ABSTRACT

Marfan syndrome is a rare connective tissue disorder manifesting with cardiovascular pathologies which are also the leading cause of death. Herein, we present the past 20 years follow up of a family with 17 members afflicted with Marfan syndrome. 3 members of the family were deceased and none were due to cardiovascular events. We assume to some extent traumas are a neglected cause for a part of mortality in Marfan syndrome.

Key words: Death, Marfan syndrome, trauma

INTRODUCTION

Marfan syndrome is a rare condition identified by disorders in connective tissue with an autosomal dominant inheritance. The prevalence and incidence rates are estimated to be 1 per 5000-10000 and 2 to 3 per 10000 individuals respectively.[1] The condition is usually caused by a mutation in the gene encoding fibrillin on chromosome 15q15 which consequently impacts multiple organs such as eyes, heart, skeleton, and vessels.[2] The main ocular pathology is Ectopia Lentis, however, it can be presented with other pathologies including cataracts and glaucoma.[3] Also, progressive aortic dilation at the level of valsalva sinus is the most common cardiovascular involvement leading to aortic dissection which is believed to be the primary cause of death.[4] In 1970, life expectancy of the patients with Marfan’s syndrome was reported to be two-thirds of unaffected individuals,[5] however, later reports showed increased life expectancy close to normal due to improvements in diagnosis and treatment techniques.[6]

In the current paper, we present the cardiovascular and ocular involvements, complications, and treatments of a family with Marfan syndrome who were followed-up for the past 20 years. Moreover, we found it noteworthy to declare none of the deaths were due to cardiovascular events which will be discussed.

CASE PRESENTATION

In 1998, a 17-year-old male reported to an ophthalmologist with a complaint of visual disturbances, and ended up with the diagnosis of Marfan syndrome (MFS). Eleven members of his family were diagnosed with MFS by 2008 and as the children were born, this number was raised to 17 members by 2018 [Figure 1].

MFS diagnosis was established according to Ghent Nosology criteria for 17 of 21 members of this family. We believe such a high genetic penetrance is a rare entity [Figure 2]. Further molecular and genetic tests confirmed the diagnosis of MFS with a high level of confidence. For 20 years they went under periodic examinations. They were followed up by a single cardiologist and a single ophthalmologist.
Cardiovascular involvements were seen in 16 members of this family, representing for more than 90% of affected individuals. The most common pathology was mitral valve disease (including mitral valve prolapse and regurgitation) followed by aortic root dilation. Three patients were operated electively for aortic root replacement and one patient underwent urgent surgery for aortic dissection via the Bentall procedure [details are shown in Table 1].

In this study, ocular manifestations included lens ectopia (100%), flat cornea (23%), on gated eyeball (29%), hypoplastic iris or ciliary muscle hypoplasia (41%), glaucoma, cataract, and retinal detachment. Four patients needed ocular surgery [details are shown in Table 1].

Unfortunately, during the 20 years, three members were deceased including two patients and one healthy individual which indicates a mortality rate of 11% among our MFS patients (2/17).

Although it is well known that cardiovascular pathologies are the leading cause of death in patients with MFS; nevertheless, no individual in this family died following cardiovascular events.

The patients died in two separate car accidents while driving, which given to their history of ocular pathologies makes us think acute visual disturbances as a possible cause of trauma and eventually death.

DISCUSSION

In recent decades, advances in diagnosis, treatment, and management of Marfan syndrome have improved the life expectancy of the patients (life expectancy was 40 years in 1970; 60 years in 1995).[6,6]

A study on 2329 patients with MFS in 2013, showed that the average mortality rate of patients with MFS was 0.23% annually and cardiovascular events were responsible for 86% of the deaths.[6] However, cardiac death is known to be the cause of sudden death in more than 90% of the cases (mostly aortic dissection, chronic heart failure, and valvular heart disease).[6] Another study conducted by Yetman et al., reported three sudden deaths had occurred in 70 patients while none was related to either aortic dissection or any other structural disorders as evidenced by autopsy. All deaths were suspected to be arrhythmogenic.[7] Additionally, further investigations confirmed an increase in LV size is linked to repolarization disturbances in MFS patients.

We followed up the family reported here over the past 20 years and 3 deaths occurred. However, patients with cardiac involvement were increased from ten in 2008 to sixteen by the time we are reporting this article,[8] none died because of cardiac events. In fact, all the mortality causes were due to traffic collisions in this study.

In the authors opinion, visual disturbances were responsible for deaths however arrhythmia also seems to be a possible cause, according to the study of Yetman.[7]

To the best of our knowledge, there are insufficient data to consider trauma as a cause of death. Hence, it is important to propose legislation against driving license for MFS patients, even in normal visual examinations. In most cases, eyeglasses or contact lenses can correct the defects, but it cannot prevent from experiencing sudden visual disturbances which lead to surgeries. Consistently, during the past two decades, some of the patients were operated for ocular disorders.[9]

Elective surgery for repairing aortic root, already known as Bentall operation, is indicated when the aortic root dimension exceeds more than 50 mm in adults or 1 centimeter over a year.[10] This technique is presumed to be the main factor of improved life expectancy in MFS patients. MFS patients who undergo surgery for mechanical valve replacement must receive lifetime warfarin to avoid thrombotic complications.

