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Case Report

Left Ventricular Noncompaction Cardiomyopathy in 2 Siblings With Underlying Tetralogy of Fallot: A Case Report

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ABSTRACT

Tetralogy of Fallot (TOF) is one of the most common congenital heart diseases. Family recurrence provides strong evidence for the involvement of a genetic component in the susceptibility to TOF. The role of genetic factors is supported by the increased risk of first-degree relatives of patients with TOF. The clinical course of this disease is unclear and unpredictable. We herein describe 2 siblings suffering from TOF with left ventricular noncompaction cardiomyopathy (LVNC) and their clinical course and treatment. LVNC is a rare disease known by prominent trabeculation of the ventricles and reduced systolic function. LVNC can manifest itself in a wide spectrum of symptoms overlapping with other cardiac diagnoses. Familial patterns of disease development and coexistence of cardiac abnormalities are also reported. ***(Iranian Heart Journal 2024; 25(1): 98-105)***

KEYWORDS: Left ventricular noncompaction cardiomyopathy, Tetralogy of Fallot, Congenital cardiac abnormality

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Left ventricular noncompaction cardiomyopathy (LVNC) is a rare congenital cardiac disorder characterized by the abnormal development of the myocardium, leading to a sponge-like appearance of the LV with deep intertrabecular recesses and prominent trabeculations that connect to the ventricular cavity. [1] This clinical entity has gained more attention in recent years owing to advances in imaging modalities and awareness regarding its clinical importance.

Since the clinical manifestations of LVNC include various symptoms ranging from no symptoms to severe heart failure, arrhythmias, and sudden cardiac death, [2-4] the clinical diagnosis of LVNC requires high levels of suspicion. Given the broad spectrum of clinical symptoms, LVNC can mimic features of other cardiac cardiomyopathies; thus, misdiagnosis of LVNC in initial assessments may occur. Echocardiography, cardiac magnetic resonance imaging, and computed tomography play major roles in the diagnosis of LVNC. [5] Accurate and precise evaluations of heart layers are critical for the detection of noncompaction in cardiac layers and the subsequent diagnosis of LVNC.

Apart from difficulties in the diagnosis of LVNC, the literature shows few associations between this disease and other congenital

heart disorders, including the LV outflow tract, the Ebstein anomaly, and tetralogy of Fallot (TOF). [6] Investigations are ongoing to determine the probable genetic origins or shared underlying mechanisms between LVNC, as a rare phenotype, and these cardiac diseases. Thus, in this study, we describe 5-year- and 6-year-old siblings with repaired TOF later diagnosed with LVNC.

