

Marfan Syndrome: A Case Study

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Abstract

Background: Marfan syndrome is an autosomal dominant, multisystem connective tissue disease, associated with a mutation in fibrillin, and occasionally a mutation in TGFBR 1 or 2. The cardinal manifestations of this condition involve the cardiovascular, ocular and skeletal systems.

Objective: To describe the features and complications of Marfan syndrome and discuss the current management.

Methods: Detailed history, physical examination and laboratory investigations.

Conclusion: This report underscores the importance of detailed family history and physical examination in the diagnosis of Marfan syndrome. Additionally, good insight about the pathogenesis and the clinical presentation of Marfan syndrome improves the effectiveness of medical therapies. Regular valvular monitoring and early initiation of beta blockers therapy as well as elective prophylactic surgical repair contribute to increasing the survival rate of Marfan patients.

Keywords: Marfan, Aortic dissection, Aortic aneurysm

Introduction:

Marfan syndrome is an autosomal dominant, multisystemic connective tissue disease, associated with a mutation in fibrillin, and occasionally a mutation in TGFBR1 or 2.^{1,2} The cardinal manifestations of this condition involve the cardiovascular, ocular and skeletal systems.³ The prevalence of Marfan syndrome is approximately 1 per 5000 population⁴ and 26% of the cases have no family history.^{5,6} Cardiovascular pathology, including aortic root dilatation, and aortic dissection, is the leading cause of death in MFS patients.⁴ Characteristic clinical features include anterior chest deformities, long fingers, aortic root dilatation and dissection, lens dislocation and myopia. Further less specific features include high arched palate, crowding of the teeth and skin striae.⁵ Medical management may not reverse the features seen, but can reduce the progression and the severity of the symptoms. Beta blockers are considered as the standard therapy, as they work by reducing the aortic shear stress and the heart rate. Diagnosis is mainly done using the

Ghent criteria and a detailed clinical examination. Although early diagnosis and refined medical and surgical management have increased median life expectancy from 40 to approximately 70 years,⁴ individuals with Marfan syndrome continue to suffer important morbidity.

Case report:

The patient, a 26-year-old Bahraini young man, was first seen in BDF on May 8th after being referred from SMC for consideration of prosthetic aortic valve implantation. As far as could be ascertained, his development, except that he was taller than the rest of his family members and friends, has been entirely normal, until the age of 18, when he was first diagnosed to have Marfan syndrome. No family history of such disease was present; everyone else seems to be fine according to the patient with no significant medical conditions, except for the mother, who suffers from G6PD. Since the age of 6, the patient suffered from severe myopia and underwent surgical correction accordingly. In 1995, surgical lens

removal for the management of congenital myopia and IOL implant were done on the patients left eye at King Khalid's Hospital, KSA. Another surgery (Scleral buckle surgery) was done on the same eye in 2011 for the management of retinal detachment. The patient also underwent a similar surgery at the age of 6 for his right eye, but the surgery wasn't successful, and as a result the patient suffered from right-eye blindness afterwards. On April 27th, during his trip to Saudi, the patient noted a mild productive but gradually progressive cough, with a high grade fever (around 40 degrees), a mild shortness of breath, fatigue and night sweats. The patient complained of severe dyspnea and chest pain when lying flat on his back or laterally on his left side. However, no headache, syncope, nausea or vomiting was noted. The patient went for checkups the following day, and was prescribed antibiotics. Fever was still high, and not responsive to the antibiotics, therefore the patient paid another visit to the doctor, and proper investigations showed a severe chest infection. The patient was given pain relief medications, cough medications and antibiotics and then he returned back to Bahrain on May 4th, where he was admitted in SMC for his chest infection. On routine evaluation he was found to have a dilated mediastinum, and on further evaluation, he was found to have an aortic dissection. Hence he was referred to BDF for further investigations. The patient is unmarried, unemployed, and lives with his parents. He is a never smoker and a never drinker, with no known allergies.

