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The Effectiveness of the Ketogenic Diet for Leigh Syndrome with Cardiomiopathy

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1. Abstract

1.1. Background: Mitochondrial Diseases (MDs) are a heterogeneous group of disorders caused by inborn defects in the Mitochondrial Respiratory Chain (MRC) and malfunctions of cellular Oxidative Phosphorylation (OXPHOS). There is a broad clinical spectrum of MDs, organ-specific and multiorgan presentations with symptoms occurring at any age. High energy-requiring organs are most frequently occupied, including heart involvement. The most common cardiac manifestations of MDs are hypertrophic and dilated cardiomyopathy. At present, there is no specific treatment for MD. The Ketogenic Diet (KD) has been proposed as a treatment option for patients with MD with seizures or myopathy. It is suggested that KD itself may trigger cardiac complications after long-term therapy, but according to an animal model study.

1.2. Method: Here we present a case report on a male infant diagnosed with Leigh Syndrome (LS) (m.12706T>C in MTND5) with severe progressive Hypertrophic Cardiomyopathy (HCM).

1.3. Results: The ketogenic diet was introduced in a male infant at the age of 8 months with LS, suffering from progressive HCM and heart failure with no significant improvement on cardiological treatment, mitochondrial cocktail therapy, and mechanical ventilation. The follow-up 4 months after KD initiation has shown significant clinical improvement and normalization of echocardiographic parameters of the thickness of left and right ventricular muscle and the disappearance of left ventricular outflow tract obstruction. During 18 months of treatment, DK was well tolerated, with no significant adverse effects.

1.4. Conclusion: The use of a ketogenic diet in a patient with Leigh's syndrome and hypertrophic cardiomyopathy significantly improved cardiomyopathy.

2. Background

Mitochondrial Diseases (MDs) are clinically heterogeneous group of disorders that are caused by defects in the Mitochondrial Respiratory Chain (MRC) and distubance cellular Oxidative Phosphorylation (OXPHOS), due to a primary genetic defect. Consequences of mitochondrial dysfunction include: ATP deficiency, aberrant calcium metabolism, excessive Reactive Oxygen Species (ROS) production, apoptosis dysregulation, and nitric oxide deficiency, all of which contribute to the pathogenesis of mitochondrial diseases [1,2,3]. There is a wide clinical spectrum of mitochondrial disorders with both isolated organ involvement and more frequent multisystem disease recognized. The clinical symptoms can manifest at any age and in almost any organ, but those with high energy requirements, including the central nervous system, skeletal and cardiac muscles, kidneys, liver, and endocrine system are most frequently involved [3,4,5].

Leigh Syndrome (LS) is a progressive neurodegenerative disorder. The mutations in more than 90 genes have been identified in patients with LS, in mitochondrial and nuclear genome. About 30% of LS cases are believed to be of Mitochondrial DNA (mtDNA) or-

igin, whereas the remaining are thought to be related to mutations of the nuclear genome (nDNA) [6,7,8,9]. The most common clinical features of LS include developmental retardation, hypotonia, followed by respiratory dysfunction, seizures, poor feeding, and weakness. Neuroimaging is characteristic: focal and bilateral lesions in the brainstem, basal ganglia, and cerebellum [2,6,10]. Cardiac involvement in mitochondrial diseases is commonly observed (in 10–40% patients with LS) and can present as a major clinical symptom or part of a multisystem disorder [11,12]. The typical cardiac manifestations is hypertrophic and dilated cardiomyopathy (HCM and DCM), arrhythmias, left ventricular myocardial noncompaction, conduction disorders and heart failure [1,11,13]. Cardiomyopathy in mitochondrial diseases can worsen during a metabolic crisis and has been associated with poor survival [12,14,15].

Pediatric patients have more severe cardiac phenotype than elder patients with mitochondrial myopathy. [16]. Long-term prognosis depend on the age of presentation and aetiology of HCM. Five-year survival was much lower for patients with an inborn errors of metabolism (66%) compared with patients diagnosed with HCM due to RASopathy syndrome (90.5%), neuromuscular disorders (97%) or sarcomeric HCM (92.7%) [17].

Currently the therapeutical options for mitochondrial disorders are limited to the treatment of the complications and supportive care with vitamins (e.g. thiamine, riboflavin, folinic acid, and others), coenzyme Q, amino acids (arginine), lipoic acid, and other components [18,19,20]. Although these supplements are safe and well tolerated, their efficacy is limited. There is not enough evidence to support the use of any treatment in mitochondrial disease [21,22].

