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Case Report

Improved lactate control with dichloroacetate in a case with severe neonatal lactic acidosis due to MTFMT mitochondrial translation disorder

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ABSTRACT

Mitochondrial methionyl-tRNA formyltransferase (*MTFMT*) is a nuclear-encoded gene that produces a protein involved in mitochondrial translation. MTFMT formylates a portion of Met-tRNA^{Met}, which allows for translation initiation of mitochondrial mRNA. Mutations in this gene have been shown to result in decreased mitochondrial translation with reduction function of the electron transport chain complexes I, III, IV, and V, thus affecting cellular energy production. Our patient presented with severe lactic acidosis in the neonatal period, and was found to be homozygous for the pathogenic mutation c.994C > T, p.(Arg332*). Her blood lactate levels normalized and her cardiomyopathy reversed after initiation of dichloroacetate (30 mg/kg/day). After two years of follow-up, she continues to show long-term lactate stability, continues to make developmental gains, and is in overall good general health. This is the first report using dichloroacetate in a patient with MTFMT deficiency, which may be a potential therapeutic option that warrants further study.

1. Introduction

Mitochondrial DNA (mtDNA) is transcribed and translated within the mitochondrial matrix [1]. Of the approximately 90 proteins involved in oxidative phosphorylation (OXPHOS), 13 are encoded by the mitochondrial genome, including key components of the electron transport chain complexes [2] . Nuclear-encoded genes rely on ribosomal translation in the cytoplasm to produce proteins that function in the mitochondria. Successful translation of mitochondrial proteins requires formylated methionine on transfer RNA (fMet-mt-tRNA^{Met}) binding to the ribosomal P-site for the initiation of protein translation, and a non-formylated form (Met-mt-tRNA^{Met}) for chain elongation [3–5]. In mammals, there is only a single Met-tRNA encoded by the mitochondrial genome, which means that post-translational modification controls the ratio of formylated and non-formylated species [3].

MTFMT (mitochondrial methionyl-tRNA formyltransferase; OMIM 611766) is a nuclear-encoded gene which codes for the 389 amino acid protein (HGNC) [6]. The function of MTFMT is to process the preliminary Met-mt-tRNA^{Met} into the formylated and non-formylated forms; the ratio of these two forms regulates initiation of translation and elongation of the polypeptide chain [7]. Altered mitochondrial protein production, through mutations in *MTFMT,* can lead to abnormal OXPHOS activity [7]. This can lead to a high NADH/NAD$^+$ ratio, inhibiting the pyruvate dehydrogenase complex (PDH), and increasing the conversion of pyruvate to lactate [8] [9].

Dichloroacetate (DCA) is a structural analog of pyruvate and functions in lowering lactate levels. Pyruvate is primarily metabolized by pyruvate dehydrogenase (PDH), a multimeric enzyme that is regulated by phosphorylation. PDH activity is regulated by pyruvate dehydrogenase kinase (PDK), which inhibits PDH by phosphorylating it in response to elevated NADH, ATP, and acetyl-CoA levels [10] . Dichloroacetate indirectly increases PDH activity by inhibiting PDK (Fig. 1) [11] . With PDH in its unphosphorylated active form, it is able to increase pyruvate oxidation to acetyl-CoA, in turn reducing pyruvate levels. Decreased activity of PDH, from decreased NAD$^+$ levels due to impaired respiratory chain activity from the *MTFMT* mutations, would

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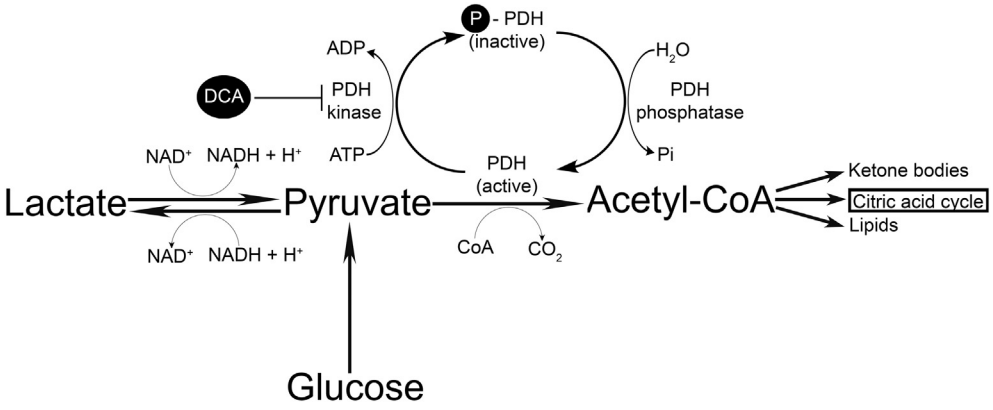

