Improvement of cardiomyopathy after ketogenic diet in a patient with Leigh syndrome caused by *MTND5* mutation

Dorota Wesół-Kucharska

Children's Memorial Health Institute: Instytut Pomnik -Centrum Zdrowia Dziecka

Milena Greczan

Children's Memorial Health Institute: Instytut Pomnik -Centrum Zdrowia Dziecka

Katarzyna Witulska

Children's Memorial Health Institute: Instytut Pomnik -Centrum Zdrowia Dziecka

Dorota Piekutowska-Abramczuk

Children's Memorial Health Institute: Instytut Pomnik -Centrum Zdrowia Dziecka

Elżbieta Ciara

Children's Memorial Health Institute: Instytut Pomnik -Centrum Zdrowia Dziecka

Paweł Kowalski

Children's Memorial Health Institute: Instytut Pomnik -Centrum Zdrowia Dziecka

Dariusz Rokicki (✉ d.rokicki@ipczd.pl)

Children's Memorial Health Institute <https://orcid.org/0000-0002-9736-2838>

Research

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Abstract

Background

Mitochondrial diseases (MDs) are heterogeneous group of disorders caused by inborn defects in the mitochondrial respiratory chain (MRC) and malfunctions of cellular oxidative phosphorylation (OXPHOS). MDs are caused by mutations both in mitochondrial and nuclear DNA. Leigh syndrome (LS) is a neurodegenerative MD with specific clinical and neuroradiological features. There is a broad clinical spectrum of MDs, including organ-specific and multiorgan presentations with symptoms occurring at any age. High energy requiring organs are most frequently involved and cardiac involvement is common. At present there is no specific treatment for MD. 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 cardiological complications after long-term therapy, but according to an animal model study, KD could be considered as a therapeutic option for some mitochondrial cardiomyopathies.

Method

Here we present a retrospective case report on a male infant diagnosed with LS (m.12706T > C in *MTND5*) with severe progressive hypertrophic cardiomyopathy, with significant cardiological improvement after KD implementation .

Results

The ketogenic diet was introduced in a male infant with clinical, biochemical and radiological features of Leigh syndrome, confirmed by next-generation sequencing (NGS) (known pathogenic variant in mtDNA), suffering from severe progressive hypertrophic cardiomyopathy and heart failure with no significant improvement on cardiological treatment, mitochondrial cocktail therapy and mechanical ventilation. The follow-up after KD initiation have shown significant clinical improvement in cardiovascular efficiency and echocardiographic parameters with no adverse effect observed so far.

Conclusion

Screening for cardiomyopathy is a standard of care (SoC) in the management of patients with mitochondrial disease. Although there are reports suggesting the efficacy and safety of KD in patients with mitochondrial disease, more studies are needed to understand the pathophysiology of mitochondrial diseases and to determine which patients are likely to benefit from this therapy.

Background

Mitochondrial diseases (MDs) are clinically heterogeneous group of disorders that are caused by defects in the mitochondrial respiratory chain (MRC) and dysfunctional 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 occur 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, affecting 1 in 40,000 live births. It is the most common childhood mitochondrial disorder and it has characteristic clinical and neuroradiologic features. The mutations in more than 100 genes have been identified in patients with LS, both in mitochondrial and nuclear genome. About 30% of LS cases are believed to be of mitochondrial DNA (mtDNA) origin, whereas the remaining are thought to be related to mutations of the nuclear genome (nDNA) (6)(7)(8)(9). The onset of disease is very early and followed by rapid progression, in most children before the age of 3 years. The most common clinical features of LS include elevated blood and/or cerebrospinal fluid (CSF) levels of lactate (72%), developmental retardation (57%), hypotonia (42%), followed by respiratory dysfunction (34%), epileptic seizures (33%), poor feeding (29%), and weakness (27%). Neuroradiological evidence is also characteristic, including focal and bilateral lesions in the brainstem, basal ganglia, cerebellum, and other regions of the brain (2)(6)(10).

The heart is highly dependent on oxidative metabolism, therefore 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 most common cardiac dysfunction is hypertrophic cardiomyopathy, followed by arrhythmia and conduction defects (1)(11)(13). Arrhythmias and conduction defects, pulmonary hypertension, pericardial effusion, dilated aortic root, and coronary heart disease can also be seen in mitochondrial diseases (1). Cardiomyopathy in mitochondrial diseases has been associated with poor survival (12)(14)(15). Pediatric patients have more severe cardiac phenotype than adult patients with mitochondrial myopathy (16).

