Chest Pain in Children With Suspected Type I Fibrillinopathy: A Case Report

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Chest pain is the second most common reason for referral to a pediatric cardiologist, because cardiovascular-related disorders are a major concern for children and their families when seeking medical attention. On the rare occasions when pediatric chest pain is a result of severe heart disease, it is usually associated with well-known cardiovascular risk factors such as fibrillinopathies. Type 1 fibrillinopathies are heritable disorders caused by mutations in the fibrillin genes that lead to a broad spectrum of connective tissue phenotypes ranging from Marfan syndrome, at the most severe end, to patients displaying mild marfanoid features, or milder Marfan (MM). We report the case of an adolescent patient with MM and suspected acute coronary syndrome, with chest pain and electrocardiographic changes suggestive of myocardial ischemia. Despite the low risk of coronary or aortic dissection/aneurysm in MM, these possibilities should be tested. Once they are ruled out, mitral valve prolapse should be considered as the main cause of chest pain with ischemic-like changes in the inferior electrocardiogram leads. We emphasize that clinical and echocardiographic follow-up over years is warranted in the pediatric population to ensure that the aortic root does not show progressive dilatation or a tendency to dissect. Finally, genotyping is clinically indicated for early and complete diagnosis in patients with MM as well as de novo Marfan syndrome to take advantage of educational and clinical programs for young carriers of the mutation.

Chest pain is a relevant pediatric emergency complaint that affects 0.14% to 0.60% of cases and is the second most common reason for referral to a pediatric cardiologist.[1,2] Although most cases are found not to be associated with organic causes, cardiovascular causes are often a primary concern of children and families when seeking medical attention.[1,2] In fact, the association of chest pain in adults with heart attack is well known, and ≤56% of patients' caregivers are likely to perceive chest pain as heart pain. Moreover, concern may be such that the child is restricted from participating in sports or strenuous physical activities even after a normal medical evaluation.[1–3] On the rare occasions when pediatric chest pain is the result of serious heart disease, it is usually associated with well-characterized cardiovascular risk factors such as Kawasaki disease, connective tissue disorders, and cardiovascular surgery involving coronary arteries or prothrombotic disorders. In this context, prompt recognition, evaluation, and intervention are essential to protect against an adverse outcome. Conversely, it has been reported that diagnosis error may lead to morbidity or mortality.[3]

CASE REPORT

A 13-year-old, previously healthy boy with myopia (left eye −5.5 diopters, right eye −4 diopters) complained of

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acute, intense, and oppressive central chest pain accompanied by sweating and pallor of 2 hours' duration. Physical examination revealed asthenic body habitus, an arm span of 181 cm (>99th percentile) for a height of 178 cm (>99th percentile), an arm span-to-height ratio of 1.03, pectus excavatum, arachnodactyly, and keloid scars. (Fig 1 A and B). No signs of hemodynamic instability were detected except for mild tachycardia secondary to pain and anxiety. His father and older brother had the same phenotype and were myopic too, but no history of heart disease was reported. The electrocardiogram (ECG) showed T-wave inversions in the inferior leads (Fig 2A), suggesting an acute coronary syndrome. He was admitted to the ICU, and therapy with morphine, aspirin, heparin, and β-blockers was initiated before evaluation by a pediatric cardiologist. The patient remained stable and the pain disappeared within a few hours. Chest x-ray showed neither mediastinal widening nor cardiomegaly. Cardiac biomarkers were negative. Transthoracic echocardiography revealed a mitral valve prolapse (MVP) (Fig 2B). No wall motion abnormalities and no other valvular anomalies were observed, whereas the aortic root was highly increased (+1.91 SD of normal for body size) (Fig 2B). A cardiac stress test showed no signs suggesting myocardial ischemia. In the absence of evident cardiovascular risk factors, cardiac catheterization and computed tomography/angiography were avoided. After 48 hours, ECG abnormalities remained unchanged. The child did not fulfill Ghent-modified criteria for Marfan syndrome,[4] and he was discharged with a diagnosis of thoracic pain secondary to MVP associated with inferior repolarization abnormalities in the context of milder Marfan (MM) phenotype. Genetic testing of the fibrillin 1 gene (*FBN1*) revealed a heterozygous missense mutation in the proband (c.7605C>G; p.Cys1084Trp), involving Cys residues of calcium-binding epidermal growth factor–like modules. Family study showed that his father and brother were carriers of the mutation, both without heart-related alterations. Six months later, the patient complained of infrequent episodes of atypical chest pain and exercise intolerance that did not affect his daily life, so no treatment was initiated. ECG abnormalities persist and echocardiographic findings remained unchanged.

