A neonate with a spongy failing heart – What could it be?

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ABSTRACT

A neonate born of third-degree consanguineous marriage presented on day 12 of life with congestive cardiac failure. A male sibling died at 3 months of age, cause of which was not known. He was treated with decongestive measures and multiple inotropes. 2D Echocardiogram revealed severe Left ventricular dysfunction with prominent trabeculations and deep recesses in the left ventricle suggestive of Left ventricular non-compaction. He was also found to have horse-shoe kidney. Considering the presence of cardiac left ventricular non compaction, horse-shoe kidney and family history of neonatal death and pregnancy loss clinical exome sequencing was done. It detected a homozygous missense variant in exon 6 of the AGK gene suggestive of Senger's syndrome. Baby was on regular follow-up and was thriving well on diuretics, sacubitril-valsartan and weekly levosimendan infusions. At 8 months of age, cardiac transplantation was successfully done and baby has been doing well post-transplantation. LVNC in children is rare with an estimated incidence of 0.11 per 100,000, the highest incidence being during infancy. Senger's syndrome is autosomal recessive in inheritance. Senger's syndrome associated with Left ventricular non compaction has been reported only once in literature so far. Renal manifestations in the form of horse shoe kidney like in our index baby has not been reported previously with Senger's syndrome.

Keywords: Cardiac transplant, left ventricular noncompaction, Senger's syndrome

INTRODUCTION

A neonate born of third-degree consanguineous marriage with significant family history of neonatal deaths presented with cardiac failure and cardiogenic shock on day 12 of life. Genetics revealed Senger's syndrome. Cardiac transplant was successfully done at 8 months of age and the infant is thriving well now. Senger's syndrome associated with Left ventricular non compaction has been reported only once in literature till date.

CASE REPORT

A neonate presented on day 12 of life with increased work of breathing. He was born of third-degree consanguineous marriage at 39 weeks of gestation with a birth weight of 2.75 kg. He did not require any resuscitation at birth, with Apgar scores of 8 and 9 at 1 min and 5-min, respectively. He had a smooth perinatal transition and was discharged home on the fourth day of life. He had three female siblings who were asymptomatic and growing well. A male sibling died at 3 months of age, the cause of which was

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DOI: 10.4103/apc.apc_193_23

How to cite this article: Archana A, Natarajan CK, Kumar VH, Subramaniyam G, Ramachandran B, Balakrishnan K, *et al.* A neonate with a spongy failing heart – What could it be? Ann Pediatr Card 2024;17:81-4.

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Submitted: 22-Dec-2023 **Revised:** 09-Feb-2024 **Accepted:** 20-Feb-2024 **Published:** 24-May-2024

not known. The mother also had a spontaneous abortion at 5 months of age; the sex of the fetus was not known. On the 12th day of life, the neonate was brought with fast breathing, retractions, and history suggestive of suck rest suck cycle while feeding. There was no history of cyanosis. At admission, the baby had tachycardia and tachypnea with subcostal retractions. He had prolonged capillary refill time with poor peripheral pulses and hypotension. Cardiac examination revealed a gallop rhythm but no murmurs. The liver was palpable 2 cm below the right costal margin. The neurological examination was normal. The chest radiograph was suggestive of pulmonary congestion with cardiomegaly. Blood gas showed mixed respiratory and metabolic acidosis. He was intubated because of increased work of breathing and shock. Because of decompensated heart failure with cardiogenic shock, he was treated with decongestive measures (furosemide and spironolactone) and inotropes (dobutamine up to 20 μg/kg/min). A two-dimensional echocardiogram revealed severe left ventricular (LV) dysfunction with an ejection fraction of 37% and a fractional shortening of 13%. In addition, he had prominent trabeculations and deep recesses in the LV, suggestive of LV noncompaction (LVNC) [Figures 1-3; Video 1]. For refractory shock, he was started on milrinone, which waslater tapered and changed to levosimendan. Decongestive measures were optimized. The baby was then started on digoxin at 5 μg/kg/day and enalapril at 0.05 mg/kg/day. An antiplatelet dose of aspirin (3 mg/kg/day) was also started. Gradually, the LV systolic function improved, and he was extubated after 8 days of mechanical ventilation. A repeat echocardiogram showed an improving LV ejection fraction (52%) with persistent LVNC changes. A cardiac magnetic resonance imaging (MRI) with contrast confirmed the LVNC changes. The thickness of the noncompacted portion was 2.3 times the compacted LV wall in most regions. MRI did not reveal any areas of poor perfusion, thrombus, infiltration, or scar.

