



Marfan Syndrome: A Study of a Nigerian Family and Review of Current Cardiovascular Management

Syndrome de Marfan: A Study of a Family nigérian et de l'examen de la gestion actuelle de cardiologie

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ABSTRACT

BACKGROUND: Marfan's syndrome is a connective tissue disorder inherited as an autosomal dominant disorder. It causes a myriad of distinct clinical problems, of which the musculoskeletal, cardiac, and ocular system problems predominate. Nearly 50 percent of patients have to undergo aortic surgery in their lifetime resulting in reconstruction or replacement of the aortic root or total of this vessel's parts.

OBJECTIVE: To describe a Nigerian family with multiple cases of Marfan syndrome and discuss current cardiovascular management of the syndrome.

MATERIALS: Detailed history, clinical and laboratory investigations including ophthalmologic assessment and echocardiography were carried out on all members of a nuclear family of a child who reported with complaints of poor eye sight later diagnosed to have Marfan syndrome.

RESULTS: Diagnosis of Marfan syndrome was made in three members of the nuclear family - a father and his two children following eye examination of one of the children. A follow up cardiovascular assessment revealed that the father required aortic surgery while the two children also had aortic root dilatation.

CONCLUSION: This report underlines the importance of a detailed history, physical examination and family study in patient assessment. Current cardiovascular management in Marfan syndrome involves β blocker therapy and an annual cardiovascular evaluation involving clinical history, examination and echocardiography. Prophylactic aortic surgery should be considered when aortic diameter at the sinus valsalva exceeds 50mm. *WAJM* 2009; 28(1): 338–343.

Keywords: Marfan syndrome, physical features, family study, cardiovascular management.

RÉSUMÉ

CONTEXTE: le syndrome de Marfan est un trouble héréditaire du tissu conjonctif selon un mode autosomique dominant désordre. Il provoque une multitude de problèmes cliniques distinctes, dont les troubles musculo-squelettiques, cardiaques, oculaires et des problèmes du système prédominant. Près de 50 pour cent des patients doivent subir une chirurgie aortique au cours de leur vie résultant de la reconstruction ou le remplacement de la racine aortique ou totale de cette partie du navire.

OBJECTIF: Pour décrire une famille nigériane avec plusieurs cas de syndrome de Marfan et de discuter de la gestion actuelle cardiovasculaires du syndrome.

MATERIALS: détail de l'histoire clinique et des examens de laboratoire, y compris l'évaluation et l'échocardiographie d'ophtalmologie ont été réalisées sur tous les membres d'une famille nucléaire, d'un enfant qui a rapporté des plaintes de la vue plus tard pauvres d'avoir diagnostiqué le syndrome de Marfan.

RÉSULTATS: Le diagnostic de syndrome de Marfan a été faite dans les trois membres de la famille nucléaire - père et ses deux enfants à la suite d'un examen de la vue des enfants. Un suivi cardio-évaluation a révélé que le père de la chirurgie aortique nécessaire, tandis que les deux enfants avaient également root dilatation aortique.

CONCLUSION: Ce rapport souligne l'importance d'un historique détaillé, l'examen physique et étude de la famille dans l'évaluation des patients. Cardiovasculaire dans la gestion courante du syndrome de Marfan implique β bloquants et d'une évaluation cardiovasculaire annuelle de l'histoire clinique, l'examen et l'échocardiographie. Prophylactic chirurgie aortique doit être envisagée lorsque le diamètre aortique au sinus Valsalva dépasse 50mm. *WAJM* 2009; 28(1): 338–343.

Mots-clés: le syndrome de Marfan, les caractéristiques physiques, de la famille d'étude, de gestion cardiovasculaires.

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INTRODUCTION

Marfan syndrome is a connective tissue disorder inherited as an autosomal dominant disorder. It was first described by Antoine-Bernard Marfan in a paper presented at a meeting of the Medical Society of Paris in 1896. He described an observation of disproportionate long limbs in Gabrielle, a 5-year-old girl.¹ The defect is as a result of mutation in the fibrillin 1 gene on chromosome 15, while other cases may be due to mutation in TGF β 1 or TGF β 2.² This abnormality of the protein leads to variable clinical problems particularly affecting the skeletal, ocular, and cardiovascular systems. Nearly 50 percent of patients have to undergo aortic surgery in their lifetime resulting in reconstruction or replacement of the aortic root or total of this vessel's parts.³

We present a proband case of Marfan's syndrome in an African child, the family study and current cardiovascular management.