At present, the therapeutical options for mitochondrial disorders are limited to the treatment of the complications and supportive care with cocktails of vitamins (e.g. thiamine, riboflavin, folinic acid, and others), coenzyme Q, amino acids (arginine), lipoic acid, and other components (17)(18)(19). 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 (20)(21).

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 (20)(22)(23)(24)(25). KDs can also constitute a first line of treatment for mitochondrial myopathies due to improvement of mitochondrial activity resulting from increased mitochondrial biogenesis (26).

Methods

We present a retrospective analysis of the clinical course of Leigh syndrome, with severe progressive cardiomyopathy, in male infant who received ketogenic diet 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.

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 heart ventricles muscle in the echocardiogram (ECHO) examination. For this reason, a heart ECHO was performed after birth, showing atrial septal defect (ASD) and right ventricular trabeculation. The boy showed no symptoms of circulatory failure in the neonatal period.

From the first month of life, the boy was rehabilitated due to abnormal muscle tone. 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). His siblings, teenage brother and sister, were healthy.

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 episodes of 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 meningitis was excluded, EEG was normal. Treatment with broad-spectrum antibiotics and acyclovir was implemented until neuroinfection was excluded. Infant's condition stabilized quickly and he was discharged home. One week later 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. ECHO and electrocardiogram (ECG) revealed left ventricle 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 bilateral 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 milrinone, bisoprolol, spironolactone and furosemide was initiated, the heart function stabilized and 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 confirmed the diagnosis of mitochondrial disorder. 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 (27, 28, 29).

At the age of 7 months the boy was admitted again to PICU due to cardiopulmonary failure with bradypnea, pleural and pericardial effusions. ECHO and ECG revealed severe hypertrophic cardiomyopathy, NTproBNP was over 35000 pg/mL. Due to bradypnea patient required long-term mechanical ventilation. Milrinone was added to the continued treatment with spironolactone, furosemide, propranolol, L-carnitine, arginine, coenzyme Q, glutathione and lipoic acid. Despite the treatment the cardiomyopathy 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 8 months 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 EEG result (burst suppression activity with progression to hypsarrhythmia), which appeared at the age of 12 months, patient required implementation of treatment with antiepileptic drugs, with good effect.

During follow-up hospitalizations every 3 months for 10 months the improvement of patient's general condition was observed. Control echocardiography after 4 months of continuous ketogenic diet revealed significant improvement, followed by NTproBNP decrease from over 35000 pg/mL to 1437 pg/mL (normal value < 320 pg/mL) and normalization of cardiothoracic ratio (Table 1) (Fig. 1.) (Fig. 2.) (Fig. 3.) (Fig. 4.). Cardiovascular efficiency improved and treatment with furosemide was discontinued.

For 10 months of ketogenic diet so far diet parameters are satisfactory and the diet is well tolerated with no adverse effects. Patient is fed by gastric tube and is gaining weight properly. According to his parents' opinion and objective neurological examination he is also more alert and more reactive.

Table 1
Patient's cardiac parameters over time

AGE (months)	4	7	7,5 and 8	12	16
	Before ketogenic diet			On ketogenic diet	
NTproBNP (pg/ml) normal value < 320	3733	> 35000	N/A	N/A	1437
CTR (X-ray) normal value < 0.55	0.57	0.65	N/A	N/A	0.49
IVSd (mm) M-mode	5.6	8.3	9.5–11	6.6	N/A
IVSd % N	105%	212 %	282%	117%	N/A
IVSd Z-score	N/A	+ 6.3	+ 10	+ 3.1	N/A
LVPWd	4.7	7.8	11	4.8	N/A
LVPWd % N	87%	190%	260%	87%	N/A
LVPWd Z-score	N/A	+ 5.7	+ 10	+ 1	N/A
LVOT gradient (mmHg)	Normal	51	70	Normal	N/A
RVAWd (mm)	3.9	6.2	4.2	N/A	N/A
RVAWd Z-score	N/A	+ 6.4	+ 2.7	N/A	N/A
SF	32	29	Normal	48%	N/A
EF	63%	61%	67%	82%	N/A
EF - ejection fraction, CTR - cardiothoracic ratio, IVSd - interventricular septal thickness, N - normal range, IVSd % N - interventricular septal thickness as % of normal range, LVPWd - left ventricular posterior wall thickness, LVPWd % N - left ventricular posterior wall thickness as % of normal range, LVOT - left ventricular outflow, N/A – not applicable, NTproBNP - natriuretic peptide B, RVAWd - right ventricular anterior wall thickness, SF - shortening fraction.					