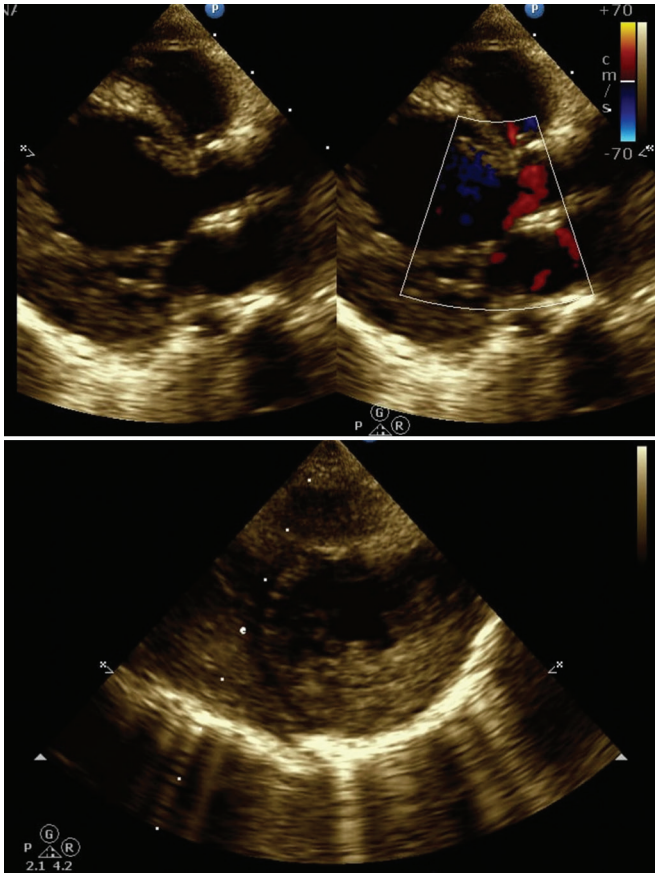

Figure 1: ECHO suggestive of Left ventricular non compaction

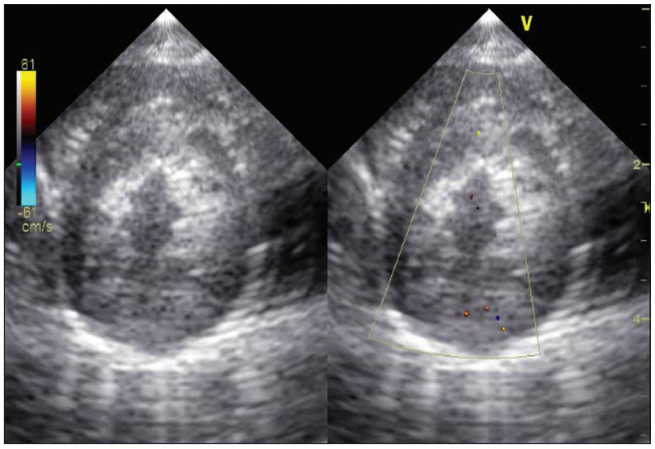

Figure 2: Prominent trabeculations and deep recesses in the left ventricle suggestive of Left ventricular non compaction

Investigations revealed elevated troponin T (443.3 pg/mL) and NTProBNP (>70,000 pg/mL). The correctable causes of myocarditis were worked up for. Serum electrolytes were within the normal limits. Serum carnitine, selenium, thiamine, copper, and chromium levels were found to be normal. Hypothyroidism was ruled out. Vitamin D levels were low-normal. An echocardiogram and electrocardiogram ruled out an anomalous origin of the left coronary artery from the pulmonary artery. Viral myocarditis qualitative panel was done, which revealed human herpesvirus-6 (HHV-6) being positive. A possibility of HHV-6 myocarditis decompensating an already failing morphologically noncompacted LV was considered. He was started on intravenous ganciclovir, which was given for 2 weeks, and then changed to oral valganciclovir, which was given for another 4 weeks. An ultrasound of the abdomen revealed the presence of a horseshoe kidney.

Considering the presence of cardiac LVNC, horseshoe kidney, and family history of neonatal death and pregnancy loss, clinical exome sequencing was done. It detected a homozygous missense variant in exon 6 of the AGK gene (chr7:g. 141611247A > G; Depth: ×81) that results in the amino acid substitution of glycine for aspartic acid at codon 117 (p.Asp117Gly; ENST00000649286.2) which is suggestive of Sengers syndrome, also known as cardiomyopathic mitochondrial