Ketogenic Diets (KDs) are high fat, moderate protein and low-carbohydrate diets, which favor mitochondrial respiration rather than glycolysis for energy metabolism, but the mechanism of its action is not fully understood. The evidence of KDs benefits in the management of mitochondrial diseases is growing, especially in the treatment of seizure disorders due to either nDNA or mtDNA defects [21,23-26]. KDs can also constitute a first line of treatment for mitochondrial myopathies due to improvement of mitochondrial activity resulting from increased mitochondrial biogenesis [27].

3. Methods

We present a retrospective analysis of the clinical course of LS, with severe progressive HCM, in male infant who received KD at 8 months of age in inpatient setting, under control of clinical dietitian.

Genetic background of the disease was established by Next-Generation Sequencing (NGS) of targeted genes panel, created by The Children's Memorial Health Institute's for the simultaneous sequencing of 1000 clinically relevant genes, including 249 items related to mitochondrial dysfunction and whole mtDNA. The NGS result was confirmed by Sanger sequencing.

Two-dimensional and M-mode echocardiography were performed at rest using standard methods. Echocardiographic measurements included Interventricular Septum (IVS) thickness and LV Posterior Wall (LVPW) thickness (mm, z-score), presence of LV Outflow Tract Obstruction (LVOTO) and Right Ventricular Anterior Wall (RVAW) thickness (mm, z-score). The IVS, LWPW, RVAW thickness in diastole were evaluated and indexed to the patient's Body Surface Area (BSA) as recommended in the literature [28,29]. Z-scores for the IVS, LVPW, RVAW thickness were calculated using the formula for z-scores, with the use of the calculator given on a website [Kampmann et al. Heart 2000 parameterz.com] and [parameter(z) org.: Z-scores of Cardiac Structures, Detroit Data 2008]. Echocardiographic evidence of LV hypertrophy was defined as a diastolic interventricular septum thickness or LV diastolic wall thickness z-score ≥2 (determined as more than two standard deviations from the mean value for the population corrected for BSA) [30].

4. Results

We present male infant, born at term by cesarean section with a birth weight of 2740 grams. From the 23rd week of pregnancy, fetal hypotrophy was observed and the thickening of the heart muscle of both ventricles on prenatal echocardiography. Echocardiography performed after birth, showing atrial septal defect and right ventricular hypertrabeculation. There was no symptoms of heart failure after birth.

His development was delayed: at 3 months of age the infant did not make eye contact, was hypotonic and had little physical activity. In the family history there was a death of maternal grandfather's brother during the neonatal period, and his sister at the age of 20 (not fully diagnosed cardiomyopathy - cor bovinum).

At the age of 3 months the boy was admitted to the hospital because of fever, seizures and dyspnea. The mother reported recurrent episodes of dyspnea, occurring usually after cry and anxiety. In laboratory tests only deep partially compensated metabolic acidosis (pH 7,25 mmHg, pCO2 15,8 mmHg, sBE -20,3 mmol/L, HCO3 10,2 mmol/L) was found, examination of the cerebrospinal fluid was normal and EEG was normal. Infant's condition improved quickly and he was discharged home. At the age of 4 months, he was admitted to PICU due to non-infectious respiratory failure. Laboratory tests showed lactic acidosis [lactate 50 - 117 mg/dL (normal range 4.5 – 19.8 mg/dL)], slightly elevated pyruvic acid concentration (1.8 – 2.1 mg/dL, normal value < 1.2 mg/dL), increased lactate, pyruvic and 2-ketoglutaric acids level in organic acids profile with use of Gas Chromatography-Mass Spectrometry (GCMS) and slightly elevated blood alanine level. Biotinidase activity and ammonia level were normal. Chest X-ray showed mildly increased Cardiothoracic Ratio (CTR) of 0.57. Echocardiography and Electrocardiogram (ECG) revealed left ventricular hypertrophy. NTproBNP level was elevated [3733 pg/mL (normal value < 135 pg/mL)] as well as troponin [3090 pg/mL (normal value < 10 pg/mL)] (Table 1). Brain MRI showed symmetrical bilater-

al hyperintense changes with restricted diffusion in T2-weighted images, located in brainstem, cerebral peduncles and middle cerebellar peduncles with lactate peak in spectroscopy. Treatment with beta-blocker, spironolactone and furosemide was initiated, NTproBNP and troponin levels diminished. Because of suspicion of mitochondrial disease, the treatment with arginine, thiamine, coenzyme Q and riboflavin (regarding the possibility of ACAD9 deficiency) was also implemented. At the age of 9 months molecular genetic tests revealed a known missense variant in MTND5 gene (m.12706T>C, p.Phe124Leu) with 69% heteroplasmy in blood was found. UniProt and Mitomap classifies this variant as pathogenic associated with Leigh syndrome [31,32,33].

