Cardiac involvement in children with TMEM70 deficiency

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Background & Objectives

Mitochondrial diseases are a heterogeneous group of disorders caused by dysfunction of the respiratory chain. Tissues with high energy demand such as the brain, muscle and heart are affected most frequently. Mitochondrial ATP synthase, a key enzyme of mitochondrial energy provision, catalyzes synthesis of ATP. The first ATP synthase deficiency of nuclear genetic origin was described in a Slovak boy with fatal neonatal lactic acidosis and hypertrophic cardiomyopathy (HCM) by Prague group in 1999. In 2008, pathogenic mutation c.317-2A>G in the TMEM70 gene on chromosome 8 was identified. Since then a number of other homozygous or compound heterozygous mutations in TMEM70 have been recognized.

TMEM70 deficiency causes early onset of hypotonia, faltering growth, developmental delay and attacks of metabolic crises. The most common results of metabolic analyses are hyperlactataemia, hyperammonaemia and 3-methylglutatconic aciduria. Cardiovascular involvement is present in over 90% of patients and typically reveals HCM. Congenital heart disease, Wolff-Parkinson-White (WPW) syndrome and persistent pulmonary hypertension of the newborn (PPHN) with cardiac failure were also reported.

Objective of the study was to determine the significance and course of cardiovascular involvement in TMEM70 deficiency.

Methods

Retrospective observational study of cardiac findings and outcome in Slovak children with confirmed TMEM70 deficiency. All 16 children diagnosed between 2008 and 2015 were of Roma ethnicity and all were homozygous for the mutation c.317-2A>G in TMEM70 protein. HCM was defined by septal and/or left ventricular free wall hypertrophy (Z score >2). Left ventricular outflow tract obstruction was defined as anatomic narrowing with peak systolic gradient >20 mmHg measured by Doppler echocardiography. Right ventricular involvement was defined by a right ventricular free wall thickness > 4mm. Continuous data were presented as median (range).

Results

Sixteen patients with TMEM70 deficiency were identified. Median gestational age at birth was 37th week (31-40) and median birth weight was 2.0 kg (1.5-2.8). Neonatal onset of metabolic deterioration was documented in 75% of patients. Eleven (69%) neonates required intubation and 5 (31%) had severe PPHN with hemodynamic compromise. Echocardiography revealed two patients with mild valvar aortic stenosis and one neonate with coarctation of aorta. Eleven (69%) children were diagnosed with non-obstructive HCM (Figure 2A), and in 4 (25%) infants left ventricular outflow tract obstruction (LVOTO) was documented (Figure 2B,C). Neonatal mortality was 25% with two early postnatal deaths, two neonates died after initial stabilization. Two children died at age of 3 and 20 months, respectively (Figure 1). Symptomatic neonatal pulmonary hypertension was associated with mortality (p=0.017).

Cardiology follow-up was performed during median of 20.4 months (range 0.1-157.2). Echocardiography at birth, 3, 6, 12, 24, 36 and 60 months of age revealed median Z scores of interventricular septal thickness of +10.4, +6.9, +11.2, +5.7, +8.4, +7.9 and +5.0, respectively and median Z scores of left ventricular posterior wall of +5.0, +5.2, +8.4, +5.7, +5.4, +2.6 and +7.7, respectively (Figure 4). Of 4 patients with LVOTO, one neonate died and in 3 infants gradient subsided during follow-up (Figure 3). Mild dilation of left ventricle and mild mitral regurgitation without systolic dysfunction developed in 5 and 3 patients, respectively. Right ventricular hypertrophy (RVH) was diagnosed in 5 neonates, 3 of them died and in 2 patients RVH regressed.

One patient had WPW syndrome and in all but 2 infants ECG showed left ventricular hypertrophy.

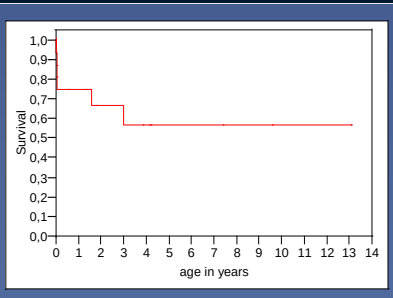

Figure 1 Kaplan-Meier survival curve for cohort of 16 patients with TMEM70 deficiency

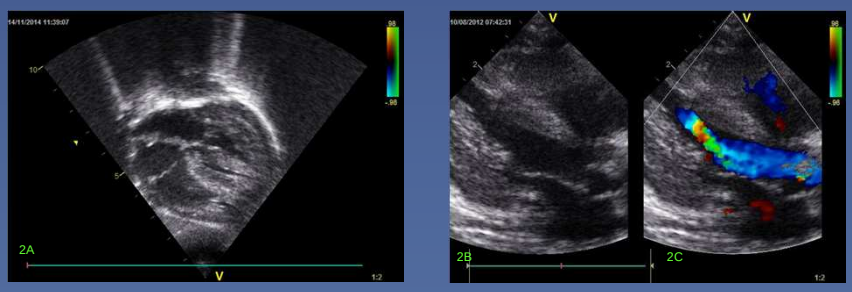

Figure 2 Septal and left ventricular free wall hypertrophy in patient with TMEM70 deficiency in subcostal (2A) and parasternal (2B) views. Color Doppler shows midventricular origin of outflow gradient in left ventricle during systole (2C)

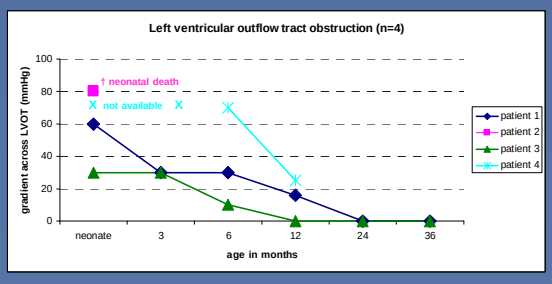

Figure 3 Trend in left ventricular outflow tract (LVOT) gradient in 4 patients with obstructive hypertrophic cardiomyopathy

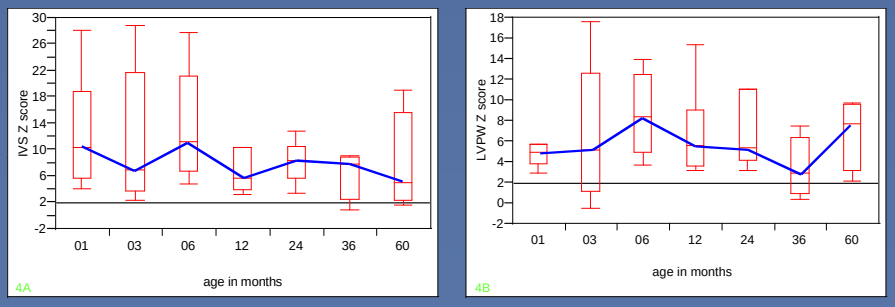

Figure 4 Medians, interquartile ranges (25th, 75th percentiles), minima and maxima of end-diastolic interventricular septal thickness (IVS, 4A) and left ventricular posterior wall (LVPW, 4B) Z scores during follow-up

Conclusions

Cardiac involvement of patients with **TMEM70 deficiency** is characterized by **infantile non-progressive non-obstructive or regressive obstructive hypertrophic cardiomyopathy.** High incidence of **persistent pulmonary hypertension of the newborn** with cardiac failure was documented and it was associated with mortality.