CASE DESCRIPTIONS

CASE 1

A 6-year-old girl was born with normal birth weight as the third offspring of a family. She developed cyanosis and flu symptoms at 4 months of age with an O_2 saturation level of 75% and a hemoglobin level of 18.7 mg/dL. The patient underwent echocardiography, which revealed pulmonary atresia, a large ventricular septal defect, small major aortopulmonary collateral arteries, mild left pulmonary artery branch (LPA) origin stenosis, and a normal coronary artery. With a diagnosis of TOF, a GORE-TEX shunt operation was performed for the patient at 4 months of age. She was then discharged with spironolactone, aspirin, captopril, ranitidine, and furosemide. The patient was again presented to the hospital at 10 months of age with head and neck edema. She was admitted with suspected heart failure. On physical examination, respiratory distress and mild-to-moderate cyanosis were present. Echocardiography showed pericardial effusion, pleural effusion, confluent pulmonary atresia, ventricular septal defect, confluent PA branches, right atrial enlargement, right ventricular (RV) hypertrophy, LV enlargement, severe RV and LV dysfunction (ejection fraction [EF] = 25%), and tricuspid annular plane systolic excursion of 1/3 cm. The patient received treatment with low-dose furosemide, aspirin, and intravenous antibiotics and was discharged with aspirin and captopril. Ambulatory echocardiography, several days after discharge, revealed a very small pleural effusion (1–2 cm) with an EF of 45% to 50%. At 6 years of age, the patient underwent angiography, which revealed that the course of the venous catheter was normal from RFV to RV. The course of the arterial catheter was normal from the right femoral vein to LV and then to PA via the left GORE-TEX shunt. The systemic sample was desaturated. Pulmonary arterial pressure was normal. LV injection in the anteroposterior view showed a dilated ventricle and relatively good contractions. The aortic root injection in the LAP view showed normal coronary arteries and a patent left GORE-TEX shunt. PA injection in the anteroposterior view showed that the PA branches had good size. The diagnosis was pulmonary atresia and ventricular septal defect with a patent GORE-TEX shunt. Surgical correction was recommended. An electrocardiogram (ECG) revealed no abnormal findings. Afterward, echocardiography indicated pulmonary atresia, confluent PA branches (RPA = 12–13 mm and LPA = 10 mm), a large subaortic ventricular septal defect (16 mm), the aorta arising from RV, mild aortic insufficiency, moderate LV enlargement with spongy myocardium, a relatively small RV cavity due to apical trabeculation and fibrosis, severe RV dysfunction, moderate tricuspid regurgitation, and a functioning left GORE-TEX shunt (EF = 40–45%) (Fig. 1). The echocardiographic findings of ventricular septal defect, pulmonary atresia, and cardiomyopathy of both ventricles raised the clinical suspicion of LVNC, and cardiac magnetic resonance was recommended. The imaging modality revealed a moderately enlarged LV without hypertrophy and with moderately reduced systolic function (LVEF = 43%). Additionally, a mildly enlarged RV with severely reduced systolic function (RVEF = 32%), a dilated sinus of Valsalva (29 mm), and a dilated

ascending aorta (27 mm) were observed (Fig. 2). LV hypertrabeculation with a noncompacted to compacted myocardium ratio (NC/C ratio) of 3.4 was detected, which fulfilled the criteria for LVNC diagnosis. The patient was subsequently discharged with enalapril, aspirin, and digoxin.

CASE 2

The second case was a 5-year-old boy, the brother of CASE 1. He was diagnosed with TOF at 4 months of age. At 5 years old, the patient was evaluated with computed tomography angiography, which revealed a subaortic ventricular septal defect, pulmonary subvalvular stenosis, pulmonary valvular stenosis (compatible with TOF anatomy), confluent PA branches (MPA = 22 mm, RPA = 11.6 mm, and LPA = 14.8 mm), a left-sided aortic arch, and normal supra-aortic branches. The origin and course of the coronary artery were normal. ECG illustrated normal sinus rhythm. Echocardiography showed a large subaortic ventricular septal defect (9 mm), subvalvular stenosis (peak pressure gradient = 67 mm), pulmonary valvular stenosis, mild pulmonary insufficiency (LPA= 11 mm and RPA = 13 mm), normal LV size with mild trabeculation (LVEF = 60%), a relatively small RV cavity due to apical hypertrophy and trabeculation with severe RV dysfunction (Fig. 3). The echocardiographic findings suggested LVNC as a probable diagnosis, and cardiac magnetic resonance imaging was recommended for the confirmation of the diagnosis. The imaging modality also demonstrated TOF, a mildly enlarged LV with mildly reduced systolic function (LVEF = 48%), a mildly enlarged RV with moderately reduced systolic function (RVEF = 39%), pulmonary valvular and subvalvular stenosis, mild pulmonary insufficiency, a left-sided aortic arch, RV outflow tract fibrosis, and a large subaortic ventricular septal defect. Also detected was LV hypertrabeculation with an NC/C ratio of 2.8, compatible with the criteria of LVNC diagnosis. The patient was then discharged with furosemide and captopril.

