CASE REPORT

Marfan Syndrome: Clinical Presentation with Congenital Glaucoma?

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ABSTRACT

Congenital glaucoma (CG), diagnosed in the first year of life, can fall into three main groups: primary CG, glaucoma associated with congenital anomalies, and secondary glaucoma of infants. The associated congenital anomaly of CG includes the autosomal dominant: Marfan Syndrome (MS), the phenotypic features of which would rarely be evident in the first year of life. Multiple other associated autosomal dominant, autosomal recessive, X-linked and chromosomal conditions that can present with CG need to be excluded. Hence, this is a retrospective diagnosis and is the first known documented case report in an Afro-Caribbean with MS presenting with CG at six weeks of age. The Marfanoid features became apparent in late childhood and adolescence.

Keywords: fibrillin, Ghent criteria, glaucoma, mitral valve prolapse

Síndrome de Marfan: ¿presentación clínica con glaucoma congénito?

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RESUMEN

El glaucoma congénito (GC), diagnosticado en el primer año de vida, puede clasificarse en tres grupos principales: GC primario, glaucoma asociado con anomalías congénitas, y glaucoma secundario de lactantes. La anomalía congénita asociada con el GC incluye el trastorno autosómico dominante conocido como síndrome de Marfan (SM), cuyas características fenotípicas serían raramente evidentes en el primer año de vida. Otras múltiples condiciones asociadas – autosómicas dominantes, autosómicas recesivas, ligadas al cromosoma X, y cromosómicas – que pueden presentarse con el GC, necesitan ser excluidas. Por lo tanto, éste es un diagnóstico retrospectivo, a la par que el primer reporte de caso documentado de que se tenga noticia en relación un bebé afrocaribeño con SM, que presentaba GC a las seis semanas de la edad. Las características marfanoides se hicieron evidentes en la última etapa de la niñez y en la adolescencia.

Palabras clave: fibrilina, criterios de Ghent, glaucoma, prolapso de la válvula mitral

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INTRODUCTION

In 1896, Antoine Marfan first described Marfan Syndrome (MS), as an autosomal dominant, connective tissue disorder with variable penetrance and phenotypic expression (1, 2). The prevalence is 1 in 10 000 in the United States of America, with 75% inherited from a parent, with a mutation in the gene encoding for the fibrillin-1 (FBNI) gene on chromosome 15q21.1. Documented are spontaneous mutations in a quarter of the cases resulting in decreased or defective fibrillin in connective tissue, in transforming growth factor b-receptor 2 on chromosome 9, TGFBR1 gene on chromosome 3 and 10481le-Thr (1–5). The gold standard for the diagnosis of MS is the Ghent Nosology in 1996, documenting clinical signs in seven body systems: skeletal, ocular, cardiovascular, pulmonary, skin/integument, dura and genetic findings. The diagnosis of MS requires two major criteria in different organ systems and one minor criterion in a third organ system, or one major and two minor criteria for diagnosis. If a mutation causing MS is confirmed in a family member, only one major criterion in an organ system and involvement in one other organ system is confirmative. The three main systems more commonly affected are cardiovascular, ocular and musculoskeletal (1–4).

The major ocular feature is ectopia lentis, and minor ocular criteria are microphakia, megalocornea, myopia, keratoconus, hypoplasia of the iris and stroma and dilator muscle, retinal detachment and, rarely, glaucoma. Dislocation of the lens can lead to secondary pupillary block glaucoma. The prevalence of glaucoma in MS ranges from 7.7% with ectopic lens by Cross *et al* to 14.8% with aphakic eyes by Wakita *et al* (1, 2, 4, 6).

Congenital glaucoma (CG) is diagnosed in the first year of life and, using the Shaffer-Weiss disease classification, can fall into three main groups: primary CG, glaucoma associated with congenital anomalies, and secondary glaucoma of infants. The associated congenital anomalies of CG are the autosomal dominant: MS, neurofibromatosis, aniridia associated with Wilm's tumour in 20%, Axenfield's and Rieger's anomaly (1, 2, 6).