The average age and mortality rate for aortic dissection were reported to be 25.6 years and 0.6%, respectively.[1] In the current study, four patients aged from 33 to 44 years underwent Bentall procedure with
| Case             | Age | Cardiovascular involvement | Ocular involvement | Complication                  | Treatment                                                                 |
|------------------|-----|----------------------------|--------------------|-------------------------------|---------------------------------------------------------------------------|
| Father           | 63  | MVP, MR, AI, ARD=31 mm     | Iridodonesis, Ectopia lentic, VA=1 m CF | Cataract                      | Lens extraction OS follow up annually                                     |
| First daughter   | 45  | MVP, MR, AI, ARD=34.9 mm   | Iridodonesis, Ectopia lentic, VA=0.1 | Three pregnancies without complication | Lensectomy + vitrectomy + buckling + silicone oil, follow up annually       |
| Second daughter  | 42  | MVP, MR, ARD=22.1 mm       | Iridodonesis, Ectopia lentic, VA=5 m CF; blindness OS | One pregnancy without complication, Bentall procedure, stroke | Glasses, Follow up annually, propranolol warfarin |
| First son        | 39  | MVP, MR, ARD=29 mm         | Iridodonesis, Ectopia lentic, VA=3 m CF | Surgery for cataract and Bentall procedure for RD | Glasses, follow up annually, propranolol warfarin |
| Second son       | 37  | MVP, MR, ARD=26 mm         | Iridodonesis, Ectopia lentic, VA=4 m CF | Bentall procedure for aortic dissection | Lensectomy + vitrectomy + buckling + silicone oil, glasses, follow up annually, propranolol warfarin |
| Third son        | 31  | MVP, MR, AVR, ARD=26.8 mm  | Iridodonesis, Ectopia lentic, VA=4 m CF | Bentall procedure for RD | Glasses, follow up annually, propranolol warfarin |
| 4th son          | 29  | Normal                     | Normal             |                               | Follow up annually                                                        |
| First grandchild | 24  | MVP MR                     | Iridodonesis, Ectopia lentic, VA=1 m CF | One pregnancy without complication | Glasses, follow-up annually                                               |
| Second grandchild| 20  | MVP, MR, ARD=29.1 mm       | Iridodonesis, Ectopia lentic, VA=1 m CF |                               | Follow-up annually                                                        |
| Third grandchild | 18  | MVP, MR, AI, ARD=21.8      | Iridodonesis, Ectopia lentic, VA=1 m CF |                               | Follow up annually                                                        |
| 4th grandchild   | 16  | MVP, MR, ARD=37.7 mm       | Iridodonesis, Ectopia lentic, VA=1 m CF |                               | Follow up annually                                                        |
| 5th grandchild   | 13  | ARD=22                     | Iridodonesis, Ectopia lentic, VA=1 m CF | Deceased                      | Follow up annually                                                        |
| 6th grandchild   | 12  | MVP, A VP, ARD=12.3        | Iridodonesis, Ectopia lentic, VA=1 m CF |                               | Follow up annually                                                        |
| 7th grandchild   | 11  | MVP, MR, ARD=23.7 mm       | Iridodonesis, Ectopia lentic, VA=1 m CF |                               | Follow up annually                                                        |
| 8th grandchild   | 10  | MVP, MR, ARD=31.1 mm       | Iridodonesis, Ectopia lentic |                               | Follow-up annually                                                        |
| 9th              | 9   | MVP, TR, ARD=13.7 mm       | Iridodonesis, Ectopia lentic |                               | Follow-up annually                                                        |
| 10th             | 5   | MVP, ARD=24.4              | Iridodonesis, Ectopia lentic |                               | Follow-up annually                                                        |
| 11th             | 7   | Normal                     | Normal             | Deceased                      | Follow-up annually                                                        |
| 12th             | 4   | MVP, ARD=23.1              | Iridodonesis, Ectopia lentic |                               | Follow-up annually                                                        |
| 13th             | 1   | Normal                     | Normal             |                               | Follow-up annually                                                        |
| First great-grand child | 2 months | Normal             | Normal |                               | Follow-up annually                                                        |

MVP: Mitral valve prolapse, MR: Mitral regurgitation, ARD: Aortic root dimension, AI: Aortic insufficiency, TR: Tricuspid regurgitation, RD: Root dilation, VA: Visual acuity, CF: Count finger, OS: Overall survival
no postoperative mortality; two of them were operated in the past ten years and they are treated by warfarin as well.

Pregnancy in women with MFS is a challenging condition which imposes on the mother a substantial risk of serious cardiovascular adverse effects such as aortic dissection. On the other hand, there is a 50% chance to birth an offspring with MFS. The risk of pregnancy-related complications for MFS patients was described thirty-eight years ago by Pyerits et al. Their study included thirty-two pregnant MFS patients, of which twenty individuals (62%) suffered an aortic dissection and sixteen (50%) died because of it.\[11\] Recently, a study by Roman et al. reported only ten (4.4%) aortic complications among 227 pregnancies of MFS patients.\[12\] Although the incidence rate of aortic dissection during the gestational period has been significantly decreased, yet it remains the most serious complication of pregnancy.\[13\] The mechanisms underlying this pathology is the result of rising maternal blood volume, pulse rate and hormonal changes affecting the abnormal aortic wall.\[14\] None of the five pregnancies in this family were complicated with aortic dissection; we believe patients benefited from early diagnosis and treatments.

Cardiovascular events are well known to be the leading cause of death in patients with Marfan syndrome, but in current study, we assumed trauma as possible cause of death and the consequence of visual disturbances in Marfan syndrome. Therefore, it is important to prohibit MFS patients from driving for their own and other people’s well-being.

**CONCLUSION**

We provided the 20 years follow-up report including demographics, cardiovascular and ocular characteristics, operations, pregnancies, and mortality in four generations of a family with Marfan syndrome. Although cardiovascular events are known to be the leading cause of death in patients with Marfan syndrome, in our current study we observed trauma as a cause of death. Further studies are recommended to explore the risk of comorbidity and mortality in oculopathy-related trauma in such patients.

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**Conflicts of interest**

There are no conflicts of interest.

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