Physical examination revealed him to be a tall, thin white man with extremely long fingers, who appeared much older than his stated age. Blood pressure was 160/100 mmHg, the pulse was 110 beats per minute, with a regular rhythm and a collapsing character. The patient had a temperature of 37.8 and was slightly tachypneic with a respiratory rate of 22 breaths per minute. Closer examination of the hands showed stage 3 clubbing (increased curvature of the nail bed), some arthritic changes such as the Z-thumb deformity. Characteristic Marfan bony changes were also present, in which wrist and thumb signs were noted as well as a mild pectus excavatum. The patient suffered from a high arched palate but no dental abnormalities were present. Upon assessment of the precordium, a hyperdynamic displaced apex beat was felt in the 6th intercostal space, midclavicular line. A

grade 4 early diastolic murmur was heard over the tricuspid and aortic areas, but it was with a greater intensity over the tricuspid region. S1 and S2 were both audible, however S2 was louder. On percussion and auscultation of the back, right basal crackles were heard with dullness over the right lower lobe of the lung. Examination of the abdomen showed visible pulsation above the umbilicus, and stretch marks. There was no venous distension, organomegaly, cyanosis, or ascites. Peripheral pulses were felt, and no edema was detected in the lower limbs. On systematic review, no abnormalities were found other than the patient's presenting symptoms, with episodic headaches and dizziness, and some mild joint pain at the knees. Regular tests were first carried out, such as CBC, U&E, and LFTs (Table 1).

Xrays were done and showed a right basal consolidation with cardiomegaly (Figure 1). CT was also done and showed a very large aneurysm affecting the ascending thoracic aorta starting at the level of the aortic valve and terminating just proximal to the arch, measuring approximately 9x7cm in maximum dimension. The dissection was shown to be starting very low at the level of the valve and involving the entire aneurysmal aorta, preserving the arch. There was no involvement of the arch or the major vessels arising from the arch. The remainder of the thoracic aorta including the arch, the descending thoracic aorta and also the abdominal aorta were all normal in caliber with no evidence of dissection. The iliac arteries were within normal limits. There was a consolidation noted affecting the right lower lobe and also some pleural fluid was noted in the right side. Some fluid was also detected in the right hilum which was felt to be reactive. No CT evidence of aortic rupture was shown. A gross cardiomegaly was also visible (Figure 2).

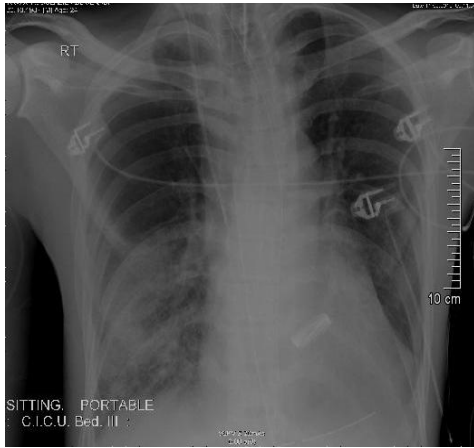
Echo was done twice, one before the surgery and one after, to allow for comparison and to assess the patient's improvement. The pre-op echo showed a severe aortic regurgitation, a mild mitral prolapse with a minor mitral regurgitation and a trivial pulmonary regurgitation. A severe dilatation of the aorta (6.8 cm) and sinus of valsalva (6.6 cm) with a type (A) dissection flap of the ascending aorta were seen. The post-op (Bentall procedure) echo showed a significant difference. Prosthetic valve was well seated with normal motion, and no

Test				
WBC	12.6	X10 ⁹ /L	-	
RBC	3.74	10 ¹² /L	4-5.5	Low
HGB	103	g/L	130-180	Low
HCT	0.316	L/L	0.4-0.5	Low
MCV	84.4	Fl	80-100	Normal
MCH	27.7	Pg	27-32	Normal
MCHC	327	g/L	310-360	Normal
PLT	490	X10 ⁹ /L	150-450	High
Potassium	4.2	Mmol/L	3.5-5.1	Normal
Urea	3.8	Mmol/L	2.9-8.3	Normal
Creatine	49.1	Umol/L	59-104	Low
Magnesium	1.01	Mmol/L	0.7-1.05	Normal
eGFR	60	ml/min/1.7m	60	Normal
AST	46.9	IU/L	0-37	High
LDH	300	IU/L	135-225	High
CK	319	IU/L	24-170	High
CK-MB	23.3	IU/L	0-24	Normal