The autosomal recessive causes of CG are primary CG, homocystinuria and Peter's anomaly. The X-linked recessive causes are Lowe syndrome, and microspherophakia associated with Weill-Marchesani syndrome; those causes with no clear hereditary pattern are Sturge-Weber syndrome and Pierre Robin syndrome; and congenital rubella is an infectious cause. Chromosoamal abnormalities associated with CG are found in 17 different autosomes, including trisomy 21, trisomy 13–15, trisomy 17–18, trisomy 20 and Turner's syndrome (1, 2, 6).

Congenital glaucoma is also seen in Rubenstein Taybi (broad thumb) syndrome, familial iris hypoplasia and persistent hyperplastic primary vitreous and familial hypoplasia of the iris with glaucoma. Secondary glaucoma is not developmental but acquired and can be caused by retinopathy of prematurity, tumours like retinoblastoma, inflammation, trauma (such as forceps injury to the eyes) and post-congenital cataract surgery (1, 2, 6).

In infancy, the collagen fibres are more elastic in the eyes, and elevation of intraocular pressure (IOP) leads to enlargement and stretching of the intraocular structures and thinning. This results in rapid cupping of the optic nerve, which can be reversible, which is not possible in the adult eyes. Advanced disease with raised IOP leads to atrophic changes of all the intraocular structures. Hence, early diagnosis is needed to prevent permanent loss of vision, with parents being the primary guide to detecting significant symptoms and signs, such as excessive tearing, large eyes, cloudy corneas and hiding from bright lights or squeezing of eyelids with bright lights indicating photophobia (1, 2, 6).

The clinical manifestation of MS is variable and unless there are significant major criteria in the cardiovascular and skeletal systems, it is not usually diagnosed until late childhood or adolescence. The likelihood of making a diagnosis of MS in infancy with glaucoma would be very rare with the other named differential diagnoses noted above. Developing Marfanoid features and satisfying the Ghent criteria in infancy would be challenging (1, 2, 3, 6, 7).

CASE REPORT

The index case was diagnosed with CG at six weeks of age after presentation with cloudy cornea, megalocornea and disparity in sizes of the eyes, with the right eye being larger than the left. This required surgical trabeculotomies on two separate occasions in infancy for satisfactory glaucoma (*ie* IOP) control, being subsequently maintained with medication.

For the right eye, vision was 20/40 and poor, and the ability to count fingers was poor. Trauma to the right eye at three years of age with a flying ball led to subtotal retinal detachment with subsequent pars plana vitrectomy and cryoretinopexy with return of pre-trauma vision. He developed a cataract in the right eye with deterioration of vision leading to pars plana removal of the cataract followed by hyphaema managed and controlled with

topical steroids and cycloplegics. His left eye had been stable with normal IOPs since infancy. The IOP of the right eye fluctuated between 6 and 10 mmHg, and its vision remained poor.

At 14 years of age, the index case presented to a cardiologist with chest pain at rest and on exertion, waking him up at nights, 3 to 10 times per week, with duration of 2 to 10 minutes at rest and on exertion. He was unable to move his left upper limb because of associated pain when pain was severe. Pain resolved spontaneously with cessation of activity. History was negative for orthopnea, paroxysmal nocturnal dyspnoea, tightness in the chest, wheezing, oedema, coughing at nights and hearing loss.

His weight was 47 kg and his height was 156 cm, giving a body mass index of 19.3. His arm span was 168 cm and lower body length 92 cm. His oxygen saturation in room air was 99%, and his blood pressure was 118/71 mmHg, with a respiratory rate of 20 breaths per minute.

His arm span was greater than his height, with a ratio 1.08. He had a positive wrist sign, mild thoracic scoliosis and a high arched palate. Significant cardiovascular examination findings were a normal pulse, and normal cardiac apical position with an ejection systolic murmur 2/6 at the mitral area.

The index case had a family history of tall stature on the maternal side of the family and short stature on the paternal side of the family. He was a full-term, spontaneous vaginal delivery with no forceps or intervention necessary. He had a good Apgar score. His paternal cousin had a congenital heart disease. There was no history of sudden infant death syndrome or sudden death below 50 years of age in the family. He is the older of two children, with an 11-year-old male sibling from the same parentage.

Blood investigations confirmed haemoglobin of 13.8 g/dL, normal thyroid function tests, normal levels of erythrocyte sedimentation rate and C-reactive protein, negative autoimmune serological tests, and a negative antistreptolysin O titer ruling out rheumatic fever which is endemic, and were negative for cardiac injury with normal CK-MB and Troponin 1 levels.

