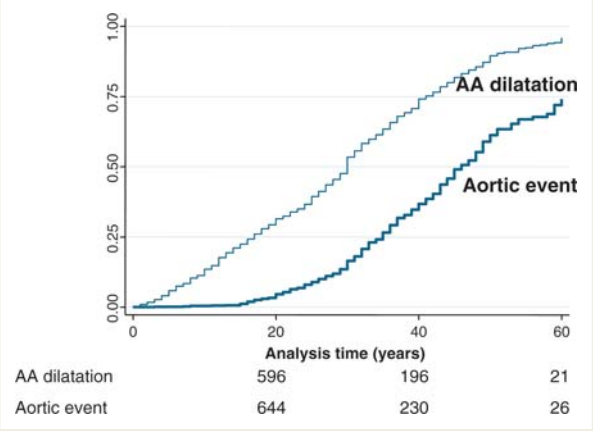

Figure 1 Kaplan–Meier analysis of the probability of diagnosing an ascending aortic dilatation (thin line) and aortic event (aortic dissection or surgery; thick line) in the study population. Number of patients at risk are indicated in the bottom.

Ascending aorta features associated with FBN1 mutations

Ascending aortic dilatation was present in 76% of the patients ($n = 730$). As shown in *Figure 1*, the percentage of patients presenting with an AA dilatation increased regularly with increasing age without limit. At the age of 60 years, 96% (95% CI: 94–97%) of the patients had documented AA dilatation, whereas only 53% (95% CI: 50–57%) of the patients had AA dilatation at the age of 30 years.

In men, in comparison with women, AA dilatation was observed significantly sooner ($P = 0.0076$) with a probability of 57% (95% CI: 52–63%) and 50% (95% CI: 45–55%) up to 30 years and 96% (95% CI:94–98%) and 96% (95% CI: 92–98%) up to 60 years in men and women, respectively (*Figure 2*, left panel).

Two hundred and seventy-nine patients (29%) incurred an aortic event, i.e. either AA dissection or prophylactic aortic surgery (*Table 1*). The probability of presenting an aortic event was 16% (95% CI: 14–20%) at the age of 30 years and 74% (95% CI: 67–81%) at the age of 60 years. After the age of 20 years the percentage of patients presenting an aortic event increased steadily.

More specifically, at 30 years 7% (95% CI: 6–10%) of the patients incurred an aortic dissection including 3% (95% CI: 2–4) with type-1 fibrillinopathy already recognized; at 60 years, figures are 51% (95% CI: 42–60) and 27% (95% CI: 17–40%), respectively. Similarly, prophylactic surgery was performed in 10% of the patients (95% CI: 8–12%) at 30 years and 40% (95% CI: 33–49%) at 60 years.

Aortic events occurred earlier in men than in women (*Figure 2*, right panel, $P < 0.0001$). The probability of an aortic event at the age of 30 years was 21% (95% CI: 17–26%) in men and 11% (95% CI: 8–16%) in women; and was 81% (95% CI: 73–88%) in men and 65% (95% CI: 54–77%) in women at the age of 60 years. Lastly, male gender remained an independent predictor of aortic events [adjusted HR 1.4 (1.1–1.8), $P = 0.005$), after adjustment for age of AA dilatation diagnosis.

Similar trends were observed for both components of the aortic event. At all ages, aortic dissection and aortic surgery were more frequent in men than in women: 9% (95% CI: 7–13%) vs. 5% (95% CI: 3–8%) at 30 years and 54% (95% CI: 44–66%) vs. 48% (95%

