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Clinical research

Homozygous loss-of-function mutation in *ALMS1* causes the lethal disorder mitogenic cardiomyopathy in two siblings

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ABSTRACT

Background: Two siblings from consanguineous parents of Turkish descent presented with isolated dilated cardiomyopathy, leading to early death in infancy. The diagnosis of mitogenic cardiomyopathy was made histologically.
Methods and results: Linkage analysis combined with exome sequencing identified a homozygous deleterious mutation in the *ALMS1* gene as the cause of this phenotype.
Conclusions: Alström syndrome is characterized by a typically transient dilating cardiomyopathy in infancy, suggesting that mitogenic cardiomyopathy represents the extreme phenotype, resulting in demise before the other clinical symptoms become evident. This observation further illustrates the role of *ALMS1* and cell cycle regulation.

1. Introduction

Cardiomyopathies are a heterogenous group of primary myocardial disorders in which the heart muscle is structurally and functionally abnormal, in the absence of other causes including coronary artery disease, hypertension, valvular or congenital heart disease [Elliott et al., 2008].The annual incidence of pediatric cardiomyopathy is low, 1/100,000 children, with the highest incidence in the first year of life [Lipshultz et al., 2003; Nugent et al., 2003]. Four major types are distinguished, i.e., dilated, hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathy [Richardson et al., 1996]. Other unclassified types, which do not meet the criteria of one of the above, include endocardial fibroelastosis and ventricular non-compaction.

Mitogenic cardiomyopathy is an extremely rare type of dilated cardiomyopathy leading to death in early infancy. To date, only 8 cases have been reported in 5 families [Chang et al., 2010; Shenje et al., 2014; Zerbini et al., 1992]. Zerbini et al. described this condition in an 8-day-old infant, who died suddenly. Pathological examination revealed normal cardiac anatomy. The right ventricle was slightly dilated and endocardial fibroelastosis was present. Histology of the myocardium showed numerous mitoses and frequently enlarged myocardial nuclei with condensed chromatin forming a serrated thread running in the long axis, termed caterpillar nuclei. They observed an increased DNA ploidy of myocardial cells. The 1-month-old sibling of this patient also presented with heart failure and severe, dilated cardiomyopathy. An endomyocardial biopsy revealed endocardial fibroelastosis, but no increased mitoses. DNA ploidy analysis, on the other hand, showed an increased ploidy of the myocardial cells. This patient responded positively to intensive treatment; however, no long term follow-up data are available. In 2010 Chang et al. described 5 cases with an identical disorder, including 2 pairs of siblings. They all presented during early infancy with symptoms of cardiac failure and died soon thereafter. There were no associated extracardiac anomalies. Autopsy showed an enlarged, dilated heart, mostly ventricular, with endocardial fibroelastosis in all cases. Distinct findings were nuclear hypertrophy of the cardiomyocytes and a markedly increased mitotic activity with a proliferative index of 10–20% (normal < 1%), as well as caterpillar nuclei. In 1 of the 2 pairs of siblings there was parental consanguinity. This, and the observation of affected males and females strongly suggested autosomal recessive inheritance. More recently, in 2014, Shenje et al. described a proband and her sibling with neonatal heart failure requiring heart transplantation. Mitotic cardiomyocytes

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were observed. The parents were not consanguineous and cardiac evaluation of the parents were normal, leading to a hypothesis of e recessive disorder. Exome sequencing identified two heterozygous *ALMS1* mutations in the proband and her sibling, both of which result in frameshift and premature termination [Shenje et al., 2014]. We here report a novel family with an identical disorder. By a combination of linkage analysis and exome sequencing, we identify mutations in the *ALMS1* gene as the cause of this distinct type of cardiomyopathy.

2. Patient data

2.1. Patient 1

The index is the second child of healthy, consanguineous parents of Turkish descent. He was born at 41 weeks of gestation after an uneventful pregnancy. Weight was 3200 g (3rd–10th centile). He presented at age 20 days with excessive crying and feeding difficulties. On clinical examination, an inguinal hernia was noted. On reducing the hernia, cardio-circulatory arrest occurred. He was resuscitated and transferred to the university hospital. Despite continuous and prolonged resuscitation, the infant demised. Post-mortem echocardiography revealed a structurally normal heart.