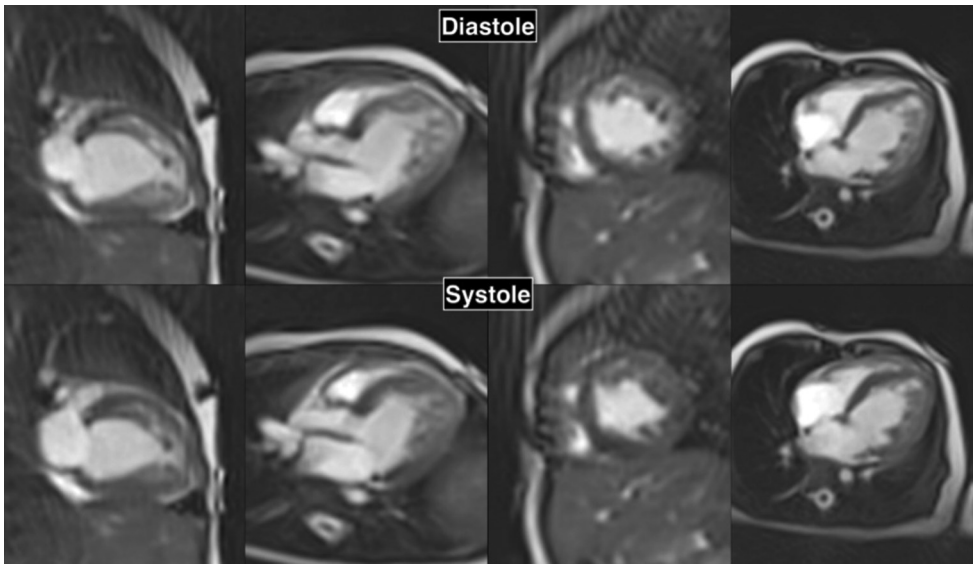

Figure 3: Cardiac MRI

DNA depletion syndrome. A screening echocardiogram for the father, mother, and three siblings revealed a structurally normal heart.

The baby was on regular follow-up and was on diuretics-furosemide (2 mg/kg/day) and spironolactone (3 mg/kg/day). Because of recurrent exacerbations of congestive cardiac failure requiring inotropic support, the baby was started on sacubitril-valsartan (initially 1.6 mg/kg/dose bd, gradually titrated up to 3.1 mg/kg/dose bd) and weekly levosimendan infusions (0.1 μg/kg/min). At 8 months of age, cardiac transplantation was successfully done. The donor was a 2-year-old brain-dead girl who had a traumatic brain injury. The ischemic time was 5 h 24 min. Posttransplantation, he required minimal inotropic support of milrinone 0.5 μg/kg/min for 72 h and was extubated on the postoperative day 3. He was closely monitored for signs of rejection by daily echocardiography and serial antibody titers posttransplant which were undetected. He received induction therapy with injection basiliximab 5 mg. injection methylprednisolone was started intra-operative and was gradually changed to oral prednisolone, which is being continued. He was started on mycophenolate mofetil and tacrolimus. Tacrolimus blood levels are being monitored once a month. The baby has been doing well posttransplantation. He is currently 9 months of age. He can sit without support, has pincer grasp, and speaks bi-syllables. He is developmentally normal and is thriving well.

DISCUSSION

LVNC occurs due to disruption of myocardial compaction during the 5th–8th weeks of intrauterine life. It results in the formation of an outer compacted epicardium, hyper trabeculated myocardium, and an inner noncompacted endocardium with deep intertrabecular recesses that connect to the ventricular chamber.[1] LVNC in children is rare, with an estimated incidence of 0.11 per 100,000 and the highest incidence during infancy.[2] LVNC can be classified into the following types: benign LVNC, LVNC with congenital heart disease, LVNC with arrhythmia, right ventricular noncompaction, dilated LVNC, hypertrophic LVNC, restrictive LVNC, and hypertrophic dilated LVNC.[3] Our index case had a hypertrophic type of LVNC. Rotterdam criteria can be used for the diagnosis of LVNC on echocardiography. According to previous studies, a noncompacted to the compacted ratio of >2 is associated with worse outcomes.[2] LVNC can be associated with facial dysmorphism: prominent forehead, low set ears, strabismus, micrognathia, and high arch palate.[4] It can be associated with neuromuscular diseases such as Beckers muscular dystrophy or Myotonic dystrophy type.[4] Renal associations with LVNC are rare. Few case reports have reported associated polycystic kidney disease and rarely horseshoe kidney like in our case.[1]

Senger's syndrome is autosomal recessive in inheritance. It is caused by homozygous or compound heterozygous mutations in the AGK gene. The onset of symptoms could be as early as the first week of life. Most babies have presented with congenital cataract during the neonatal period.[5] However, our index case was not found to have cataract. Hypertrophic cardiomyopathy has been described to be associated with Senger's syndrome in cases reported in the past.[5] *Senger's syndrome associated with LVNC has been reported only once in literature so far.*[6] Mental development is usually normal.[5] Hypotonia, skeletal myopathy, exercise intolerance, and lactic acidosis have been reported in previously diagnosed cases. This could be due to defective mitochondrial oxidative phosphorylation

in skeletal muscles.[7] The onset of these neurological symptoms could be in late infancy.[7] *Renal manifestations in the form of horseshoe kidney, like in our index baby, have not been reported previously with Senger's syndrome.*

Due to the heterogeneity and variety of phenotypical presentations of Senger's syndrome, management calls for a multidisciplinary team approach involving a pediatrician, cardiologist, and neurologist. Death usually occurs due to heart failure or arrhythmia secondary to hypertrophic cardiomyopathy. There could be severe lethal forms causing death during infancy to less severe forms where individuals have survived into the fourth decade of life.[5] Patients with Senger's syndrome who do not have severe neurological symptoms can be considered as the candidates for cardiac transplantation.[8]

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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