Case Report

The patient was a 5-year old girl, the third child of four siblings of a non-consanguineous marriage. She was referred to the Guinness Eye Centre of the Lagos University Teaching Hospital from a private clinic for Ophthalmologic evaluation because of poor vision in both eye. The medical history was unremarkable and mother did not express any other concern regarding her health. The child appeared tall for her age with a height of 120cm (95th percentile for age is 108cm). When this observation was made, mother mentioned that a sibling of the patient was actually the tall one in the family. This same sibling was also said to have a history of recurrent chest pain and easy fatigability. This warranted a call for the whole family to be brought to the hospital for evaluation. Ophthalmologic, cardiovascular and radiologic assessment was performed on all members of the family when physical findings indicated Marfan syndrome.

RESULTS

Proband: General physical examination revealed microstomia (abnormally small mouth), dolichocephaly (long and narrow head), enophthalmos (recession of the

eyeball within the orbit), retrognathia (underdevelopment of the maxilla and/or mandible) and downward slanting of the palpebral fissure. His chest was remarkable for pectus.

Musculoskeletal examination revealed dolichostenomelia positive wrist (Walker) and thumb (Steinberg) sign demonstrating arachnodactyly mild scoliosis and high arched palate. The central nervous system and abdomen were normal.

Eye examination showed best corrected visual acuity to be 6/60 on the right and hand movement on the left, intraocular pressure right, 16mmHg; left, 14mmHg. Anterior segment examination was unremarkable. She had bilateral superotemporal subluxation of the lens (ectopia lentis). The fundi were normal. The blood pressure was 80/50mmHg with a regularly irregular pulse and an apical midsystolic murmur with a click. ECG showed sinus arrhythmia. Echo-cardiography showed mitral valve prolapse with mitral regurgitation. The aortic root was dilated at 26.9mm against 12–21 for size. (Fig. 1).

First Sibling: An 8-year old boy who appeared tall for his age with height of 150cm (95th percentile for age is 138cm). Physical examination revealed Marfanoid features as follows: High arched palate, dolicho-cephaly, retrognathia, dolichostenomelia, positive wrist (Walker) and thumb (Steinberg) signs demonstrating

arachno-dactyly, pectus excavatum and mild scoliosis. The central nervous system and abdomen were normal. Eye examination showed slight inferionasal subluxation of the lens bilaterally. Visual acuity was right, 6/24⁺¹, left, 6/24 without any improvement with pinhole. The intraocular pressures were right, 13mmHg, left, 12mmHg. Fundal examination was unremarkable. Examination of the cardiovascular system revealed blood pressure of 90/70mmHg, a regularly irregular pulse and an apical midsystolic murmur with a click. ECG showed sinus arrhythmia. Echo-cardiography showed mitral valve prolapse with mitral regurgitation and dilated aortic root at diameter of 34.4mm against 14–23mm for his size. This had increased to 35.6mm after eight months.

Third sibling: A six-year, old girl. Physical examination only revealed a high arched palate. All other examinations including ophthalmologic and cardiovascular evaluation with echocardiography were normal.

Fourth sibling: A one-year old boy in whom examination only revealed a high arched palate. All other examinations including ophthalmologic and cardiovascular evaluation with echocardiography were normal.

Mother: All examinations on mother including ophthalmologic and cardio-

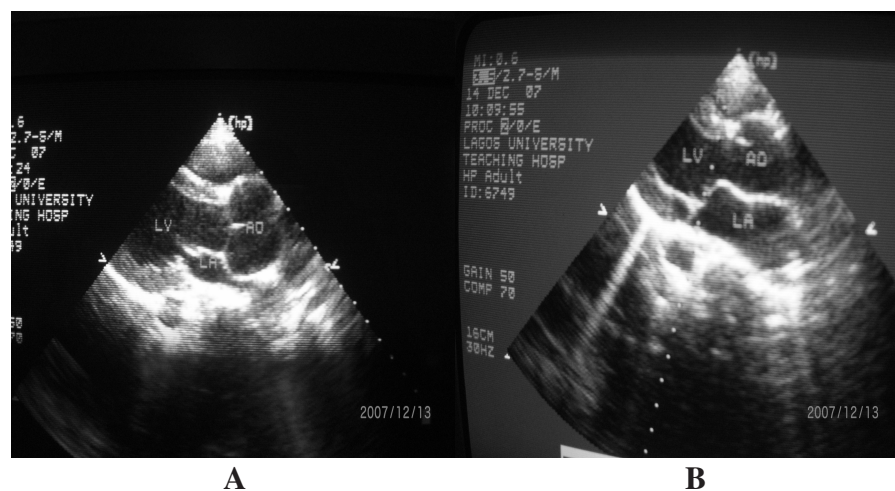


Figure 1: Echocardiographic findings in the four-year old proband.