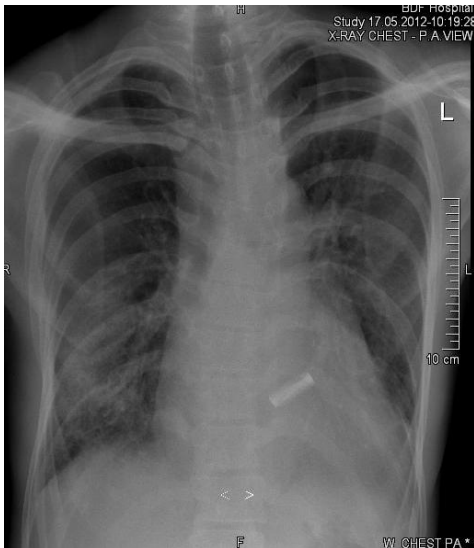
Figure 1. Xray



Chest x-ray done on the 9th showing a mediastinal widening with right basal to mid zone consolidation



Chest x-ray done on the 11th showing a partial resolution of consolidation.



Chest x-ray done on the 17th showing a gradual resolution of consolidation

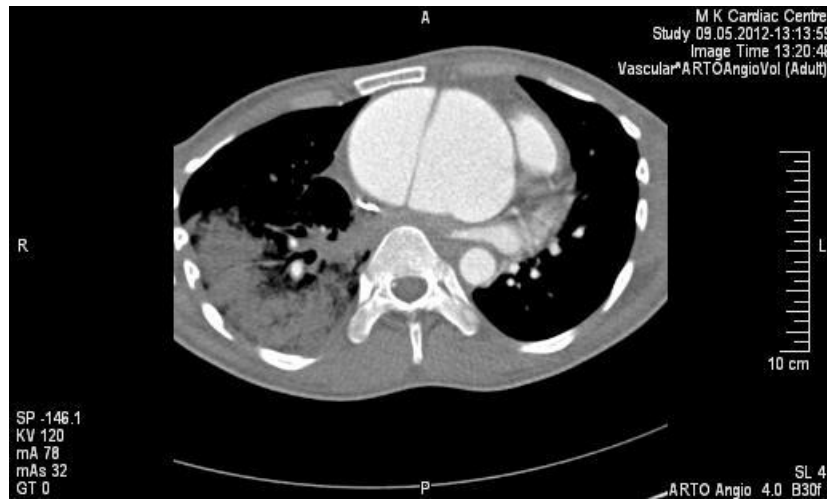
significant aortic incompetence or mitral incompetence (Figure 3).

After initially controlling the patient's chest infection, the patient underwent Bentall surgery on May 10th for dissection of ascending aorta, a severe aortic regurgitation, and an aortic aneurysm of around 8 cm. The surgery was performed through mediansternotomy and vertical pericardiotomy. After cardioplegia, aortotomy was done with resection of the aneurysm and the AV. Coronary arteries were dissected with 10.0mm buttons. Replacement

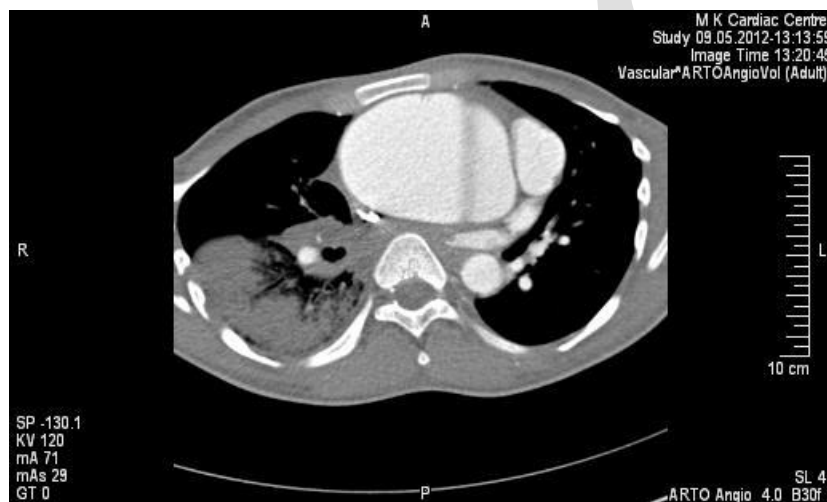
of valve was done using 29 carbosial valsalva bileaflet composite graft. This is the worldwide used procedure for such indications (Figure 4).