His chest X-ray was normal. His electrocardiogram showed sinus rhythm with a heart rate of 78 beats per minute, with no signs of pre-excitation syndrome, ion channelopathy, Brugada or Short Q-T syndrome. There was normal early repolarization seen in adolescence.

The 24-hour Holter showed episodes of atrial fibrillation when panic button was pressed for chest pain with a maximum heart rate of 127 beats per minute. Transthoracic echocardiogram showed prolapse of the anterior leaflet of the mitral valve with posteriorly directed mitral regurgitation. The aortic root and left atrium were normal with a normal aortic root to left atrium ratio. There was normal origin of the right and left coronary arteries. No signs of coronary artery anomalies or fistulous communication were found. There were normal cardiac dimensions with normal left ventricular functions and no signs of diastolic or left heart failure. The tricuspid, aortic and pulmonary valves were normal with normal right ventricular pressures and pulmonary artery pressures. The 64-slice multidetector computed tomography coronary angiography was normal with no coronary artery anomalies.

DISCUSSION

The index case satisfied the Ghent criteria for the diagnosis of MS, meeting major criteria of an arm-span ratio of greater than 1.04 and a positive wrist sign and minor criteria of cardiac evidence of prolapse anterior leaflet of the mitral valve with mitral regurgitation, mild thoracic scoliosis, high arched palate and a positive maternal family history of tall stature. Marfan Syndrome's inherent deficiency of elastin leads to reduced strength of the eye and blood vessel wall, which in retrospect contributed to retinal detachment with a blunt injury to the index case's right eye at three years of age and cataract formation after the ophthalmic surgery. His systolic blood pressure was maintained at less than 100 mmHg with anti-hypertensive medication, losartan and atenolol, documented to reduce the risk of aortic dilatation. Dissection was started with no development of postural hypotension, and digoxin controlled the episodic atrial fibrillation occurring concomitantly with his chest pain. Competitive sports were prohibited and with a CHADS2 score of zero, for atrial fibrillation stroke risk, no antiplatelet medication was started, which in an active teenager would potentially lead to significant bleeding complications. Medications would thus prevent aortic valve and pulmonary valve aneurysmal dilatation of the sinuses of valsalva documented, but aorta involvement predominates and is the major cause of morbidity and mortality in adults (1–5, 7–9).

The use of β-blocker is not contraindicated with open-angle glaucoma which the index case had. Other prophylactic medications suggested for patients are calcium antagonists, angiotesion converting enzyme (ACE) inhibitors and enalapril (1–5).

The cardiovascular manifestations in MS can be sudden death, secondary to aortic dissection and rupture,

or can be totally asymptomatic where there is aortic root dilatation and mild valvular pathology being an incidental finding, as in this index case, of suspected MS. Marfan Syndrome leads to aortic dissection and rupture in 20–40% of patients. This occurs predominantly in the third and fourth decades of life, contributing to the increased morbidity and mortality of this specific group of patients, hence the need for a high index of suspicion and early diagnosis. The mean life expectancy of patients with MS is 32 years, with cardiac disease involving the aortic valve, aorta from the aortic root and its branches to the bifurcation and mitral valve causing death in over 90% who succumb (1, 2, 5, 7–10).

The morbidity and mortality of patients with MS can be markedly improved with early detection, close follow-up with a multidisciplinary team of ophthalmologists, cardiologists and radiologists, routine radiological evaluation at appropriate intervals with CT scan of the aorta, prophylactic medication and surgical intervention when indicated, and genetic counselling (1–3, 6–10).

This is a fascinating case of MS diagnosed in adolescence but presenting in retrospect with CG which has never been documented in an Afro-Caribbean. Globally, the incidence of MS varies from 1 in 5000 to 1 in 20 000, hence precluding routine screening of this condition which would not be cost-effective. Therefore, a high index of suspicion is required for diagnosis. This index case supports the need for close follow-up, jointly by ophthalmologists and paediatricians, of all patients diagnosed with CG, to facilitate identification of the myriad of secondary causes leading to the appropriate and optimal management which, in this case, was MS.

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