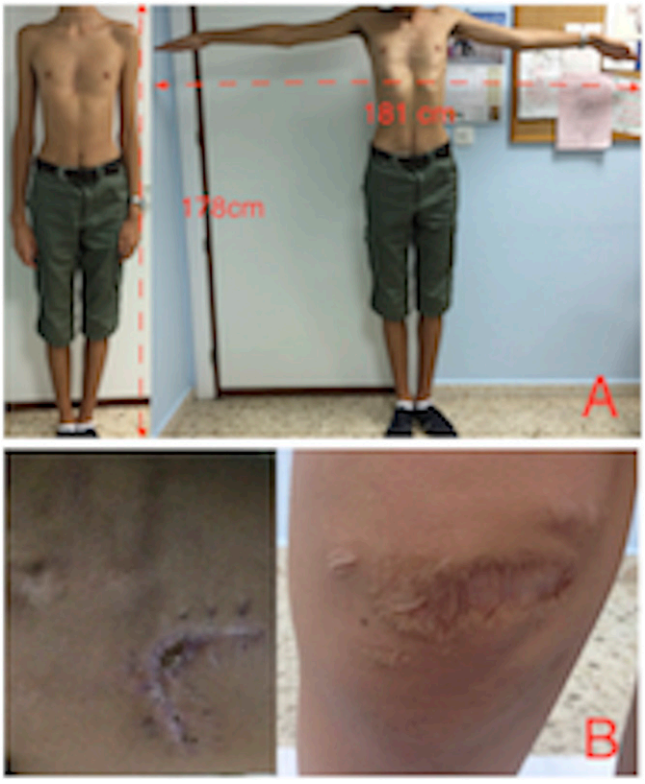

FIGURE 1
A, Image of asthenic body habitus of the patient. B, Keloid scars on the right knee and right arm.

DISCUSSION

Type 1 fibrillinopathies are heritable disorders caused by mutations in the fibrillin genes (*FBN1* and *FBN2*) that lead to a broad spectrum of connective tissue phenotypes, ranging from Marfan syndrome, at the most severe, to patients displaying mild marfanoid features, including familial ectopia lentis; familial thoracic aneurysm/dissection; familial MVP syndrome; mitral valve, aorta, skin, and skeletal features (MASS) phenotype; and familial marfanoid habitus.[5,6] Progressive dilatation of the aortic root with increased risk of aortic/coronary dissection represents the most severe clinical problem for many patients.[6,7] Knowing whether a certain patient will develop this complication remains a challenge for several reasons. First, because of the evolving nature of some clinical manifestations of Marfan syndrome, classic signs are rarely present in younger children and usually appear as the disease progresses over time.[4] Second, the broad spectrum of type 1 fibrillinopathies, as well as the wide clinical heterogeneity among individuals and families affected with the same mutation, result in a challenging phenotypic-genotypic correlation.[8,9] Furthermore, extensive phenotypic overlapping is observed