During the post-op phase, 10 packs of cryoprecipitate, and 2.4 mg IV of factor 7 were given to maintain the patient hemodynamically. The patient was also given morphine and IV panadol to relieve the pain. A mild productive but gradually improving cough with white sputum was present. The patient was managed with medication throughout his hospital stay (Table 2). Warfarin dosage was given depending on the INR (Table 3).

Figure 2. CT



Aortic flap with a consolidation in the right lung



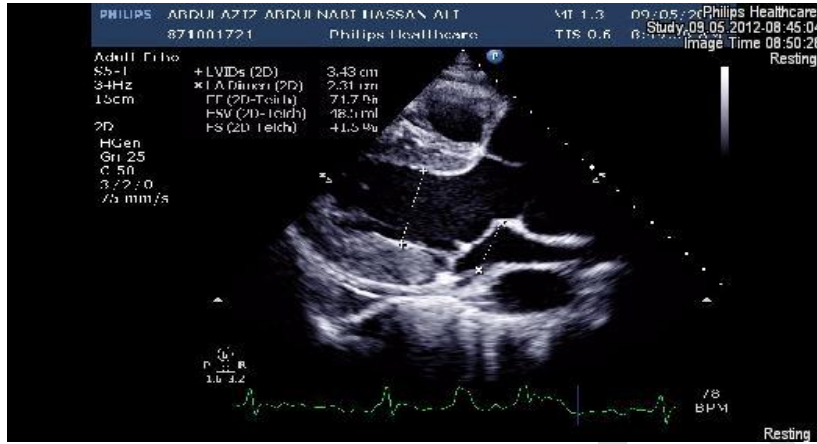
Aortic flap/dissection.

Discussion:

Pathophysiology and Etiology: Fibrillin is an important component of the microfibrillar system that acts as a scaffold for elastogenesis. Classical Marfan syndrome is associated with a mutation in FBN1, the gene that encodes for fibrillin-1. The pathophysiological outcomes of the degeneration of elastic fibers in Marfan syndrome seem to explain the majority of manifestations of this condition. Stiffness and reduced distensibility of the aorta in response to increased pulse pressure, is the main most important

consequence of elastin degeneration.⁵ Recently, another hypothesis has emerged trying to explain the pathophysiology behind Marfan syndrome. Transforming growth factor β (TGF β), a cytokine that regulates cell morphogenesis, is thought to contribute to the Marfan syndrome phenotype. Abnormal fibrillin causes failure of the sequestration of the inactive latent precursor of TGF β , resulting in excessive TGF β activation, and thus producing the phenotypical manifestations of Marfan's.⁴