Fig. 1. DCA mechanism of action. PDH oxidizes pyruvate to acetyl co-A. PDH is regulated by PDH kinase, which phosphorylates and inactivates PDH. DCA inhibits PDH kinase, thus reducing the phosphorylation of PDH into its inactive form. DCA increases the active form of PDH, which subsequently increases the conversion of pyruvate to acetyl co-A and decreases the production of lactate.

be expected to promote conversion of pyruvate to lactic acid instead of promoting conversion of pyruvate to acetyl-CoA [12] . In fact, addition of DCA has been shown to increased NAD^+ levels, thereby lowering the NADH/NAD^+ ratio, in cells and using hyperpolarized ^{13}C-magnetic resonance spectroscopy shown to reduce conversion of pyruvate-to-lactate [9] [13]. The end result is that DCA increases PDH activity, reducing the conversion of pyruvate to lactate.

While congenital lactic acidosis has many potential causes stemming from a multitude of inborn errors of metabolism, *MTFMT* mutations appear to result in lactic acidosis in the majority of patients. To date there have been 38 patients described with *MTFMT* mutations [7,14–16] . Our case describes a 39th patient who is the first to receive DCA as part of a treatment plan, and who remains in good health 2 years after a severe presentation as a newborn.

2. Case Report.

1.1. Clinical summary

An infant female was delivered at term to parents of Hutterite ancestry. She became tachypneic and progressed rapidly to respiratory distress requiring intubation. Her blood lactate level rapidly increased to > 19.9 mmol/L (above the quantifiable limit; normal reference range 0.5–2.2 mmol/L; Fig. 2) and her blood pH decreased to 6.99 (normal reference range 7.35–7.45); she was diagnosed with a primary congenital lactic acidosis. She was initially treated with intravenous saline (to improve circulating volume), high rate ventilation, then high rate oscillatory ventilation, and a sodium bicarbonate infusion but with minimal effect. We then started treatment sequentially with thiamine, biotin, and then DCA. The use of DCA resulted in improved lactate levels, which subsequently increased again when the DCA was briefly discontinued after the patient self-extubated (the DCA was temporarily held since it can only be given enterally). She was re-intubated and DCA administration was resumed. Her lactate levels normalized to 1.0 mmol/L six weeks after birth.

The long-term normalization of lactate levels was achieved with a daily dose of DCA (30 mg/kg/day) in either 2 or 3 divided doses (Fig. 3). As our patient gained weight, her dose of DCA was adjusted to prevent lactate levels rising. Fig. 3 shows fluctuations in lactate levels related to changes in DCA dosing.

Initial investigations identified hypertrophic cardiomyopathy and grade 3 intraventricular hemorrhage. Magnetic resonance spectroscopy identified a lactate peak in the basal ganglia but no other features suggestive of mitochondrial disease. An echocardiogram on the first day of life showed a structurally normal heart for age, with normal biventricular systolic function, a patent foramen ovale, a large patent ductus arteriosus shunting bidirectionally, and evidence of elevated pulmonary pressures (as expected for age). However, by 8 days of age she had developed moderate hypertrophy of the interventricular septum and mild hypertrophy of the left ventricular wall. Over the next two months, there was progressive hypertrophy of the left ventricle (LV) with the septum affected to a greater degree than the posterior wall. However, after 75 days of life there was substantial and relatively sustained normalization of LV wall thicknesses (Figs. 4 and 5). The ventricular function of both the left and right ventricles was normal throughout.

