Marfan Cardiomyopathy and Arrhythmia

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Marfan syndrome (MFS) is a heritable systemic connective tissue disease with important cardiovascular involvement, including aortic root dilatation and mitral valve prolapse. Life expectancy in patients with MFS is mainly determined by cardiovascular complications, among which aortic dissection or rupture are most dreaded. In recent years, heart failure and ventricular arrhythmia have drawn attention as extra-aortic cardiovascular manifestations and as additional reported causes of death. Imaging studies have provided data supporting a primary myocardial impairment in the absence of valvular disease or cardiovascular surgery, while studies using ambulatory ECG have demonstrated an increased susceptibility to ventricular arrhythmia.

Keywords: Marfan syndrome ; heart failure ; myocardial ; ventricular arrhythmia

1. Introduction

Marfan syndrome (MFS) is a systemic connective tissue disease with autosomal dominant inheritance and a reported prevalence ranging from 1.5 to 17.2 per 100,000 individuals [1]. Cardiovascular, ocular and skeletal organ systems are most frequently involved in the Marfan phenotype. The most common clinical manifestations include aortic dilatation, mitral valve prolapse, lens luxation and skeletal abnormalities (disproportionally long limbs, scoliosis and pectus deformities). Other manifestations can be found in the integumental, pulmonary and central nervous organ systems. A wide phenotypic variability reflects the different extent to which various organ systems can be affected [1][2]. Diagnosis is based on the revised Ghent nosology, including aortic root dilatation and lens luxation as the two cardinal manifestations (Table 1) [2].

Table 1. Revised Ghent criteria for diagnosis of MFS [2].

In the Absence of Family History of MFS:
(1) Ao * (Z-score ≥ 2) AND EL = MFS
(2) Ao * (Z-score ≥ 2) AND causal *FBN1* mutation = MFS
(3) Ao * (Z-score ≥ 2) AND systemic score ≥ 7 points = MFS
(4) EL AND causal *FBN1* mutation with known Ao = MFS
In the Presence of Family History of MFS:
(5) EL AND family history of MFS = MFS
(6) Systemic score ≥ 7 points AND family history of MFS = MFS
(7) Ao * (Z-score ≥ 2 above 20 years old, ≥ 3 below 20 years) + family history of MFS = MFS

* Ao = Aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection. EL = ectopia lentis; MFS = Marfan syndrome.

In the majority of patients, a (likely) pathogenic variant is found in the *FBN1* gene, encoding the extracellular matrix glycoprotein fibrillin-1, an important element in the assembly of microfibrils. Microfibrils may perform a structural role individually (in the extracellular matrix of elastic and non-elastic tissues), or unified as a supporting scaffold for elastin, thereby forming elastic fibers [3]. Elastic fibers play a central role in the structural integrity of connective tissues (e.g., in the aorta) by providing elasticity and tensile strength. In addition to the structural role, fibrillin-1 also plays a communicative role in biosignaling (regulating local bioavailability of TGF-β) and mechanosignaling (by interacting with mechanosensors and providing feedback to regulate the response to hemodynamic changes). Therefore, defects in fibrillin-1 may alter the structural integrity of connective tissue and may result in abnormal cellular signaling [3][4][5].

Life expectancy in patients with MFS is mainly determined by cardiovascular complications. Progressive dilatation of the proximal aorta is an important manifestation, rendering these patients at risk of aortic dissection or fatal rupture [6]. Although the aortic sinus is most commonly affected, aneurysms and dissections in more distal aortic regions and in extra-aortic arteries can also occur [7][8]. The reported prevalence of aortic root dilatation is slightly lower in children compared to adults (approx. 80% vs. 90%) [9][10]. Furthermore, data from the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry indicate that adult males are more likely than females to have aortic root dilatation (92% vs. 84%), aortic regurgitation (55% vs. 36%), and to have undergone prophylactic aortic root replacement (47% vs. 24%) [10]. Increased awareness, early detection, careful follow-up, life-style adjustments, pharmacological treatment and prophylactic surgery are currently established as the cornerstones of treatment in MFS. Implementation of these aspects in the treatment strategy has shown to substantially reduce the risk of type A dissection [6][11]. In patients with known (or suspected) MFS, echocardiography plays a central role in the identification, severity assessment and follow-up of cardiovascular abnormalities [6].

In recent years, heart failure and ventricular arrhythmia have drawn attention as additional cardiovascular manifestations of MFS [12]. Several imaging studies have provided data supporting a (sub)clinical, primary myocardial impairment in the absence of valvular disease or cardiovascular surgery in patients with MFS. In addition, studies using ambulatory ECG have demonstrated an increased susceptibility to ventricular arrhythmia [13][14]. These manifestations are also reflected in studies reporting on survival in patients with MFS, with heart failure and arrhythmia or sudden cardiac death (SCD) included as additional causes of death [14][15][16]. In this paper, we review current literature in order to provide insights in characteristics, pathophysiology and evolution of myocardial function, heart failure and ventricular arrhythmia in MFS.