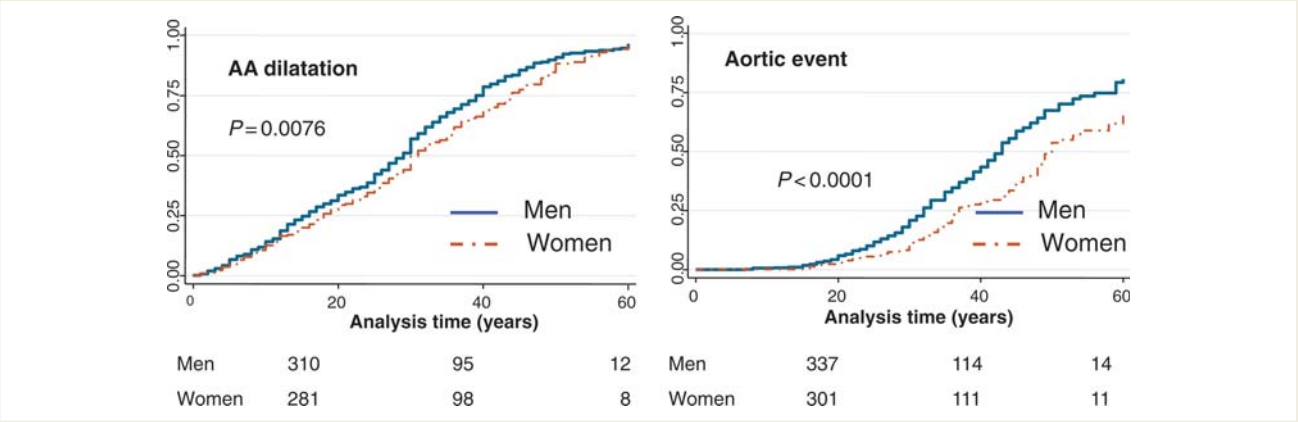

Figure 2 Kaplan–Meier analysis of the probability of diagnosing an ascending aortic dilatation (left panel) and an aortic event (right panel) in the study population according to gender.

CI: 35–62%) at 60 years ($P = 0.03$) for aortic dissection; and 12% (95% CI: 9–16%) vs. 7% (95% CI: 4–11%) at 30 years and 46% (95% CI: 37–57%) vs. 32% (95% CI: 21–47%) at 60 years ($P = 0.002$) for aortic surgery for men and women, respectively.

Mitral valve features associated with FBN1mutations

As shown in *Figure 3*, the percentage of patients presenting with a MV feature increased steadily with age. The probability of presenting an MVP increased from 43% (95% CI: 40–47%) at 30 years of age to 77% (95% CI: 72–82%) at 60 years of age. Similarly, the probability of presenting a MR increased from 24% (95% CI: 21–28%) at 30 years of age to 61% (95% CI: 53–69%) at 60 years of age. Surgery for MR only was uncommon, performed in 3% (95% CI: 2–5%) and 13% (95% CI: 8–21%) of the patients at 30 and 60 years, respectively.

In contrast to AA dilatation, the risk of MVP ($P = 0.23$), MR ($P = 0.61$), and surgery for MR ($P = 0.20$) was not influenced by gender (*Figure 4*).

Temporal trends

The number of diagnoses of type-1 fibrillinopathy during each time period is illustrated in *Figure 5A*. It significantly increased from 4% (between 1985 and 1989) to 46% (after 2000) of all tests performed during the study, (P for trend = 0.008). As this population is selected on molecular genetic criteria, this indicates an increasing use of the molecular biology over the years.

However, the prevalence of AA dilatation remained stable (from 71 to 79% of the patients, *Figure 5B*, P for trend = 0.88), suggesting stable severity of patient disease at the time of diagnosis. Conversely, aortic dissection (from 20 to 14%, *Figure 5C*, P for trend = 0.01) significantly declined, suggesting better management. No trends in referral to surgery were observed throughout the study period (from 14 to 15% *Figure 5D*, P for trend = 0.70) suggesting that better medical care may be responsible for improvement.