At the age of 7 months the boy was admitted again to PICU due to cardiopulmonary failure with bradypnea, pleural and pericardial effusions. In echocardiography and ECG features of severe left and right ventricular hypertrophy was observed. NTproBNP value was over 35000 pg/mL. Due to bradypnea patient required long-term mechanical ventilation. Milrinone was added to the continued treatment with spironolactone, furosemide, beta-blocker, L-carnitine, arginine, coenzyme Q, glutathione and lipoic acid. Despite the treatment the degree of myocardial hypertrophy has gradually worsen (Table 1), with persisted symptoms of heart failure, such as low diuresis and mild oedemas. Because of lack of any other treatment options, when the patient turned 8months ketogenic diet was implemented. The diet was based on ready-to-eat preparations at 3:1 ratio. The boy was fed through a nasogastric tube with good tolerance. The patient was discharged from the hospital under Home Ventilation Program care. Because of seizures with abnormal electronencephalography result (burst suppression activity with progression to hypsarrhythmia), which appeared at the age of 12 months, patient required implementation of treatment with antiepileptic drugs (vigabatrin and levetiracetam), with good effect.

During follow-up for 18 months of ketogenic diet in a ratio of 3: 1 the improvement of the patient's general condition was observed. Control echocardiography after 4 months of continuous ketogenic diet revealed significant reduction of myocardial hypertrophy to normal values in relation to BSA, followed by NTproBNP decrease from over 35000 pg/mL to 125,3 pg/mL (normal value <320 pg/mL) and normalization of cardiothoracic ratio (Table 1) (Fig 1.) (Fig 2.). Symptoms of heart failure resolved and treatment with furosemide was reduced.

At the time of the last visit the patient was 27 months old, he has been treated with the ketogenic diet for 18 months. The diet parameters are satisfactory and the diet is well tolerated with no adverse effects. Additionally, an improvement in nutritional status was obtained. The patient requires gastric tube feeding and continues to be mechanically ventilated at home.

Table 1. Patient's cardiac parameters over time

Age (months)	4	7	8	12	19	27
BSA (m²)	0.3	0.33	0.35	0.38	0.44	0.56
Before ketogenic diet			On ketogenic diet			
NTproBNP (pg/ml) normal value <320	3733	>35000	N/A	N/A	454,9	125,3
CTR (X-ray) normal value <0.55	0.57	0.65	N/A	N/A	0.49	0,49
IVSd (mm) M-mode	5.6	8.3	9.7	5.9	6.0	5.5
IVSd Z-score Kampmann Detroit	+2.4	+6.3	+8.3	+2.9	+2.5	+1.2
	+1.6	+3.3	+4.0	+1.5	+1.4	+0.6
LVPWd (mm)M-mode	4.7	7.8	8.9	4.1	4.8	4.8
LVPWd Z-score Kampmann Detroit	+0.9	+5.7	+7.4	0	+0.9	0
	+1.9	+4.4	+5.0	+0.8	+1.3	+0.7
LVOT gradient (mmHg)	no gradient	51	70	no gradient	no gradient	no gradient
RVAWd (mm)	3.9	6.2	5.2	3.6	3.5	3.2
RVAWd Z-score	+2.2	+6.4	+4.5	+1.6	+1.4	+0.8
LV SF	32%	29%	45%	30%	33%	40%
LV EF	63%	61%	79%	60%	64%	75%

BSA – body surface area, LVEF – left ventricular ejection fraction, CTR - cardiothoracic ratio, IVSd - interventricular septal thickness, LVPWd - left ventricular posterior wall thickness, LVOT - left ventricular outflow, N/A – not applicable, NTproBNP - natriuretic peptide B, RVAWd - right ventricular anterior wall thickness, LV SF – left ventricular shortening fraction.