2. Current View on Marfan Cardiomyopathy and arrhythmia

Current literature indicates that ventricular dimensions as well as systolic and diastolic function are well within normal limits in the vast majority of patients with MFS. However, even in the absence of cardiac surgery or significant valvular disease, a mild biventricular dilatation with diastolic and systolic dysfunction in a subgroup of patients with MFS has been repeatedly reported [17][18][19][20][21][22][23][24]. Since myocardial involvement was reported in the absence of any cardiac surgery or significant valvular abnormalities, this phenotypic expression was designated an “intrinsic” or “inherent” dysfunction of the myocardium and was termed “Marfan cardiomyopathy”. Advanced imaging techniques (such as CMR, TDI, strain and strain rate imaging) appear to be more suited to detect these alterations. Despite these findings, almost no patients were diagnosed with clinical heart failure in aforementioned studies. Follow-up studies to better identify those patients at risk of clinically relevant myocardial dysfunction are still required.

In addition to aortic complications and cardiomyopathy, arrhythmia should be recognized as a relevant manifestation of the cardiac phenotype observed in MFS [14][25][26]. Several studies have associated MFS with an increased risk of arrhythmia. Studies based on data from ambulatory ECG in adults have demonstrated the presence of significant ventricular ectopy (defined as >10 premature ventricular contractions per hour) in 20–35% [14][27][28]. In children with MFS, the reported frequency of ventricular arrhythmia is much lower (7% demonstrating ventricular ectopy) [29]. Similarly, non-sustained ventricular tachycardia (NSVT) is reported in 10–20% of the adult patients with MFS and appears to be very rare in children [14][27][28][30]. However, ventricular tachycardia (VT) and SCD have been reported in both adults and children with MFS [14][31]. Four studies reported life-threatening arrhythmias in 7–9% of the patients and SCD, most likely due to arrhythmia, occurred in up to 4% [14][27][32][33]. Furthermore, fatal arrhythmias are reported in 12–19% of patients with MFS after aortic surgery, making it the 2nd most frequent cause of death in this setting [25][34][26].

3. The Intertwined Mechanism of Marfan Cardiomyopathy and Ventricular Arrhythmia

The relation between a reduced amount or quality of extracellular fibrillin in the myocardium, a primary impairment of myocardial function and affinity for ventricular arrhythmia remains unclear. It is possible that, due to the reduced amount or quality of fibrillin, mechanical forces imposed on the cardiomyocytes in patients with MFS may be less adequately compensated than in healthy individuals. Therefore, chronic or acute myocardial dilatation and associated stretch could perhaps induce (complex) ventricular ectopy more easily in these patients. In addition, the impairment of myocardial function observed in some patients may also signify inherent abnormalities in the underlying electrophysiological substrate. The combination of (complex) ventricular ectopy together with the alterations in electrical and/or mechanical properties of the heart may be severe enough to induce SCD in some patients with MFS, as suggested in studies by Hoffmann et al. [32] and by Yetman et al. [14]. Furthermore, increased NT-proBNP has been demonstrated as independent predictor of both diastolic dysfunction and severe arrhythmic events [32][35]. This may signify that long-term mild myocardial stretch potentially predisposes these patients to (severe) ventricular arrhythmia [32][35].

4. Current Limitations and Evidence Gaps

To date, large multicentre studies reporting the overall incidence or prevalence of heart failure and severe arrhythmia in MFS are lacking. Therefore, identification of predisposing factors is limited. Additional studies are necessary to evaluate the clinical relevance of Marfan cardiomyopathy and ventricular ectopy, to elucidate the underlying mechanisms in MFS and to allow better risk stratification of patients with MFS. Information on these aspects could hold important implications for developing strategies to treat heart failure and ventricular arrhythmia in MFS.

We should also take into account that—certainly in the case of older studies—some of the patients enrolled may have had some other form of Heritable Thoracic Aortic Disease, caused by pathogenic variants in genes other than *FBN1*. Advancing insight in recent years shows us that caution is advised in grouping all these conditions.

5. Conclusions

Myocardial involvement in the absence of valvular disease can be observed in patients with MFS, usually presenting as mild, asymptomatic impairment of LV systolic and diastolic function. In addition, some patients with MFS present (complex) ventricular arrhythmia as well as alterations in repolarization. A subgroup of patients with MFS tends to develop heart failure, severe arrhythmia and SCD, in which the effects of cardiac stressors may play an important role. Reduced myocardial function, heart failure and ventricular arrhythmia should be considered an essential concern of medical care for patients with MFS. Careful assessment of these features should be added to the standard aortic evaluation.

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