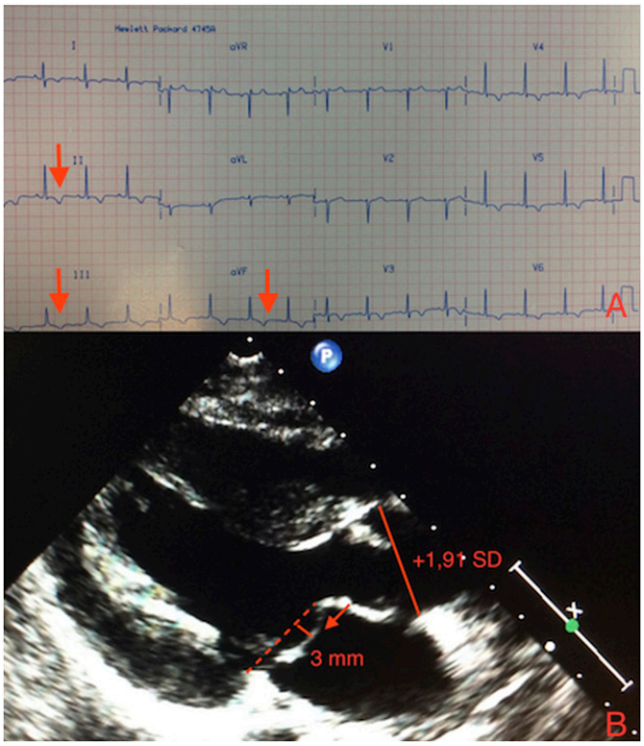

FIGURE 2

A, ECG showing T-wave inversions in the inferior leads (arrows). B, Echocardiography on a parasternal long-axis view showing prolapsed mitral valve (arrow) and an aortic root at the upper limits (+1.91 SD) of normal for body size.

in the general population, with high prevalence of MVP or skeletal marfanoid disorders[10,11] and so-called MM conditions.[12,13,14] Finally, whereas this latter group shares ≥1 clinical features with Marfan syndrome, patients may differ in their clinical evolution and prognosis, showing a low risk of aortic/coronary dilation or dissection.[6,7] In summary, the diagnosis of Marfan syndrome may be hindered, particularly in children, and therefore chest pain may be considered a warning sign in this population.

MVP or mitral insufficiency can be the earliest cardiovascular manifestation of Marfan syndrome in some patients.[11,12] It can be defined as a ≥2-mm superior displacement of the mitral valve leaflets into the left atrium during systole.[15] MVP is considered the most common primary valvular abnormality in young populations (prevalence 2% to 5%),[16,17] and it is often associated with heritable connective tissue disorders.[4,15,18] It is usually a benign asymptomatic condition, although it is also related to a confusing array of seemingly unrelated symptoms of dysautonomia that cannot be explained on the basis of mitral regurgitation alone, such as palpitations, orthostatic hypotension, syncope fatigue-exercise intolerance, chest pain, shortness of breath, and panic attacks, which are collectively called MVP syndrome.[17,18] Moreover, inferior ECG lead abnormalities may occasionally be found, as well as typically early repolarization patterns and ST-segment depression or T-wave inversion, mimicking myocardial ischemia. Altogether, these symptoms make the evaluation and management of these patients very difficult when consulting for chest pain.[18,19] Various combined mechanisms are hypothesized to explain observed symptoms and ECG findings. First, there is a decrease in the effective stroke volume and cardiac output secondary to a functional third left chamber generated by the systolic withdrawal of the mitral valve to the left atrium which decreases left ventricular volume.[17,18] Second, traction of the papillary muscles with stretch receptor activation occurs, resulting in membrane depolarization, cardiac arrhythmias, and self-limited episodes of papillary muscle ischemia.[17,18] Finally, mechanical stimuli caused by abnormal coaptation of the mitral valve may cause an abnormal autonomic nerve feedback to the central nervous system and the mitral valve.[17,18] All of the above could lead to neuroendocrine-autonomic nervous system dysfunction with high and excessive adrenergic activity or response.[20] Also, recent studies propose that low levels of magnesium may cause some dysautonomia.[21]

Acute chest pain in children with connective tissue disorders may be considered a warning sign, and they should be carefully studied to discard severe complications such as myocardial ischemia or aortic or coronary dissection, especially when ischemic-like ECG abnormalities are observed. In patients with MM phenotype, despite the low risk of coronary or aortic dissection/aneurysm, these possibilities should be tested. Once they are rejected, MVP should be considered, since this is the main cause of chest pain and ischemic-like changes in the inferior ECG leads. Because it remains unclear how to identify high-risk MM patients, detailed clinical and echocardiographic follow-up over years should be carried out to ensure that the aortic root does not show progressive dilatation or a tendency to dissect. Finally, we emphasize the necessity to perform *FBN1* genotyping studies due to the high incidence of *FBN1* mutations in young children with incomplete or atypical Marfan syndrome[5,9,10,12,22] and the difficulty of making strong

genotype-phenotype correlations. Genetic assessment is indicated for early diagnosis and decision-making about completion of the diagnostic work-up, as well as for patient follow-up, preventive cardiovascular treatment, and tailoring educational and clinical programs in young carriers of the mutation.

ABBREVIATIONS

ECG: electrocardiogram
MASS: mitral valve, aorta, skin, and skeletal features
MM: milder Marfan
MVP: mitral valve prolapse

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