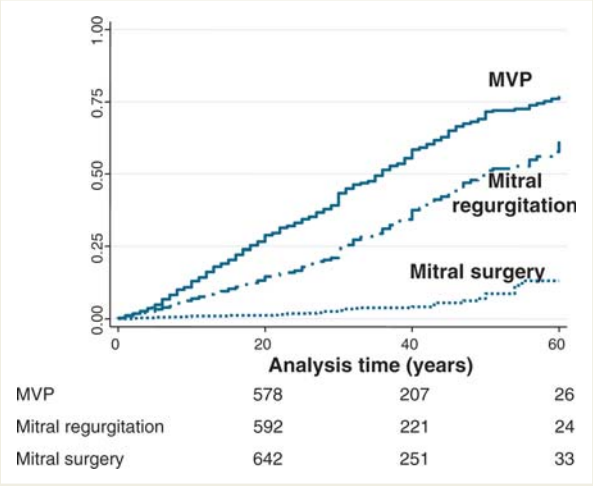

Figure 3 Kaplan–Meier analysis of the probability of diagnosing a mitral valve. Plain line indicates the probability of mitral valve prolapse (MVP), dotted line indicates the probability of mitral regurgitation, and pointed line indicates the probability of surgery on the mitral valve only.

Subgroup of adults fulfilling criteria for Marfan syndrome

In this subgroup ($n = 543$) the probability of the CV features was close to that reported for the overall population with at the age of 60 years a probability of presenting an aortic dilatation of 97% (95% CI: 95–99%), aortic event of 78% (95% CI: 70–85%), MVP of 77% (95% CI: 69–83%), MR of 62% (95% CI: 52–73%), and mitral surgery of 14% (95% CI: 8–24%).

Genotype phenotype correlation

Most of the CV features were not significantly different between patients with (i) premature termination codons vs. inframe mutations; (ii) with misense vs. nonsense or frameship mutations. A higher probability of AA dilatation, aortic event and MVP ($P = 0.0025$) were found in patients with mutations altering a cysteine (all $P < 0.03$).

Mutation within exons 24–32 vs. other exons were associated with higher probability of all the CV features ($P < 0.0003$ for all).

Discussion

The clinical availability of molecular genetics has increased considerably over recent years, with earlier use in MFS and with more and more mutations being recognized early in the course of the disease. This study includes the largest reported number of patients selected on a genetic basis to-date, and clearly indicates that the CV burden is considerable in patients with an *FBN1* mutation and remains so throughout life.

In particular, the incidence of aortic root dilatation steadily increases from infancy up to the age of 60 years. A normal aortic diameter, even measured in adulthood, does not indicate that it will remain normal throughout life, and there is no cut-off of age above which definitive reassurance can be given to patients with a *FBN1* gene mutation. Hence a normal diameter in adulthood

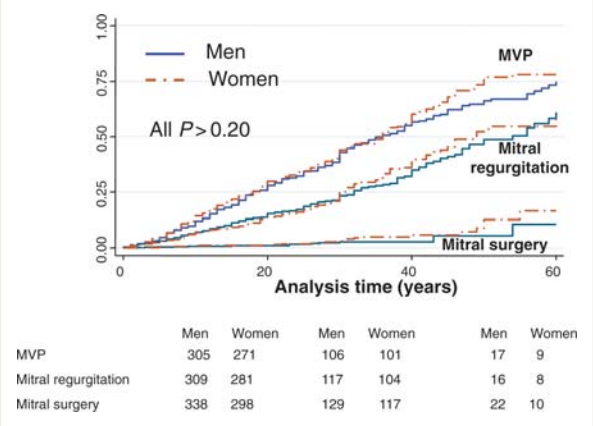

Figure 4 Kaplan–Meier analysis of the probability of diagnosing a mitral feature in the study population according to gender.