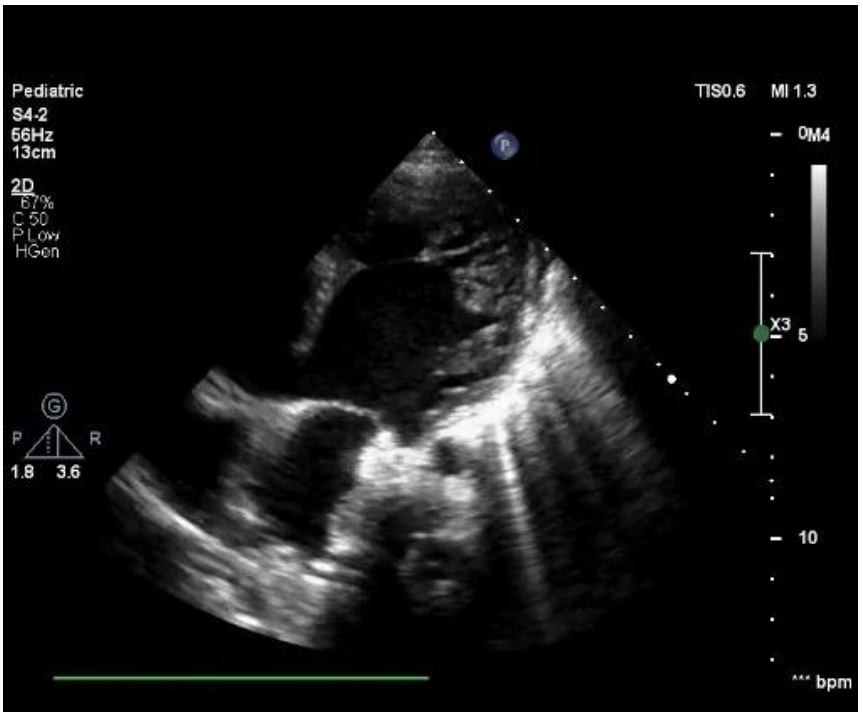

Figure 1: The image shows the echocardiography of the first case.

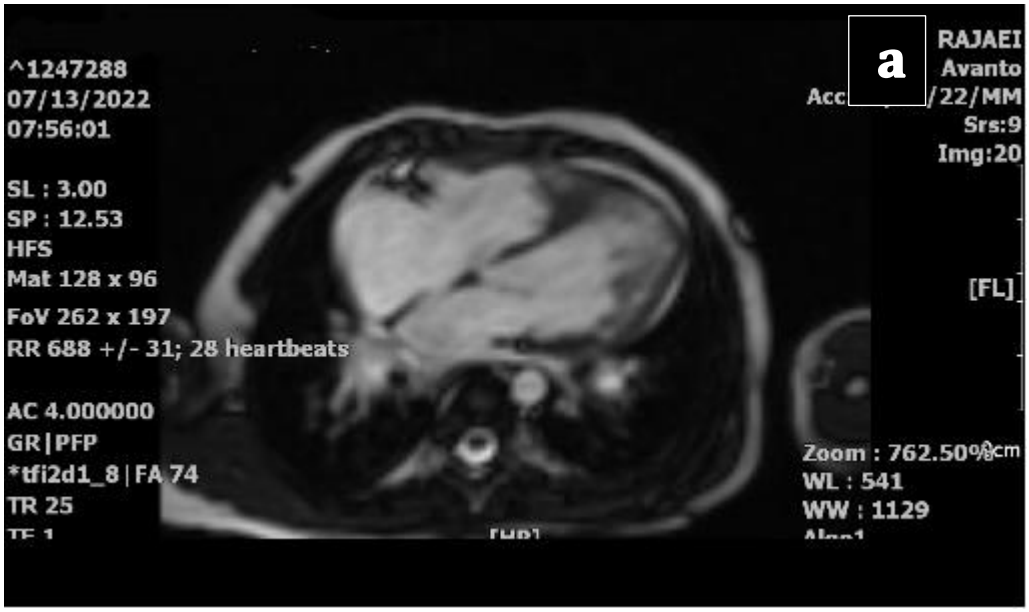

Figure 2: The image presents the cardiac magnetic resonance imaging of the first case.