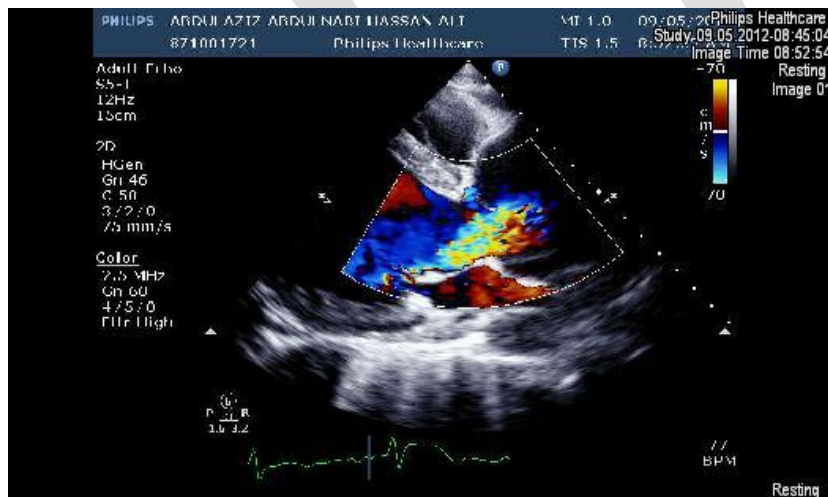
Figure 3. Echocardiogram



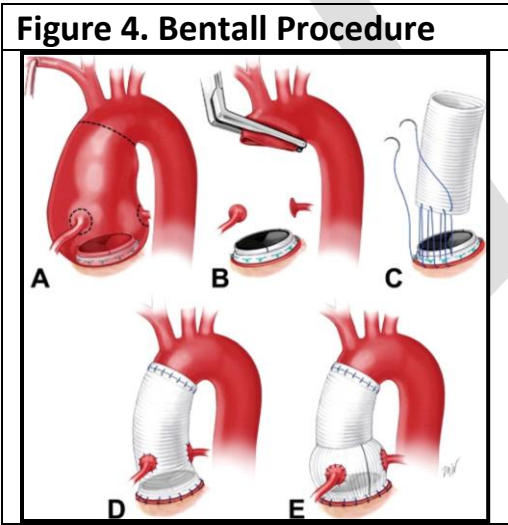
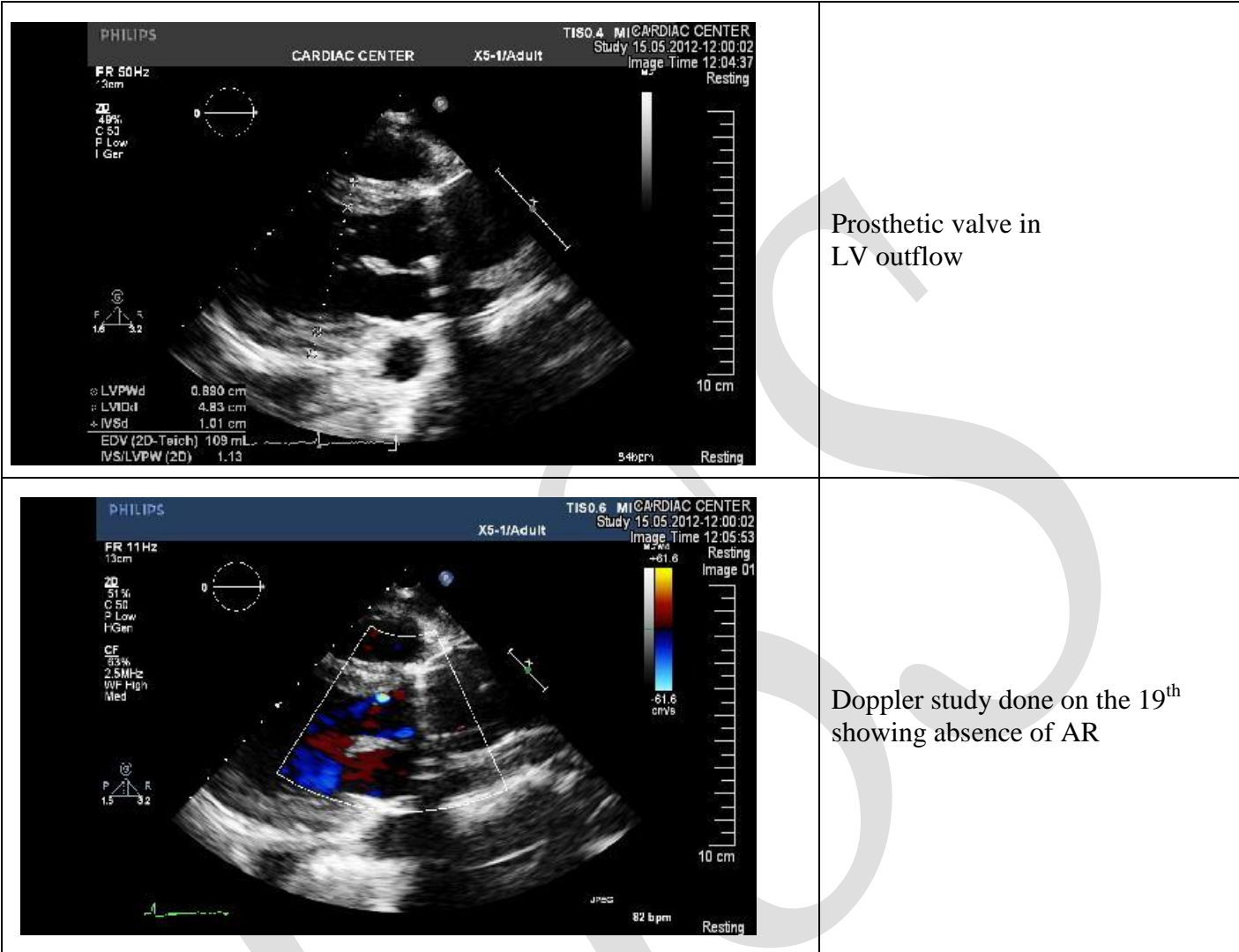
Aneurysmal aorta in diastole



