Familial left ventricular noncompaction cardiomyopathy due to a novel mutation in the MYH 7 gene

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ABSTRACT

Left Ventricular Non Compaction (LVNC) is considered a unique cardiomyopathy according to the American Heart Association guidelines. The genetic ethology of LVNC in children is not completely understood although upto 41% of LVNC are thought to be genetic. We report a family with LVNC due to a novel mutation in the MYH 7 gene.

Keywords: Genetic cardiomyopathy, left ventricular noncompaction, massive parallel sequencing

INTRODUCTION

Left ventricular noncompaction (LVNC) or spongiform cardiomyopathy is a rare disorder characterized by excessive trabeculations in the left ventricle (LV)[1] and is associated with LV systolic dysfunction and arrhythmias. Although a number of genes have been implicated in this disorder, some of these genes have only been reported in a handful of families. Our understanding of the genetic basis of this disorder hence continues to evolve. In this manuscript, we report a family with LVNC and LV systolic dysfunction in the mother and child with a novel pathogenic mutation in the MYH7 gene.

CASE REPORT

A 6-month-old infant was referred to us with an acute respiratory illness of 1 week duration. He had clinical evidence of heart failure with tachycardia, tachypnea, an enlarged liver palpable 5 cm below the right costal margin, cardiomegaly, and a gallop rhythm on auscultation. His echocardiogram revealed an enlarged LV with evidence of hypertrabeculation. The hypertrabeculation was predominant in the apical and lateral walls of the LV with a noncompacted to compacted layer ratio of >3:1 in end systole and evidence of blood flow into and out of the recesses on color Doppler thus satisfying the criteria for LVNC [Figure 1a and b]. There was severe systolic dysfunction as evidenced by an ejection fraction (EF) of 15%. The heart was otherwise structurally normal.

He was born to nonconsanguineous parents. An elder sibling had died after a similar brief respiratory illness at 7 months of age. The sibling had not been subjected to a cardiovascular evaluation before his death. There was a history of seizures in multiple members of the mother's family with one death attributable to seizures [Pedigree in Table 1]. This raised a possibility

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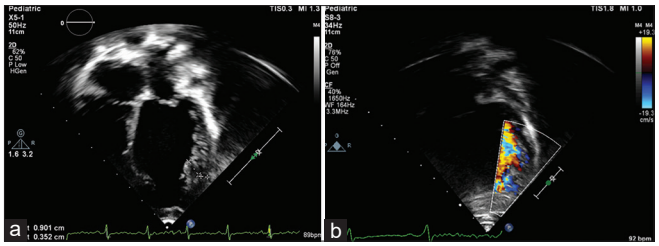
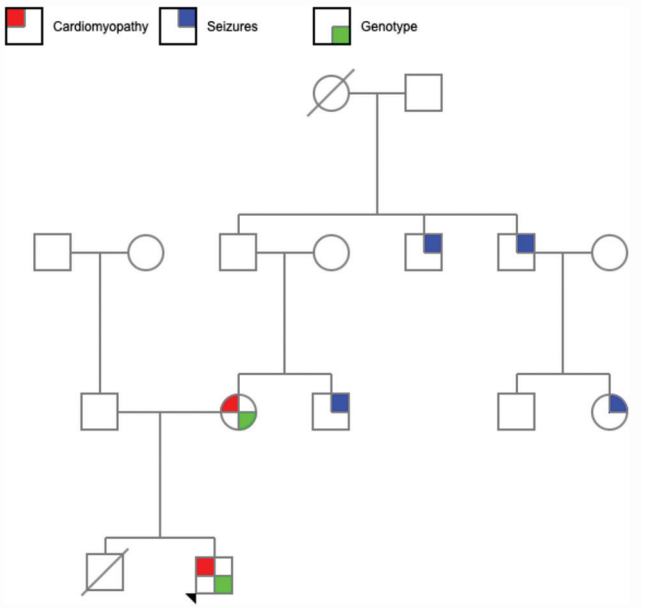


Figure 1: (a) Two-dimensional echocardiogram in the apical four chamber view demonstrating ventricular noncompaction with a noncompacted to compacted myocardium ratio of >2.5:1. (b) Echocardiogram with color Doppler imaging in the apical four chamber view demonstrating blood flow into the crypts of the noncompacted myocardium

Table 1: Pedigree of the family. The proband and his mother were found to have LVNC and a pathogenic mutation in the MYH 7 gene. Multiple members in the mother's family were diagnosed to have seizures but a detailed cardiac evaluation had not been performed



of a genetic cardiomyopathy. Hence, the parents were subjected to cardiac screening. The father's evaluation was normal. The mother's evaluation revealed evidence of LVNC with LV systolic dysfunction on echocardiogram and cardiac magnetic resonance (CMR) imaging although she remained clinically asymptomatic [Figure 2].