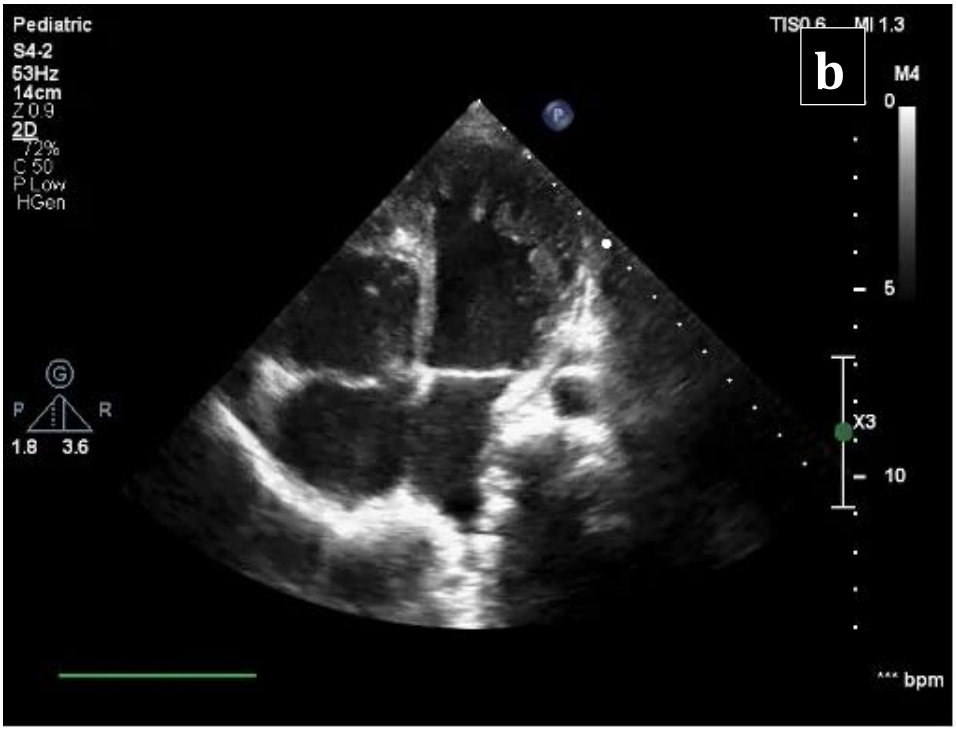

Figure 3: The image presents the echocardiography of the second case.

DISCUSSION

We herein described 2 siblings with familial LVNC and coexisting TOF. LVNC, as a rare clinical entity, is a cardiomyopathy in which portions of "spongy" myocardium do not convert into mature and compact muscles. This failure leads to the presence of noticeable myocardial trabeculae, deep intra-trabecular recesses, and reduced heart function. [1, 7] This

disease was first introduced in 1990 by Chin et al [7] in a series of children with cardiac disorders. Nevertheless, most reports since then have described the adult population. [8-12] The prevalence of LVNC in children is not clear since it is a rare congenital heart condition, but some studies suggest that LVNC may be found in 0.05% to 0.24% of children undergoing echocardiography. [13]

The differences between adult and pediatric populations vis-à-vis LVNC epidemiology concern the proportion of sporadic and familial cases and coexisting abnormalities. Adults exhibit fewer familial LVNC cases than children. In addition, frequent coexistence of anatomical abnormalities is common in children. [14] Our cases both suffered from LVNC with a familial origin and had coexisting TOF. As mentioned earlier, LVNC development can occur sporadically or through familial inheritance. The most common route of inheritance is autosomal dominant with X-linked inheritance in the next rank. Albeit less likely, an autosomal recessive route has also been reported in the literature. [15, 16] The genetic basis of LVNC is not thoroughly understood; still, numerous genes, including *TAZ*, *LMNA*, *MYH7*, *ACTC*, *TNNT2*, and *ZASP*, could be responsible in cases of LVNC. [17] Each gene might lead to LVNC with different characteristics and clinical courses. Thus, genetic assays may be considered a critical guide in diagnosing patients and their family members as well as a key in understanding and predicting the clinical course of the disease. We did not evaluate our cases genetically. Although one of the components of the original criteria of LVNC is the absence of any comorbid congenital cardiac abnormalities, [10] modifications in its definition have recognized the presence of other cardiac conditions accompanying LVNC. One of the most comprehensive studies evaluating LVNC in patients with various types of congenital heart diseases reported the coexistence of the Ebstein anomaly in 15% of patients with LVNC, followed by aortic coarctation in 3%, TOF in 2%, and unicuspid/bicuspid aortic valves in 1%. [6] Thus, TOF, as was the case in our patients, has been previously reported in the literature as a comorbidity of LVNC, as much as its prevalence is very low. At the same time, it is very rare to report LVNC in affected siblings with TOF.