Aneurysmal aorta in systole

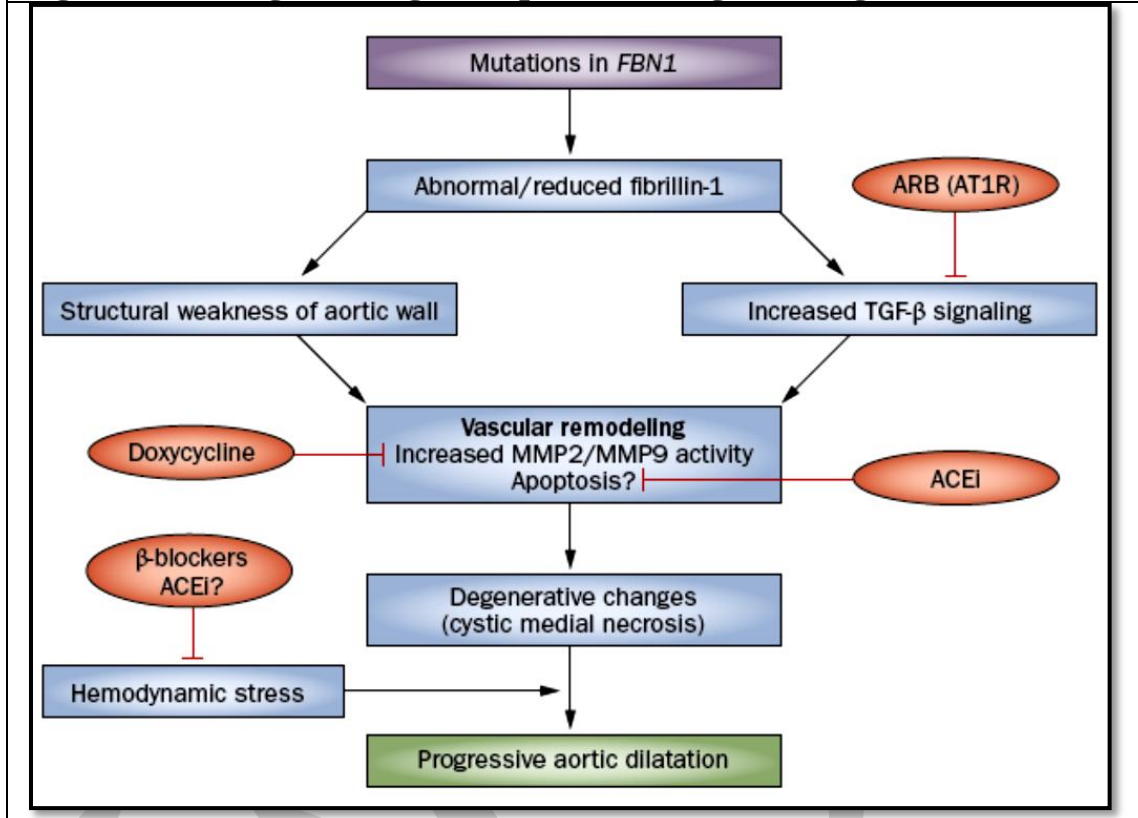


AR Doppler study showing AR jet



Medication	Generic name	Dose	Route	Date started	Date stopped
MgSO4	MgSO4	1.5 g BD	IV	11 th /5	13 th /5
Rocephen	Ceftriaxone	2g OD	IV	11 th /5	13 th /5
Clarithromycin	Clarithromycin	500 mg BD	PO	8 th /5	13 th /5
Aspirin	Acetylsalicylic acid	75mg OD	PO	11 th /5	12 th /5
Warfarin	Warfarin	OD (dose depends on INR)	PO	11 th /5	15 th /5
Nexium	Esomeprazole	40mg OD	PO	11 th /5	13 th /5
Panadol	Paracetamol	1g TDS	PO	11 th /5	13 th /5
Combigan	Brimonidine/timolol	1 drop, left eye, BD	Ophthalmic solution	11 th /5	15 th /5
Combivent	Ipratropium bromide and albuterol sulfate	2ml TDS	Inhalation	11 th /5	15 th /5
Lasix	Furosemide	40mg OD	PO	11 th /5	13 th /5
Metoprolol	Metoprolol	12 th /5 → 12.5mg BD 13 th /5 → 25mg BD 14 th /5 → 50mg BD	PO	12 th /5	14 th /5
Lexotanil	Bromazepam	1.5mg TDS	PO	11 th /5	14 th /5
Morphine	Morphine	2mg OD	IV	11 th /5	13 th /5
Maxalon	Metoclopramide	10mg TDS	IV	11 th /5	11 th /5

Date	Time	INR	Dose
11 th /5	6:00	0.97	5mg
12 th /5	6:00	1.4	5mg
13 th /5	6:00	1.9	4mg
14 th /5	6:00	3.1	HOLD
15 th /5	6:00	2.6	2mg

Figure 5. Pathogenic targets of pharmacological drugs.⁸**Clinical Presentation:**

Marfan syndrome primarily involves the skeletal, ocular and cardiovascular systems. Typically patients with Marfan syndrome present with tall stature, ectopia lentis, aortic root dilatation, and positive family history. Our patient presented with all the mentioned symptoms except for the family history.

Differential diagnosis:

Clinical diagnosis of Marfan syndrome is challenging because of the increased marfenoid features of other connective tissue diseases. Differential diagnosis could include homocystinuria, familial aortic dissection, familial arachnodactaly, Ehler Danlos syndrome and MEN IIb. Serum methionine must be carried out to rule out

homocystinuria.³ Molecular techniques have not been undertaken widely as a method to distinguish between Marfan syndrome and other similar-featured disorders, as it is not clear whether they can differentiate between those conditions with overlapping symptoms.⁵

Management:

Although clinical management of genetic disorders is not backed up by extensive clinical trials on humans, numerous studies conducted in vivo managed to establish a direct link between the administration of angiotensin receptor blockers (ARBs) and the inhibition of TFG β signaling.⁴ Various retrospective studies have assessed the beneficial effects of beta blockers (BB) therapy in Marfan syndrome, and considered it to be the standard of care. The potential benefit of beta blockers is

attributed to the reduction of aortic wall stress and heart rate.⁸ All Marfan syndrome patients who can tolerate beta blockers should be treated regardless of the presence or absence of aortic dilatation. No randomized trials reported solid evidence on the use of angiotensin converting enzyme inhibitors (ACEI), however this class of drugs has the theoretical advantage of reducing the ejection impulse and vascular smooth muscle apoptosis which is implicated in cystic medial degeneration.⁵ Recent trials have been aiming to manufacture drugs that are directed at the fibrillin-1 or TGF β axis to produce the maximum desirable effect.⁹ The various pharmacological therapies and their actions in Marfan syndrome are shown in figure 5.

Many comparative studies have shown that there is a better outcome with early aortic root surgery than with an emergency or later surgery. Prophylactic surgery is recommended when the diameter at the sinus of Valsalva exceeds 5.5 cm in adults.

Conclusion:

Marfan syndrome is the most common inherited connective tissue disorder with diverse clinical manifestations. Although many studies have been conducted which aimed at improving the medical aspect of management, those trials produced conflicting results and generally involved relatively few patients.

This report underscores the importance of detailed family history and physical examination in the diagnosis of Marfan syndrome. Additionally, good insight about the pathogenesis and the clinical presentation of Marfan syndrome improve the effectiveness of medical therapies. Regular valvular monitoring and early initiation of beta blockers therapy as well as elective prophylactic surgical repair contribute to increasing the survival rate of Marfan patients.

Acknowledgment:

Many thanks to Cardiology team at BDF hospital, especially my supervisor Dr. Husam Noor.

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