Panel A, Left parasternal long axis echocardiographic view showing aortic root dilatation (26.9cm). **Panel B,** Left parasternal long axis Echocardiographic view showing mild mitral valve prolapse.

vascular evaluation with echocardiography were normal.

Father: A 38-year old mechanical engineer whose examination of the musculoskeletal system revealed Marfanoid features as follows: Tall stature with height of 1.91m with an arm span of 1.92m, high palatal arch and hyperextended joints in the hand. His weight was 85kg with body mass index of 23.3. The central nervous system and abdomen were also normal. Ophthalmological examination was normal with a normal visual acuity. The arterial pulse rate was 89/min and regularly irregular and the blood pressure – 140/80 mmHg. The heart sounds were normal. ECG showed unifocal ventricular ectopic beats. Echocardiography showed a dilated aortic root (48.1mm) (Fig. 3), mild aortic regurgitation and minimal mitral

regurgitation. The aortic root size had increased to 50.2mm after eight months.

The father volunteered history of sudden death of his 45-year old elder brother and of the treatment of his immediate elder brother for heart disease. He also said his late mother had hyperextended joints of the fingers similar to his own. Radiological examinations were essentially normal.

The proband, father and first sibling having both major and minor manifestations and having met the 1996 Ghent diagnostic criteria⁴ for Marfan syndrome were diagnosed as cases of Marfan syndrome.

Management

The scoliosis in the two children was not severe and so surgery was ruled out. Counseling was provided and myopia

corrected with refraction. The three cases with Marfan syndrome were given oral propranolol at a dose of 2mg/kg/day in four divided doses. All affected persons were also counseled not to engage in contact sports e.g. boxing, competitive athletics, or isometric exercise such as weight lifting, climbing steep inclines, participating in gymnastics and performing pull-ups, but may engage in moderate aerobics and walking. Echocardiography is to be performed on them yearly to monitor aortic root size and surgery considered if aortic size is 50mm or more. The father, however, was counseled on the need for surgery as his aortic size was then beyond 50mm. The affected persons are to have bacterial endocarditis prophylaxis prior to any dental or invasive procedure.

The parents were counseled on the chances of another offspring getting Marfan syndrome and risk of the two children having an offspring with Marfan syndrome.

DISCUSSION

Diagnosis

The diagnosis of Marfan syndrome is made on a combination of clinical findings. A detailed medical and family history, ophthalmologic evaluation and echocardiography are needed. The diagnostic criteria proposed for making a diagnosis of Marfan syndrome have evolved over the years. They began with the Berlin criteria where Marfan syndrome was diagnosed on the basis of the involvement of the skeletal system and two other systems with requirement of at least one major manifestation (ectopia lentis, aortic root dilation or dissection, or dural ectasia).⁵ This was later revised and the 1996 Ghent diagnostic criteria came to be.⁴ (Table 1). These current criteria involve major and minor manifestations, the major being clinical features that are highly specific for Marfan syndrome and rarely occur in the general population. The diagnosis requires that at least two of the major manifestations of the condition be present in patients without other affected family members. In families in which Marfan syndrome is known to occur, only one major criterion is required. The major features necessary for the diagnosis include aortic root



Figure 2: Sibling 1 showing dolichocephaly and dolichostenomelia (left panel) and his left parasternal long axis echocardiographic view with aortic root dilatation (35.6mm) (right panel).

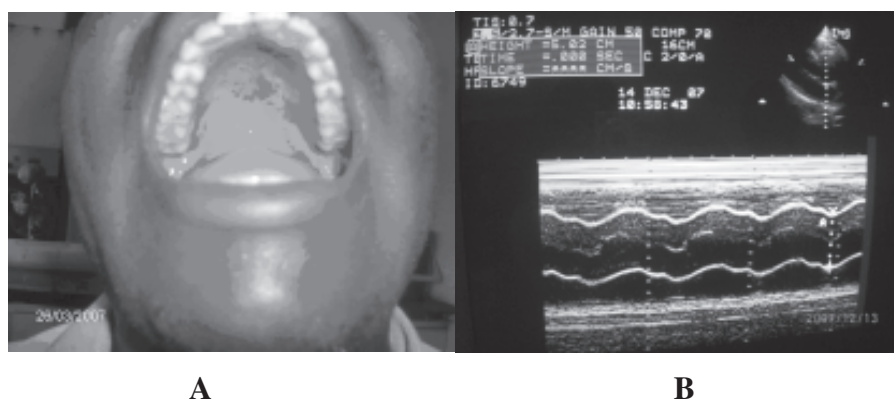


Figure 3: Father of the proband showing high arched palate (left) and his M-mode echocardiography picture showing a grossly enlarged aortic root (52mm) (right).