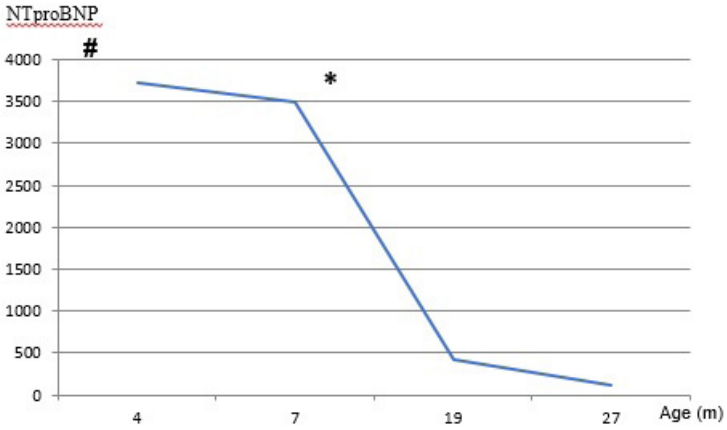

Figure 1: NTproBNP change over time; # start cardiac treatment, *start ketogenic diet

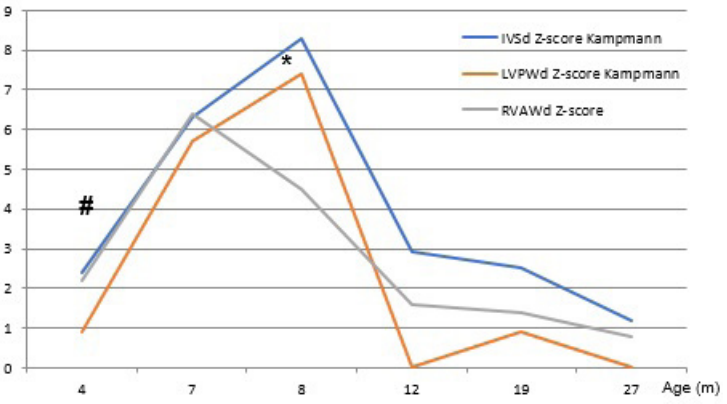

Figure 2: Echocardiographic findings over time; # start cardiac treatment, *start ketogenic diet

5. Discussion

Here we present a case report of mtDNA mutation (m.12706T>C) in patient with Leigh Encephalopathy and Hypertrophic Cardiomyopathy (HCM). The ND5 protein is one of the 46 subunits that constitute the Oxidative Phosphorylation (OXPHOS). Seven subunits are encoded by mtDNA, the other subunits by nuclear genes. Mutations in the MTND5 gene are responsible for Complex I Deficiency (CI) and this is the most common cause of OXPHOS disease. The most commonly reported clinical phenotypes due to mutations in this gene are Mitochondrial Encephalopathy Lactic Acidosis Stroke-Like Episodes (MELAS) and LS. HCM has also been reported in some patients with mutation in the MTND5 gene – similarly to the presented male infant [10,32-35].

The percentage of mtDNA-mutant cells in an individual, known as heteroplasmy, is a very important determinant in pathogenesis of MDs [18]. In the presented patient heteroplasmy (69%) was detected in the blood.

Mitochondrial cardiomyopathies can vary in severity from asymptomatic to severe manifestations, including heart failure, arrhythmias, and sudden cardiac death. Cardiac symptoms can worsen during metabolic decompensation episodes that are often caused by stressors, such as febrile illnesses or surgery, and can be accompanied by acute heart failure [1]. 36 Patients who develop cardiomyopathy in the course of MD have earlier symptoms and they have a poorer prognosis, as compared to children with MD but with no accompanying cardiomyopathy. The analysis of 113 children with mitochondrial disease with and without cardiomyopathy (most of them had HCM, and few had left ventricular dilatation and LV-noncompaction) showed a significant difference in 16-year survival (18% and 92%, respectively) [11,37].

In patients with MDs the standard medical therapies for heart failure are used, however both clinical improvement and progression is observed despite therapy [11]. The management of cardiac complications, including heart failure, bradyarrhythmias, and tachyarrhythmias, follows the same guidelines as those for the general population [36]. Current use of beta-adrenergic receptor antagonists or calcium channel blocker medications and angiotensin-converting enzyme inhibitors or angiotensin receptors blockers in patients with mitochondrial diseases and hypertrophic remodeling is empirical, based on results from animal studies and good results of such treatment in patients with sarcomeric HCM [38]. Cardiac transplantation, although controversial in metabolic disease with potential multisystem involvement, has been performed successfully in patients with MDs [39].