The range of clinical symptoms of LVNC varies from no symptoms to the triad of arrhythmias, thromboembolism, and heart failure. [17] Adults usually experience clinically overt heart failure, while children usually show no symptoms except for a reduced EF [11, 18] One of our patients showed degrees of heart failure symptoms, whereas the other one only had a mildly decreased EF. Abnormalities on ECG have been reported to be common in patients with LVNC with a lower frequency in children. [19, 20] Supraventricular and ventricular arrhythmias, in addition to conduction abnormalities, have been known to occur, but ventricular tachycardia is the most prominent finding on ECG in patients with LVNC. [17-19] Reduced LV function and subsequent blood stasis within the intertrabecular recesses can lead to thromboembolic events, [19, 21] although the condition is more frequently seen in adult patients. [20]

The most commonly used criteria for the diagnosis of LVNC is the Jenni criteria, introduced in 2001 [10] and updated in 2010. [22] The Jenni criteria are based on echocardiographic assessments as the first imaging modality in the workup of LVNC. According to these criteria, LVNC is defined by the presence of 2 major criteria or 1 major and 2 minor criteria. The major criteria include the presence of prominent, excessive, and deep trabeculations in the LV myocardium (typically ≥ 2/3 of the thickness of the adjacent compacted myocardium) and

an NC/C ratio of ≥ 2.3:1 at end-diastole. The minor criteria include LV systolic dysfunction, the presence of a thrombus or embolus within LVNC, and the absence of any other cardiac or systemic disease that could explain the clinical manifestations. [10, 22] Inappropriate echocardiographic windows, problems with the depiction of the apex, and operator dependency are some of the limitations of echocardiography. [23] Therefore, in cases with inconclusive results of echocardiography, cardiac magnetic resonance imaging is recommended to overcome the deficits and limitations of echocardiography in the diagnosis of LVNC. Different criteria for the diagnosis of LVNC in cardiac magnetic resonance imaging have been proposed. Petersen et al [24] suggested an end-diastolic NC/C ratio > 2.3 in the long-axis view measured at the site of most trabeculations. Stacey et al [25] were in favor of an NC/C ratio > 2 at the end-systole in the short-axis view. Captur et al [26] used a loss-of-the-base-to-apex fractal dimension gradient ≥ 1.3 at end-diastole for the diagnosis of LVNC. Jacquier et al [27] also published a formula for the diagnosis of LVNC based on the measurement of trabeculated LV mass at end-diastole. Given the differences in the definitions and diagnostic criteria of LVNC in cardiac magnetic resonance imaging, other modalities, such as multidetector computed tomography, may be used for equivocal cases. [17]

No specific therapy for LVNC is determined in the guidelines. Treatments should be focused on the symptoms of each individual. [17] In our patients, heart failure and reduced EF were treated medically. Due to the rarity of the disease and inconsistent definitions and diagnostic criteria used in the literature, the prognosis and mortality rate of patients with LVNC cannot be determined precisely. A meta-analysis reported a cardiovascular mortality rate of 1.92 per 100 person-years for LVNC, while this rate for the general population was 0.08 per 100 person-years. [28] In summary, LVNC, as a rare cardiac disease, exhibits a wide range of symptoms. Careful assessments with imaging modalities are necessary to prevent misdiagnosis. Genetic analysis of patients and their family members can yield useful information and guide the diagnostic and therapeutic plan. This clinical entity must be kept in mind, even in the presence of other congenital heart diseases.

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