Table 1: Revised Criteria for the Diagnosis of Marfan Syndrome⁴

System	Major Criteria	Minor Criteria
		Skeletal System
	Presence of at least four of the following manifestations * Pectus carinatum * Pectus excavatum requiring surgery * Reduced upper to lower segment ratio or arm span to height ratio greater than 1.05 * Wrist and thumb signs * Scoliosis > 20d or spondylolisthesis * Reduced extensions at the elbows (<170d) * Medial displacement of the medial malleolus causing pes planus * Protrusio acetabulae of any degree (ascertained on radiographs)	* Pectus excavatum of moderate severity * Joint hypermobility * Highly arched palate with crowding of teeth * Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slating palpebral fissures)
	Ocular System	
	* Ectopia lentis (dislocated lens)	* Abnormally flat cornea (as measured by keratometry) * Increased axial length of globe (as measured by ultrasound)
Cardio-vascular System	* Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva; or; * Dissection of the ascending aorta	* Mitral valve prolapse with or without mitral valve regurgitation * Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 * Calcification of the mitral annulus below the age of 40 * Dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50
Pulmonary System	None	* Spontaneous pneumothorax * Apical blebs (ascertained by chest radiography)
Skin and Integument	None	* Stretch marks not associated with marked weight changes, pregnancy or repetitive stress * Recurrent incisional hernias
Dura	*Lumbosacral dural ectasia by CT or MRI	None
Family/ Genetic History	* Having a parent, child or sibling who meets these diagnostic criteria independently * Presence of a mutation in FBN1 known to cause the Marfan syndrome * Presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family	None

The major features necessary for the diagnosis include the following: aortic root enlargement (aortic aneurysm), aortic dissection, lens dislocation, dural ectasia, presence of at least 4 major skeletal features, which include chest wall deformities, long, thin arms and legs (assessed by detailed measurements), and scoliosis greater than 20°. The diagnosis requires that at least two of the major manifestations of the condition be present in patients without other affected family members. In families in which Marfan syndrome is known to occur, only one major criterion is required.

enlargement (aortic aneurysm), aortic dissection, lens dislocation, dural ectasia and presence of at least four major skeletal features, which include chest wall deformities, long thin arms and legs (assessed by detailed measurements), and scoliosis greater than 20°.

The proband aged four years seen in the eye clinic in this study had major criteria in the cardiovascular and ocular system thus satisfying the Ghent criteria in addition to a family history where a sibling also met these criteria independently. There were also some major and minor features in the skeletal system. The sibling aged 8 years had same features as the proband thus satisfying three major criteria. Their father had two major manifestations involving the cardiovascular system and the family history of having two children who met these diagnostic criteria independently.

To make the diagnosis the physician has to be very observant. It was rather unfortunate that this family was only being diagnosed at this point despite having been to other hospitals on several occasions for other illnesses such as malaria. This may also be so because the disease evolves with age and some features may not manifest until later in life. The other children with high arched palate have to be evaluated regularly as the features can be evolving. This phenomenon of partial expression of Marfan syndrome in a child that is suspected will meet the full criteria at an older age has been termed "emerging Marfan syndrome".

Simple observation and anthropometry measurement of children could identify a patient. In this report, a simple observation of the height and family history led to the suspicion of the diagnosis which was further confirmed with more investigations. Also a holistic approach should be employed always in patient assessment. Even though the child complained of poor eyesight, examination of the pulse and other examinations made this diagnosis possible eventually.

Inheritance

Patients with Marfan syndrome have a 50% risk of passing the gene to the offspring regardless of sex but approximately 25-55% of Marfan cases are

Table 2: Findings in Family Members Studied

Family member	Age (years)	Sex	Systemic Findings for Diagnostic Criteria of Marfan Syndrome in the Family Members			
			Skeletal	Ocular	Cardiovascular	Family/Genetic
Father	38	Male	<ul style="list-style-type: none"> Joint flexibility High arched palate 	Nil	Dilatation of ascending aorta (50.2mm against (>39mm)	Present
Mother	31	Female	Nil	Nil	Nil	Present
Sibling 1	8	Male	<ul style="list-style-type: none"> High arched palate Wrist & thumb sign Mild Scoliosis Pectus excavatum 	Ectopia lentis	Dilatation of ascending aorta (35.6mm against 14-23mm for size) Mitral valve prolapse.	Present
Sibling 2	6	Female	High arched palate	Nil	Nil	Present
Proband	4	Female	<ul style="list-style-type: none"> High arched palate Wrist & thumb sign Mild Scoliosis Pectus excavatum 	Ectopia lentis	Dilatation of ascending aorta (26.9cm against 12-21mm for size) Mitral valve prolapse	Present
Sibling 3	1	Male	High arched palate	Nil	Nil	Present