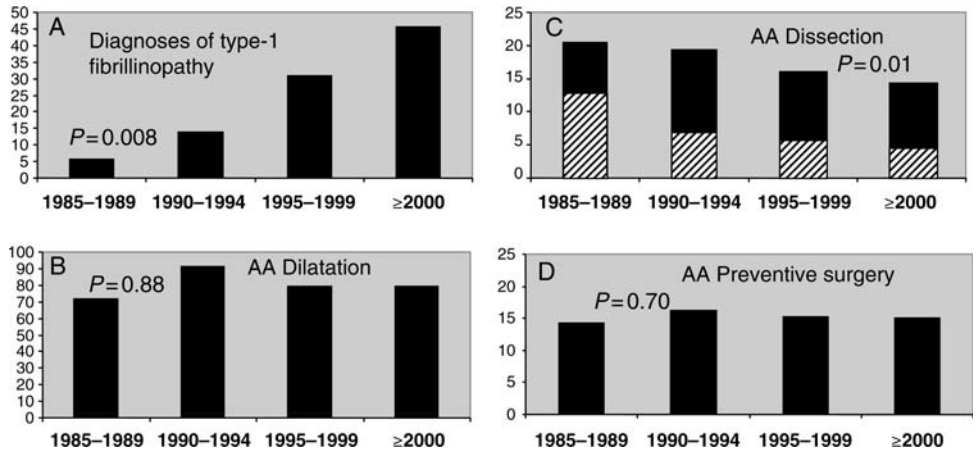

Figure 5 Evolution over time. (*A*) Evolution in the number of diagnosis of type-1 fibrillinopathy over time. (*B*–*D*) Rate of aortic manifestations over time. The rate of aortic manifestation is expressed as the ratio of number of patients with the aortic manifestation during the time period over the number of type-1 fibrillinopathy diagnosis during the same period. (*B*) Rate of AA dilatation. (*C*) Rate of aortic dissection; among aortic dissection, the rate of aortic dissection occurring once the diagnostic has been made is represented by the black-and-white bars. (*D*) Rate of preventive aortic surgery. *P*-values for trends are indicated. AA, ascending aorta.

should not prevent patients from aortic follow-up and access to preventive medical therapy including the beta-blocker therapy.[16–18]

Aortic dilatation remains the best predictor of the occurrence of an aortic event.[3,19–21] In the present study, where neonatal MFS are excluded, the aortic events (either prophylactic aortic surgery or aortic dissection) are rare in childhood. In adulthood, the occurrence of an aortic event increases progressively, and by the age of 60 years, an aortic event had occurred in 75% of the patients. As for the appearance of AA dilatation, no upper age limit can be given as almost half of the patients without an aortic complication by the age of 40 years will have an aortic event later on. This also stresses the importance of yearly echocardiographic monitoring.

Men appear to be at higher risk for an aortic event than women. Indeed they are more prone to AA dilatation and consequently to either aortic dissection or surgery with an adjusted risk 1.4 times higher than women for the combined aortic event. Twenty-five per cent of men had an aortic event at the age of 32 years (50% by 43 years), whereas a similar figure was reached 5 years later in women (25% of women had had an aortic event by the age of 37 years; 50% by 50 years). In fact, aortic root dimension is smaller in women vs. men both in healthy and MFS population.[22–23] In the Framingham Study that includes healthy men and women, the aortic root diameter was on average 2.4 mm smaller in women than in men, even after adjustment for age and body surface area.[23] Similarly, the aortic root diameter was on average 5 mm smaller in MFS women than in MFS men in the study of Meijboom *et al.*[24] The question therefore arises as to whether the threshold proposed for prophylactic aortic root surgery should be lower in women. In a study of 221 adults with MFS (113 males, 108 females), three dissections in women may have been prevented by reducing the cut-off value of aortic root diameter of 5 mm during the follow-up of 7 years.[24] However, in the current study, aortic dissection occurred at a lower frequency in women than in men, suggesting that the similar threshold used for prophylactic surgery in both sexes did not lead to an increased risk of aortic dissection in women.

