Cardiology in the Young (2012), **22**, 466–468
doi:10.1017/S1047951111001776

Brief Report

Diagnostic challenges of Marfan syndrome in an XYY young man

Ana Lebreiro,[1] Elisabete Martins,[1,2] José Carlos Machado,[3] Cassiano Abreu-Lima[2]

[1]*Cardiology Department, Hospital São João;* [2]*Medicine Department, University of Porto Medical School;* [3]*Institute of Molecular Pathology and Immunology, University of Porto, Porto, Portugal*

Abstract Tall stature is a common feature of both Marfan syndrome and XYY syndrome. Differential diagnosis between these entities has important prognostic implications. We report the case of a 21-year-old young man with a previously known diagnosis of XYY syndrome, in whom the identification of a fibrilin-1 mutation was determinant to establish an appropriate diagnosis, medical follow-up, and genetic counselling.

Keywords: Tall stature; molecular diagnosis; fibrillin-1 mutations

Received: 10 April 2011; Accepted: 8 September 2011; First published online: 4 November 2011

MARFAN SYNDROME IS A CONNECTIVE TISSUE disorder that affects multiple organ systems. Skeletal and cardiovascular systems are typically involved, and aortic dilatation or dissection is the principal cause of death in this population.[1] It is a rare syndrome affecting two to three cases per 10,000 individuals, and is mainly caused by mutations in the gene encoding fibrillin-1, an important protein of the extracellular matrix.[2]

XYY syndrome is a common sex chromosome anomaly. It affects one in 1000 male births and is characterised by physical findings such as tall stature, normal to mildly diminished general intelligence, delayed speech development, and impaired fine and gross motor function, coordination, and tone. Those affected are usually fertile and present normal testicular function and testosterone levels.[3]

Differential diagnosis of these two entities is of major relevance, given their different prognosis, need for clinical follow-up, and genetic counselling.

Correspondence to: Dr Ana Margarida Lebreiro, MD, MsC, Hospital de São João, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. Tel: +351966895567; Fax: +351225503015; E-mail: ana.lebreiro@gmail.com

Case report

We report the case of a 21-year-old young man, previously followed up in a paediatric clinic and recently transferred to our hospital for follow-up.

Owing to a phenotype of tall stature, marked skeletal abnormalities – scoliosis, *pes planus*, and *pectus excavatum* (the last two features, both requiring corrective surgery, at the age of 4 and 14 years, respectively) – and learning difficulties, at the age of 14 years, he was asked to do a chromosome analysis from a peripheral blood sample, which revealed a karyotype with 47 chromosomes and an XYY pattern.

A cardiologic work-up was required once he was transferred to our institution, as he had history of a cardiac murmur.

In our clinical evaluation, taken in conjunction with a rheumatologist and an ophthalmologist, the patient presented with a history of recurrent inguinal hernia, and physical examination revealed a tall stature (197 centimetres), slightly increased arm to height ratio (1.04), signs of previous surgery to the sternum – *pectus excavatum* – scoliosis, *pes planus*, joint hypermobility – positive wrist and thumb signs, knee hyperextension, facial features – high-arched palate, malar hypoplasia, and retrognathia – and skin *striae* in both shoulders. Auscultation of the heart revealed a systolic murmur grade II/VI, louder at

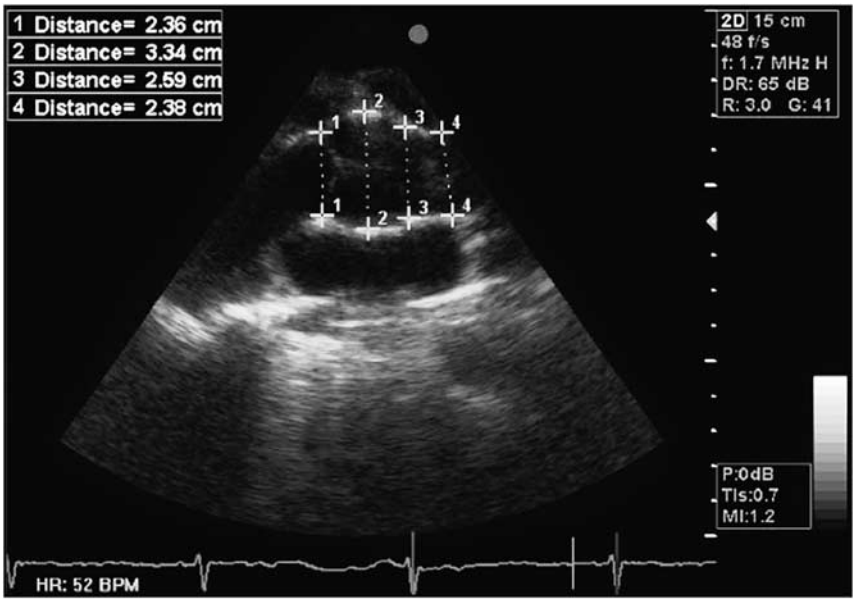

Figure 1.
Parasternal long-axis view of a transthoracic two-dimensional echocardiogram, showing an ascending aorta with normal dimensions and morphology.

the cardiac apical area. The electrocardiogram showed a normal sinus rhythm, and the echocardiogram showed a normal-sized root and ascending aorta – 33 and 24 centimetres, respectively (Fig 1), a mitral valve prolapse with a non-significant jet of mitral regurgitation, and a normal biventricular systolic function. These measurements followed the recommendations for chamber quantification from the American Society of Echocardiography in conjunction with the European Association of Echocardiography.[4] Ocular examination excluded *ectopia lentis*.