*None of the subjects had abnormalities in the lungs, dura, skin and integument.

sporadic due to de novo mutations with no family history.^{6,7} It would appear as though the father of the proband passed the genes here to his son and daughter and probably inherited it from his late mother who he vividly remembers had hyperextension of the joints like him. The history of sudden death of proband's paternal uncle at 45 years of age and history of another paternal uncle being currently managed for heart disease may be further supportive of the diagnosis. Marfan syndrome can be diagnosed at any age from perinatal period to adulthood. Neonatal presentation is usually severe.

Cardiovascular Management

Treatment of Marfan syndrome depends on which systems are involved and the severity of the manifestation. The manifestation most likely to cause death is the cardiovascular involvement. The mitral and aortic valves are most often affected as was the case unfortunately in this family with all three cases. Prior to the advent of pharmacologic and surgical therapy for aortic root and valvular disease, the life expectancy for patients with Marfan syndrome was about two-thirds that of the healthy population. Aortic dissection and congestive heart failure due to aortic and mitral valvular

anomalies accounted for over 90% of known causes of death.⁸ A more recent assessment however describes a near normal life expectancy indicating improved diagnosis and treatment.⁹ Repair of the aorta is recommended at aortic size of 50mm. The rate of aortic dissection is in direct proportion to the maximum diameter of the aorta.^{10,11} If the increase in aortic size exceeds 10mm/year or there is history of aortic dissection in the family at a lower aortic size then earlier surgery is recommended. The father had aortic size that was beyond 50mm and required surgery. The first sibling, an 8-year old had an aortic size of 36.5mm as against normal of 14–23mm for his age and body surface area.

Unfortunately because no autopsy was done on the proband's uncle who died suddenly, it is difficult to say if the cause was a ruptured aorta and what size it was. This information would also have guided management decisions in this family.

For the cardiovascular manifestation of aortic dissection, the red flag is abrupt onset of pain especially chest pain. In a study of 1256 patients with acute aortic dissection, an abrupt onset of pain was noted in 83.8% of patients, any type of pain was reported in 92.6% of patients and chest pain in 59.3%.¹² Sudden chest pain can therefore be a symptom of aortic

dissection following weakening of aortic walls. The pain can be either in front or behind and usually in the midline. Severe chest pain is therefore a medical emergency for a Marfan patient.

Complications of aortic pseudoaneurysm post surgery could arise at the area of anastomosis and have contributed to nearly 40% of late deaths after aortic surgery. Therefore, the patients with cardiovascular manifestations need a lifetime follow up with echocardiography and blood pressure checks for new or recurrent disease as well as progression of old disease. Medical treatment with β -adrenergic receptor blockers is regarded as standard of care in Marfan patients.¹³ This treatment first proposed by Halpern is meant to prevent or slow down aortic aneurysm or dissection.¹⁴ The treatment has been shown to be effective in both adults and children.^{15–17} Beta blockers inhibit chronotropic, inotropic, and vasodilatory responses to beta-adrenergic stimulation thus reducing stress on the aorta. Of the beta-blockers, Atenolol is longer acting and more cardio selective than the others. Calcium channel blocking agents like verapamil also slow down growth of the aorta but cannot be used in children less than two years of age. Medical therapy with angiotensin inhibitors has also been shown to be

somewhat effective in slowing the rate of growth of the aorta.^{18,19} Lifestyle adaptations, such as avoidance of strenuous exercise and contact sports, are often necessary to reduce risk of aortic dissection. Risk factors for aortic dissection include increased aortic diameter, extent of aortic dilatation, rate of aortic dilatation, and family history of aortic dissection.^{3,17} Our hospital presently lacks the capacity for this surgery and the patient had to be referred abroad for the surgery which is very expensive for the family. This again shows the need for capacity building in surgical management of cardiac patients in our country. Government, private sector participation and international collaboration are greatly needed to achieve this.

CONCLUSION

This report underscores the importance of detailed history and physical examination in patient assessment as one organ complaint could lead to discovery of a multiorgan involvement syndrome. The whole family should be invited for assessment if a hereditary disease is suspected. Current cardiovascular management in Marfan syndrome involves β blocker therapy and an annual cardiovascular evaluation including clinical history, examination and echocardiography. Prophylactic aortic surgery should be considered when aortic diameter at the sinus valsalva exceeds 50mm.

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