Discussion

Here we present a case report of mtDNA mutation (m.12706T > C) in patient with Leigh encephalopathy and cardiomyopathy. 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. Hypertrophic cardiomyopathy has also been reported in some patients – similarly to the presented male infant (10)(28)(29)(30)(31).

The percentage of mtDNA-mutant cells in an individual, known as heteroplasmy, is a very important determinant in pathogenesis (17) of MDs. 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 manifestations 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)(32). Patients who develop cardiomyopathy in the course of MDs 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 showed a significant difference in 16-year survival (18% and 92%, respectively) (11)(33).

In patients with MDs the standard medical therapies for heart failure with systolic dysfunction 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 (32). Current use of beta-adrenergic receptor antagonists or calcium channel blocker medications and angiotensin-converting enzyme inhibitors or angiotensin receptors blockers in mitochondrial disease patients with hypertrophic remodeling is empirical, based on results from animal studies regarding other genetically determined abnormalities (predominantly sarcomeric hypertrophic cardiomyopathy) (34). Cardiac transplantation, although controversial in metabolic disease with potential multisystem involvement, has been performed successfully in patients with MDs (35).

There are currently 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 (19)(36)(37).

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 (26)(38), improve mitochondrial function, decrease oxidative stress and contribute to reducing the glycolytic rate due to increase in lipid oxidation and

mitochondrial respiration (39)(40). KD may exert neuroprotective effects by diminishing ROS production through activation of mitochondrial uncoupling protein (41)(42).

Ahola et al. 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 (43). Jarrett et al. 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 (20)(44). Geffroy et al. 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 (45). 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 (46).

Knowing the potential beneficial effects of KD, it was implemented in the presented patient. Significant improvement in cardiovascular efficiency has been observed [intraventricular septal thickness (IVSd) and right ventricular anterior wall thickness (RVAWd) has decreased, shortening fraction (SF) and ejection fraction (EF) has improved, LVOTO (left ventricular outflow obstruction) echocardiographic features have subsided, NTproBNP has markedly diminished and CTR has normalized] with significant improvement in diuresis, allowing furosemide discontinuation. 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. On this basis, we can assume, that the improvement is achieved by applying KD.

We have not found during literature search a description of patients with MD cardiomyopathy treating with KD. However, 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 (47).

Note that KD can lead to serious cardiac complications itself, such as bradycardia, reduced QRS tone, 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 (48)(49). Therefore, KD treatment requires careful supervision of dietician and physician (23).

Conclusion

Screening for cardiomyopathy is a standard of care in the management of individuals with known or suspected mitochondrial disease. Although there are studies suggesting the efficacy and safety of KD in patients with mitochondrial disease, more studies are needed to understand the pathophysiology of mitochondrial diseases and to determine which patients are likely to benefit from this therapy.

Abbreviations

EF - ejection fraction, IVSd - interventricular septal thickness, IVSd % N - interventricular septal thickness as % of normal range, LVPWd - left ventricular posterior wall thickness, LVPWd % N - left ventricular posterior wall thickness as % of normal range, N - normal range, SF - shortening fraction.

Declarations

Ethics approval and consent to participate: Not applicable

Manuscripts reporting studies involving human participants, human data or human tissue must:

include a statement on ethics approval and consent (even where the need for approval was waived)

include the name of the ethics committee that approved the study and the committee's reference number if appropriate

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Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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All financial and non-financial competing interests must be declared in this section.

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Authors' contributions

D. W. – K. – prepared conception of the manuscript, was a major contributor in writing the manuscript (analysis of literature, discussion)

M. G. – prepared conception of the manuscript, was a contributor in writing the manuscript (case study, discussion)

K. W. –

D.P.-A. – performed and interpreted genetic sequencing of the patient

E.C. – performed and interpreted genetic sequencing of the patient

P. K. – performed biochemical tests of the patient

D. R. - revised the work for important intellectual content, corresponding author

All authors read and approved the final manuscript.

The individual contributions of authors to the manuscript should be specified in this section.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

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Figures

Figure 1

Chest X-ray, age of 7 months. Heart silhouette enlargement, CTR 0,65. Features of pulmonary congestion.

Figure 2

Chest X-ray, age of 16 months. Heart silhouette in normal range, CTR 0,49. No pulmonary congestion features.

Figure 3

Echocardiographic findings over time, part I

Figure 4

Echocardiographic findings over time, part II