Our data rather suggest the existence of a male susceptibility to aortic fragility. This is in keeping with the International Registry of Acute Aortic Dissection which reports that acute aortic dissection is twice as common in males,[25] even in the subgroup of patients with MFS. Despite large intra-familial clinical variability in MFS, no modifier gene has been reported yet. No clear explanation has been proposed up to now. Experimental investigations suggest that differences in proteinases involved in medial wall destruction may contribute to gender-related differences in aneurysm development.[26,27]

Interestingly, this male predisposition appears to be limited to the aorta. In contrast to aortic manifestations, MV abnormalities appear at a similar rate in both genders in patients with *FBN1* mutations. The reported incidence of MVP associated with MFS in the literature is highly variable from one study to another and ranges from 28 to 80%.[28–30] Regular increases in prevalence with age may explain some of these variations, as well as the evolution of diagnostic criteria for MVP with time. A clear observation in our study is that MV surgery is required much less often than aortic surgery.

Aortic manifestations: trends over the years and genetic implications

The rate of patients newly recognized as presenting an aortic dilatation remains stable over the years, suggesting that diagnosis is made in patients of similar severity (only probands were included in this study).

However, the risk for aortic dissection has significantly decreased whereas reference to surgery remained stable. This

probably reflects the improvement in management with time, due to a better knowledge of the disease by cardiologists and others practitioners, closer echocardiographic patient follow-up, and also perhaps a higher rate of prescriptions for beta-blockers.[16,31–34] More systematic familial screening, facilitated by recognition of a *FBN1* gene mutation in the proband,[13] should allow earlier diagnosis in other family members and therefore also improve outcome in those related patients.

The present study indicates that aortic dissection occurring in patients aged from 9 to 60 can be related to mutations in the *FBN1* gene, and that aortic dilatation may also be discovered throughout life. Clinical suspicion of a genetic aetiology should therefore be high. This is not to say that molecular analyses looking for FBN1 mutations should be performed in all patients with aortic dissection: the success rate of molecular screening is heavily dependent on the clinical picture, and the probability of a positive result in the absence of extra-cardiac signs is very low.[35] Actually, the presence of an aortic dissection or dilatation should be accompanied by some extra-cardiac features and/or affected family members to justify mutation screening for FBN1.[13,36] Besides, mutations in the other genes[37–43] (TGFBR2, TGFBR1, ACTA2, MYH11) may lead to familial aortic aneurysm with or without other clinical features (developmental defects, PDA, livedo reticularis, iris floculi). Molecular screening for mutations in all these genes may be warranted in familial forms.

Limitations

The reasons leading to molecular screening for FBN1 mutations have not been collected, and the inclusion of probands only may contribute to an overestimation of the CV features (as the presence of significant clinical features is necessary to justify the test). However, this bias may be balanced by the huge increase in the number of genetic tests performed in the last years of the study, which included patients with only a few signs. Although the definitions of AA dilatation, MVP, MR, and thresholds for prophylactic surgery may fluctuate from one centre to another, the expertise of the participating centres and the awareness of guidelines on the subject[44] suggest that these definitions were relatively uniform overall.

This study is retrospective by design and does not provide clinical follow-up for all individuals. However, the transversal view given here enabled the description of the burden of CV features associated with FBN1 gene mutations.

Conclusion

Despite progress made in the understanding and management of patients with MFS, the burden of CV manifestations remains considerable. The probability of presenting with an AA dilatation or an aortic event (aortic surgery or dissection) increases from childhood to adulthood. This emphasizes the need for continuing aortic follow-up throughout life as the aortic risk remains even in an adult patient with a normal aortic diameter if carrying an FBN1 mutation. Aortic dilatation or dissection should always trigger suspicion of a genetic background leading to thorough examination for extra-aortic features and comprehensive pedigree investigation. Thus, in clinical practice, a search for *FBN1* mutation should be proposed in presence of extra-cardiac features and/or an affected family member.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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