The child was not dysmorphic. Weight was 4180 g (50th centile), length 56.5 cm (75th–90th centile) and head circumference 37.5 cm (50th centile). Pathological examination revealed signs of congestive cardiac failure (Fig. 1). The weight of the heart was 31.1 g (75th–5th centile) which is within normal range for age [Pryce et al., 2014]. There was cardiomegaly, caused by globular dilatation of the left ventricle [Guzeltas and Eroglu, 2012]. The endocardium was pale and thickened, indicative of endocardial fibroelastosis, which was confirmed histologically. Apart from this "dilated cardiomyopathy", the heart was structurally normal, including normal origin of the coronary arteries and normal aortic and mitral valves. There were no signs of noncompaction cardiomyopathy. Histology showed no signs of myocarditis, nor was there any evidence for a metabolic disorder. Myofibrillar disarray was absent. The most striking phenomenon was a marked mitotic activity in the cardiac myocytes (Fig. 2). The myocardium also showed myocyte nuclear hypertrophy with the frequent occurrence of binuclear and even trinuclear myocytes. Some myocytes contained caterpillar nuclei (Fig. 3), thus named due to condensed chromatin forming a serrated thread in the long axis. Immunohistochemical staining for Ki-67 (Mib1) showed a markedly increased proliferative activity of the myocardium. The proliferation index was 20% (normal value <1%).

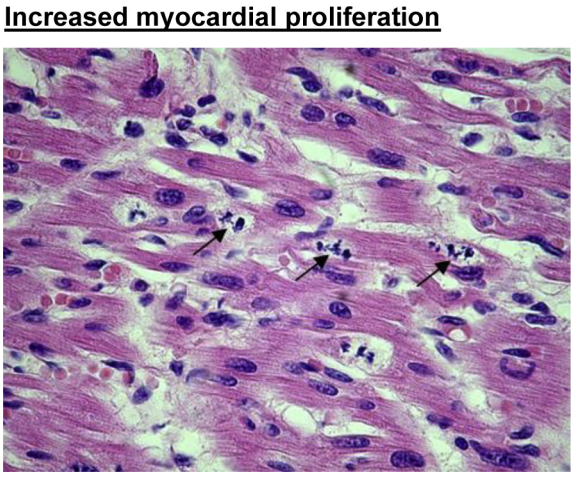

Fig. 2. This image shows markedly increased proliferative activity of the myocardium.

These findings led to the diagnosis of mitogenic cardiomyopathy.

2.2. Patient 2

Because of the high recurrence risk, the following pregnancy was closely followed. Repeated prenatal cardiac ultrasound investigations remained normal. A female infant was born at 41 weeks gestation, weighing 2840 g (3rd–10th centile). Early neonatal echocardiography was normal. However, at day 19, she was admitted with overt heart failure. Echocardiography (Fig. 4) revealed a dilated cardiomyopathy with left ventricular inner dimension at end-diastolic (LVIDd) of 25 mm (normal 12.9–19.1 mm) [Guzeltas and Eroglu, 2012]. There was endocardial fibroelastosis and severe mitral and tricuspid regurgitation. Cardiac function was poor, with a fractional shortening (FS) of 12% (normal ≥30%) and retrograde pulmonary hypertension. Despite respiratory and circulatory support, she progressively deteriorated and demised at the age of 22 days. No autopsy was performed.

Family history was otherwise negative; cardiac investigations of both parents and the 5 year old sibling were normal (Fig. 4).

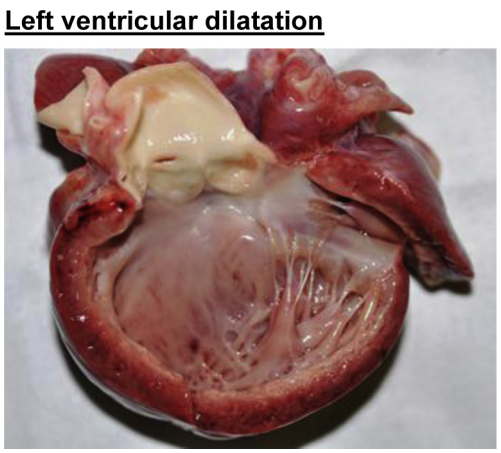

Fig. 1. This specimen (patient 1) of the left ventricle clearly shows left ventricular dilatation and endocardial fibroelastosis. The heart was structurally normal.

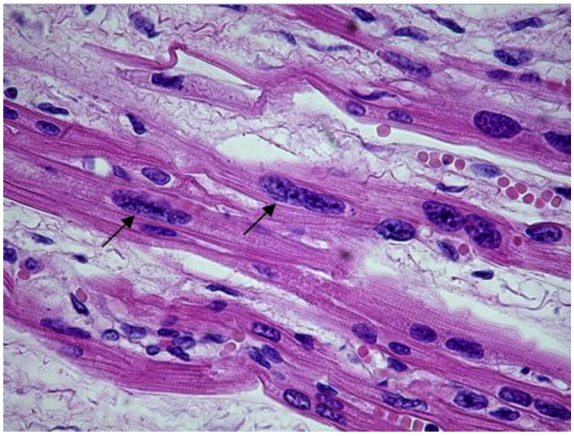

Fig. 3. Caterpillar nuclei with condensed chromatin.