Both the mother and child were stabilized on antifailure medications including diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers. There was a rapid improvement in LV function with therapy. Genetic testing was organized for the child. Massive parallel sequencing of 151 genes implicated in inherited cardiomyopathies revealed a novel variant in the MYH7 gene encoding the myosin heavy chain beta isoform in Chromosome

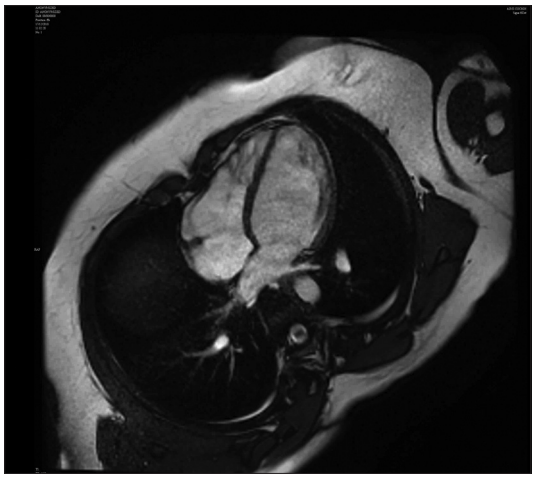


Figure 2: Cardiac magnetic resonance image from a 4-chamber steady-state free precision acquisition demonstrating left ventricular noncompaction of the posterior wall and the apical region

14 (Variant c. 3830G > C [p. Arg1277Pro]). The observed variation was in the myosin tail 1 domain of the protein. This region was noted to be conserved across species and predicted to be damaging on *in silico* predictions. The variant was hence classified as "likely pathogenic" based on the American College of Genetics and Genomics guidelines.[2] Cascade testing confirmed the presence of this variant in the mother and it's absence in the father.

On follow-up over a 2-year period, both the mother and child had no clinical worsening and their systolic function improved with EF of approximately 50% on serial echocardiograms. It is plausible that the seizures in multiple family members in the mother's side of the family were related to a genetic cardiomyopathy. Hence, cascade testing of the mother's family with cardiac evaluation and genetics was advised and the family were counselled about the importance of cascade testing.

DISCUSSION

LVNC is a disease entity which is increasingly recognised due to improvements in noninvasive imaging modalities. It was initially believed to be due to the failure of regression of the embryonic trabeculated myocardium due to an arrest in maturation. The American Heart Association classified LVNC as a distinct cardiomyopathy in 2006 although the European Society of Cardiology does not make a similar distinction.[1] Inherited and sporadic forms have been described as well as an association with other congenital heart disease. The early description of LVNC was based on sick patients who presented to tertiary cardiac facilities and led to an erroneous conclusion that LVNC was a severe form of cardiomyopathy with a high association of ventricular dysfunction, arrhythmias, and thrombo-embolic episodes.[3] The most widely used diagnostic criteria for LVNC are the Jenni's criteria based on

echocardiography. A ratio of noncompacted to compacted myocardium >2 in end systole is considered diagnostic.[4] There are additional criteria based on CMR findings.

The genetic basis of LVNC is not clearly established. Depending on the criteria used for diagnosis and the number of genes analyzed, pathogenic mutations have been identified in 9%–41% of LVNC.[1,5,6] The most common mode of inheritance described in literature is autosomal dominant. Our index child inherited the heterogeneous mutation from his mother. The genetic profile varies among children and adults. Disorders with extra-cardiac manifestations such as tafazzinopathies and Danon's disease are almost exclusively described in children while mutations in sarcomeric mutations have been described in both adults and children. A family history of cardiomyopathy or sudden unexplained death (SUD), as was present in our child, should prompt early referral for genetic testing.

Among, the sarcomeric genes MYH7 mutations are the most commonly described.[5] Although the variant described in our family has not been reported in the medical literature, the variant was deemed likely pathogenic based on standard classification guidelines and a review of ClinVar genetic database maintained by the National Institute of Health revealed that the variant had previously been identified in a person with LVNC. Phenotype-genotype correlations are difficult to describe because of heterogeneity among the genetic testing panels utilized by various institutions. In the largest cohort of adults and children with LVNC reported, patients with a genetic mutation were at a higher risk for systolic dysfunction as well as major cardiac adverse events. However, patients with MYH7 mutations tend to fare better (lower incidence of LV systolic dysfunction as well as cardiovascular adverse events) than those with other mutations as well as sporadic cases.[5] This may explain the rapid and sustained response to therapy noted in our index child.

The long-term outcomes of LVNC have not been clearly defined. A population-based cardiomyopathy registry concluded that infants who present with LVNC and LV dilation with systolic dysfunction fare worse than infants with dilated cardiomyopathy with an increased mortality and lower survival without cardiac transplantation during a median follow-up of 25 years.[7] Although our index child responded rapidly to medications, life-long cardiac follow-up is mandatory to identify late worsening of LV function and initiate appropriate management. Management is usually symptomatic with heart failure therapy and anti-arrhythmics. Aspirin is frequently used by most cardiologists because of a perceived higher risk of thrombus formation within the recesses and systemic embolization.[8] Cardiac resynchronization therapy and heart transplantation are reserved for those with intractable heart failure.

In conclusion, genetic testing is indicated in children with LVNC and a family history of cardiomyopathy or SUD. This may provide important prognostic information and also permit screening of family members to identify those at risk and in need of continuous cardiac surveillance.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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