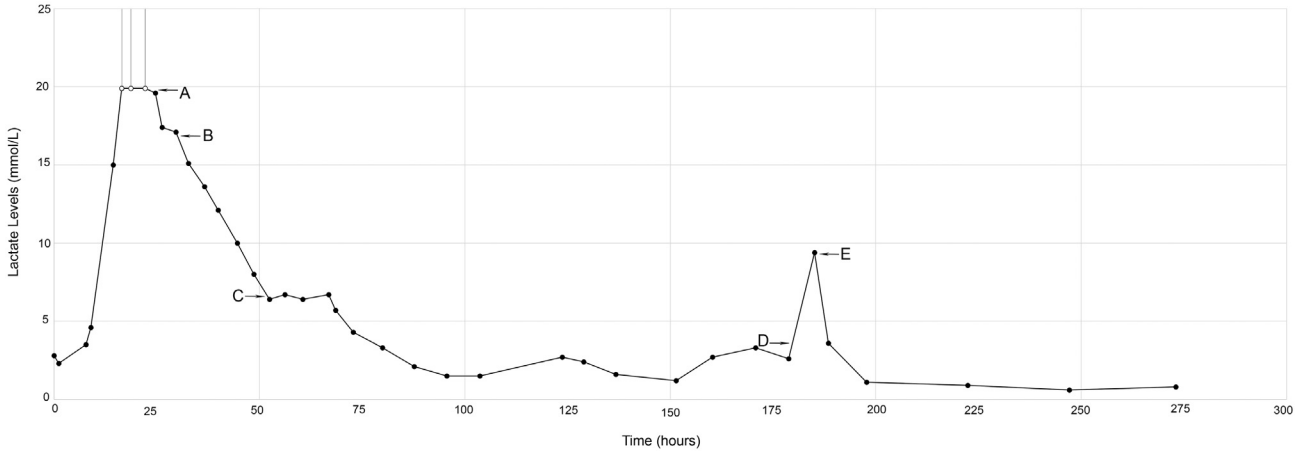

Fig. 2. Blood gas arterial lactate levels for 13 days following birth. Our patient's lactate levels began to rise rapidly after birth, to > 19.9 mmol/L by x hours of age. Multiple strategies were implemented to stabilize our patient but DCA was the only successful intervention. (A) Our patient was started on biotin (5 mg/day) and IV thiamine (100 mg/kg/day). (B) First administration of oral DCA. (C) Patient was switched from an oscillator to conventional ventilation which required an adjustment period. (D) Patient self-extubated, and DCA was withheld resulting in a transient increase in lactate levels. (E) Patient was re-intubated and DCA administration resumed, with improvement in lactate levels.