The patient's family medical history was unremarkable. He was an only child. His mother had a normal stature (163 centimetres), no skeletal features or ectopia lentis, and her echocardiographic examination was also within normal values – that is, no aortic dilatation or mitral valve prolapse. She had a healthy sister, of about the same height, with no anomalous systemic features. The patient's father was an only son and was living abroad, precluding a clinical evaluation. We were told that he was approximately 180 centimetres tall and that he had no ophthalmologic or obvious skeletal features and did not know about any cardiac involvement. In the rest of the family, there was also no history of sudden death, aortic disease, or *ectopia lentis*.

Taking into account the described features, the diagnosis of Marfan syndrome was suspected. In fact, according to the Ghent criteria published in 1996,[1] and still used at the time of clinical examination, our patient displayed major skeletal system criteria – *pectus excavatum* necessitating surgery, *pes planus*, scoliosis, wrist and thumb signs – and involvement of the cardiovascular system – mitral valve prolapsed – and skin – inguinal hernia and *striae* – which led us to suspect, but not be sure, the diagnosis of Marfan syndrome. According to the recently revised Ghent criteria,[5] our patient has a systemic score of nine – wrist and thumb signs, *pectus excavatum*, *pes planus*, scoliosis, facial features, skin *striae*, mitral valve prolapse – also compatible with systemic involvement of Marfan syndrome. Considering the clinical and prognostic implications of this diagnosis, and in spite of a negative family history, we decided to perform a molecular screening of the gene encoding fibrillin-1. After appropriate written informed consent, deoxyribonucleic acid was extracted from a peripheral blood sample and all 65 exons of fibrillin-1 gene were amplified. Mutation screening of the entire coding sequence of fibrillin-1 gene was then preformed, using polymerase chain reaction.

A *nonsense* mutation (C2581T) was found in fibrillin-1 gene, leading to the formation of a premature termination codon (Arg861X) in exon 21, the region of the hybrid module two. This is a previously described fibrillin-1 mutation, already known to be associated with Marfan syndrome.

Discussion

The molecular identification of a previously described fibrillin-1 mutation was determinant to make the diagnosis of Marfan syndrome, as established by the criteria used at the time of clinical examination,[1] disclosing the genetic nature of the phenotypic

https://doi.org/10.1017/S1047951111001776 Published online by Cambridge University Press

features described and contributing to plan a proper and timely medical follow-up and genetic counselling.

By that time, our patient fulfilled the Ghent criteria; he had a fibrillin-1 mutation known to be associated with Marfan syndrome, major criteria in one organ system, and involvement of two other systems.[1] Currently, based on the revised Ghent criteria, we would probably be more accurate if we used the term "potential Marfan syndrome". In fact, he lacked the two main diagnostic features of this entity, aortic dilatation and *ectopia lentis*, and the sole presence of a systemic score greater than seven, in the absence of a family history of Marfan syndrome, does not allow an unequivocal diagnosis of this disease. On the other hand, the association of a fibrillin-1 mutation known to be associated with Marfan syndrome, with all the systemic features depicted above, will make it inevitable to provide a regular clinical and echocardiographic follow-up of the evolution of aortic dimensions, especially because our patient was only 21 years old and the phenotypic expression of this disease is known to be age dependent.[5]

We reinforce that repeated cardiovascular screening of all patients with fibrillin-1 mutations is essential, because, although the precise risk of aortic aneurysm formation and progression is not known, it is well acknowledged that a life-long risk of aortic complications exists.[1] On the other hand, given the 50% chance of offspring transmission, genetic counselling is also an extremely important issue in this disorder.[6]

This is not the case with XYY syndrome. Those affected are tall, with a normal to mildly diminished general intelligence, delayed speech development, and impaired fine and gross motor function, coordination, and tone. There is no transmission to offspring, skeletal features are not usually described, and most importantly these individuals do not have an increased cardiovascular risk.[3] Differential diagnosis between Marfan syndrome and XYY syndrome may pose some difficulties to the clinician, mainly because of the overlap of tall stature, a phenotypic feature readily identified, and because the other accompanying physical characteristics are not always so easily disclosed. A mildly diminished intelligence quotient or slight motor discoordination may be difficult to appreciate in a young boy or teenager, as may be the skeletal features, which are common in the general population and often discrete. In order to avoid misdiagnosis, a thorough family history and physical examination should be made, including, in selected cases, an echocardiographic evaluation. A genetic test may help to confirm the diagnosis when clinical data are considered insufficient.

The association between Marfan syndrome and chromosomal anomalies is a rare finding. There are only three case reports published in the literature referring to the simultaneous occurrence of Marfan syndrome and an XYY chromosome pattern.[7–9]

Although we acknowledge that this is most likely just a coincidental finding, we believe that this case is particularly important to draw clinicians' attention to the impact of maintaining regular medical assessment, especially in young individuals, and a critical judgment about phenotype progression or patients' new signs and symptoms. It is imperative not to let a previously established diagnosis hamper the formulation of new clinical hypotheses, especially in face of a condition like Marfan syndrome, known to have incomplete or discrete phenotypes, particularly in children and adolescents.

In the case described, this approach may have contributed to change not only our patient's prognosis, but also the prognosis of his offspring.

Acknowledgement

The molecular analysis of this patient was included in a study supported by a grant from the Research Department of Hospital S. João, Porto, Portugal.

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