Currently, there are no effective or disease-modifying treatments available for the majority of patients with MDs. Note that in selected MDs, appropriate vitamins supplementation greatly improves prognosis, for example in biotin-thiamine-responsive basal ganglia disease (SLC19A3, SLC25A19 genes) early treatment with thiamine and biotin improves the prognosis, and in the MD-induced mutation in ACAD9 gene riboflavin prolongs survival [20,40,41].

There are reports about the effectiveness of ketogenic diet in patients with MDs, especially in, but not limited to, the treatment of seizures, therefore it has been proposed as a possible treatment option for MDs. Ketogenic diet, which consists of a low carbohydrate and high lipid content, helps the lipid utilization by the mitochondria. The diet was found to stimulate mitochondrial oxidative metabolism, reduce the amount of COX-negative fibers, prevent mitochondrial ultrastructural abnormalities in skeletal muscle and induce mitochondrial biogenesis[27,42,] improve mitochondrial function, decrease oxidative stress and contribute to reducing the glycolytic rate due to increase in lipid oxidation and mitochondrial respiration[43,44] KD may exert neuroprotective effects by diminishing ROS production through activation of mitochondrial uncoupling protein[45,46].

Ahola et al [47]. used a ketogenic diet - called the modified Atkins Diet (mAD) - in five patients with mitochondrial myopathy with either single or multiple mtDNA deletions. A 2-year follow-up revealed an improvement in muscle strength, with potential activation of muscle regeneration. Jarrett et al [21,48]. demonstrated that the KD confers protection to the mitochondrial genome

against oxidative insults, increasing the levels and stimulating de novo biosynthesis of mitochondrial glutathione and improving mitochondrial redox status. The improved cellular metabolism may explain the KD's efficacy in mitochondrial diseases. Geffroy et al [49]. showed that significantly lowering glucose concentration in cell culture carrying the m.3243A>G mutation (associated with a severe complex I deficiency) improved CI assembly in this cells. In addition, OXPHOS protein expression and mitochondrial DNA copy numbers were significantly increased in mutant cells exposed to glucose restriction. The mechanism of ketogenic diet in mitochondrial diseases is still not well understood. KD can probably promote mitochondrial breathing through complex II activity and FADH2 oxidation, and thus bypass inactive complex I [50].

Note that KD can lead to serious cardiac side effects, such as bradycardia, reduced QRS voltage, and prolonged QT intervals that significantly correlate with selenium deficiency, low serum bicarbonate, high levels of β-hydroxybutyrate and carnitine deficiency in patients treated with KD. Cardiomyopathy is a rare but serious and often fatal complication of KD [51,52]. Therefore, KD treatment requires careful supervision of dietician and physician [24].

Knowing the potential beneficial effects of KD, it was implemented in the presented patient. Significant changes in myocardial thickness were found after 4 months of treatment with a ketogenic diet. The thickness of the interventricular septum, left ventricular posterior wall, right ventricular anterior wall has decreased and normalized to the normal values. It is worth emphasizing that the features of left ventricular outflow tract obstruction in echocardiography also disappeared. NTproBNP value has decreased to normal and CTR has normalized. No such improvement was seen after the implementation of the "mitochondrial cocktail" (thiamine, coenzyme Q10, arginine, glutathione and alfa-lipoic acid) nor mechanical ventilation from 7 months of age. Our observations indicate that the use of a ketogenic diet significantly improved cardiomyopathy in the presented patient with Leigh's syndrome.

A similar therapeutic effect, reducing HCM in a 3-year-old girl with an abnormal variant in mtDNA (m.559A>G) was described by Deberles E. et al [53]. Krebs et al. presented an animal model study of missense mutation in the Mediator complex, which lead to lethal mitochondrial cardiomyopathy. In vivo studies on mutant mice showed, that mutants fed with ketogenic diet had a significantly increased lifespan and increased expression of cardiac OXPHOS genes [54].

6. Conclusion

The use of a ketogenic diet in a patient with Leigh's syndrome and hypertrophic cardiomyopathy significantly improved cardiomyopathy. Although there are studies suggesting the efficacy and safety of KD in patients with mitochondrial disease, more studies is needed to understand the pathophysiology of these diseases and to determine which patients are likely to benefit from therapy with KD.

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