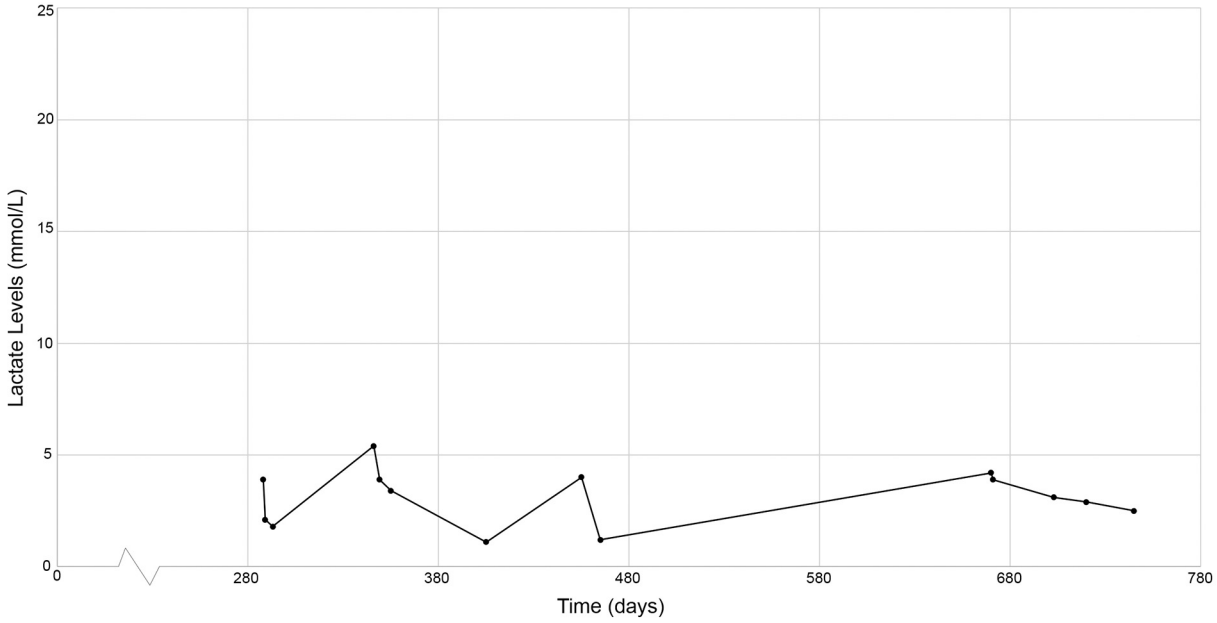

Fig. 3. Patient's long-term lactate levels from 288 days of life until 744 days of life (after initial recovery and discharge). Her lactate levels fluctuated between 1.1 and 5.4 mmol/L. We noted higher lactate levels commensurate with increases in weight, which decreased rapidly after increasing total DCA given with a target DCA dose of 30 mg/kg/day.

Incidental note was made of a bicuspid aortic valve without significant stenosis or regurgitation .

The patient developed tonic-clonic seizures at 15 months of age and was treated with levetiracetam which has helped reduce the frequency of seizures. Developmentally, the patient has some ongoing delays, but is gaining skills and has not shown any developmental regression. At two years of age, she has absence seizures approximately once per week, has generalized hypotonia, can sit without support in a tripod position for approximately 20 s, and can roll from back-to-front and front-to-back but cannot crawl. She babbles and is socially interactive, appears to be in no distress, and has a pleasant disposition. Feeding is done exclusively through a gastrostomy tube, inserted at 9 months of age due to a risk of aspiration, although she does have non-nutritive oral skills.

1.2. Genetic and mitochondrial respiratory chain enzyme testing

Due to the suspected inborn error of metabolism, our patient underwent rapid exome sequencing through our MITO-FIND (mitochondrial functional and integrative next generation diagnostics) research study (University of Calgary Conjoint Research Ethics Board Ethics ID# REB13–0753), and simultaneous clinical testing through Blueprint Genetics (Espoo, Finland), which both identified a homozygous nonsense mutation in *MTFMT,* c.994C > T, p.(Arg332*) that had previously been classified as pathogenic. Both parents were found to be heterozygous carriers.

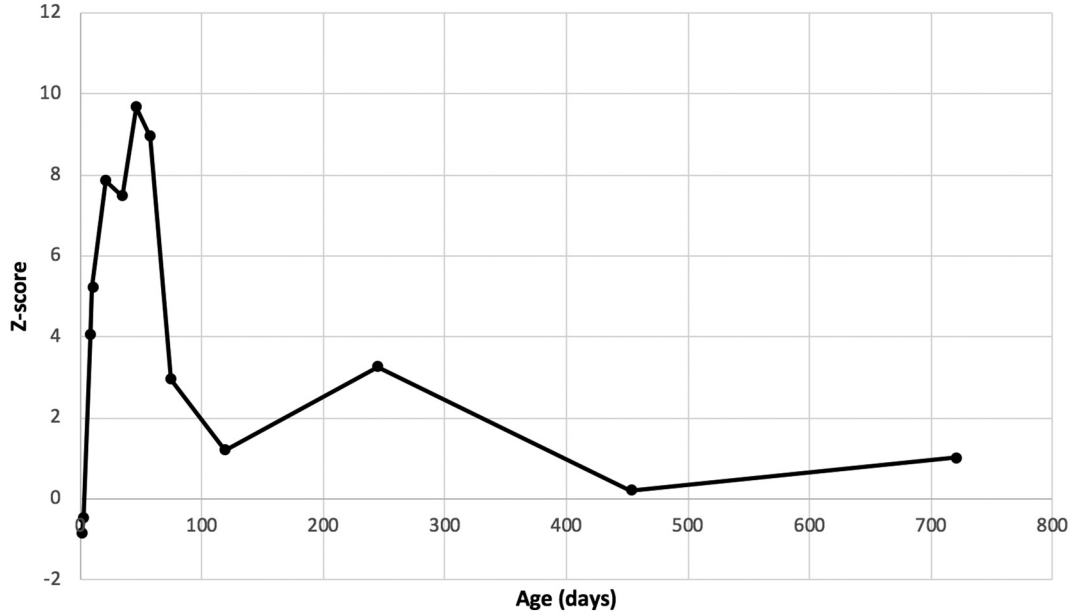

Fig. 4. Changes in interventricular septal dimensions over time. The thickness of the septum in diastole is plotted based on *Z*-scores (normal < +2). There was an initial rapid increase in septal thickness that essentially normalized by 75 days of life.

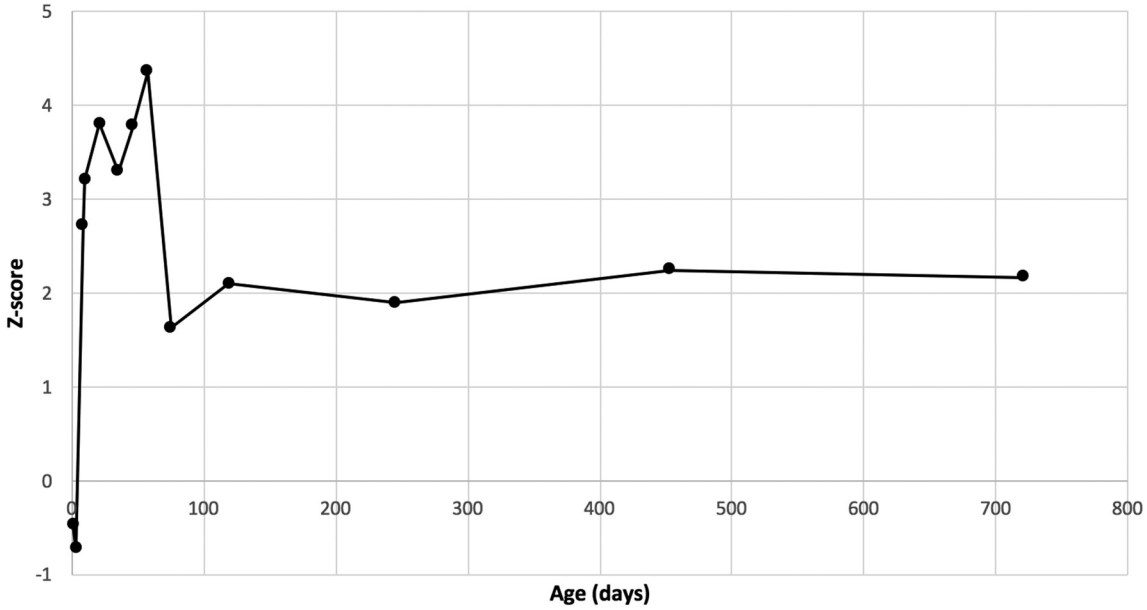

Fig. 5. Changes in left ventricular posterior wall dimensions over time. The thickness of the posterior wall in diastole is plotted based on Z-scores (normal < +2). There was an initial rapid increase in wall thickness that normalized by 75 days of life.

The MITO-FIND testing sample was collected from a buccal swab using an ORAcollect DNA oral sponge kit (DNA Genotek, Ottawa, Canada) and sequencing was performed using targeted library preparation with an Ion AmpliSeq™ Exome RDY Kit (Waltham, Massachusetts). The Ion Chef System was utilized for automated chip loading (540 chip) and templating, followed by whole exome sequencing on the Ion S5™ XL System (GeneStudio S5). Torrent Suite 5.8.0 was used for the secondary analysis optimized for Ion data. It performed raw data analysis, alignments using Torrent Mapping Alignment Program (TMAP), and default map4 algorithm, which implements Burrows-Wheeler Aligner [1–5]. Torrent Variant Caller (TVC) was used to generate a variant call file (vcf). The assembly used was GRCh37/hg19. The vcf was imported into VarSeq 2.1.1 (Golden Helix ®) software which was utilized for tertiary analysis. The filtering workflow excluded data where the quality assurance measures, such as read depth and genotype quality, were lower than 10 and 20, respectively. Additionally, those variants with a minor allele frequency > 1% (NHLBI, ExAC and gnomAD databases) were removed. Effect, dbNSFP (database for nonsynonymous SNPs functional predictions), ClinVar, and *in silico* predictors were utilized in the filtering process to assist in the identification of the variant that was potentially the cause of the phenotype observed in the patient. HPO terms were implemented to reduce the number of resultant variants.

Our bioinformatics analysis identified a homozygous, stop-gain mutation, (NM_139242.3:c.994C > T; p.Arg332Ter), in a conserved (PhyloP & GERP++), deleterious (CADD) nucleotide in the gene *MTFMT*. This variant is present in ClinVar (ID 39830) with an interpretation of pathogenic. Computational analysis showed that *MTFMT* has a low rate of benign loss of function (LoF) variants, as indicated by a high LoF variants' *Z*-Score of +1.64. The variant is predicted to cause loss of normal protein function through protein truncation. With a read depth of 114× and a Phred Quality Score of 40, it is unlikely that this is a false read. This variant occurred in the 9th exon. and is predicted to cause a premature stop codon at amino acid residue 332 of 389 residues. A loss of normal protein function likely occurs through truncation, as the variant occurred in the final exon, and it is therefore likely that the affected gene transcript escapes nonsense mediated mRNA decay; the affected C-terminal region is highly conserved. Based on the computational evidence and the literature, we concluded that the variant was biologically impactful, and hence we reported it as pathogenic.

The patient was deemed too sick to undergo a muscle biopsy. Therefore, as part of our MITO-FIND research study, we used a non-invasive method for mitochondrial DNA collection, and obtained an aliquot of the DNA from the same oral sponge sample listed above for nuclear DNA analysis. We used the Oxford Nanopore Rapid Barcoding Sequencing Kit (SQK-RBK004) according to the manufacturers protocol (Oxford Science Park, United Kingdom) to sequence the mitochondrial genome for this patient. Briefly, genomic DNA (gDNA) extracted from a buccal swab was tagmented, transposon-mediated cleaving and tagging of the double-stranded DNA, to an average length of 5 Kbp. Following this reaction, adapters were ligated, then sample loaded onto an R9 flow cell (FLO-MIN106) on a MinION device (Oxford Nanopore, Oxford Science Park, United Kingdom), and then sequenced until the entire 16, 569 bp mitochondrial genome was obtained at an average read depth of 100× or more. MinION device control, data acquisition, and real-time base-calling were carried out by the MinKNOW software. We have used this method to detect mtDNA deletions and point mutations in our laboratory previously. No pathogenic variants were found in mtDNA.

Mitochondrial respiratory chain enzyme activities and citrate synthase were measured spectrophotometrically in post 600 ×g supernatants from fibroblasts. The ratio of enzyme activity to citrate synthase activity was calculated, and also expressed as *Z*-scores of the normal distribution established in control samples as previously described [17] [18]. Solubilized inner mitochondrial membrane fractions isolated by differential centrifugation from patient fibroblasts were separated by blue native polyacrylamide gel electrophoresis (BN-PAGE) and evaluated by in-gel activity staining assays as described [17] [18]. The respiratory chain enzyme assays showed decreased activity ratios of complexes I and IV over citrate synthase (Table 1). On blue native PAGE analysis with in-gel activity staining, there was decreased activities of complexes I and IV, and added bands of F1 subunit of complex V (Fig. 6). This pattern is consistent with a disorder of mitochondrial translation affecting mtDNA encoded complexes, and is consistent with the effect from a pathogenic *MTFMT* mutation.

2. Discussion

The first human cases with MTFMT deficiency presented with Leigh syndrome, complex I and IV deficiencies [7], and more than 30 cases

Table 1
Respiratory chain enzyme activities. The activities in fibroblasts of each respiratory chain enzyme complex and of the combined complex II-III are shown expressed as the ratio over the activity of citrate synthase. The patient values are followed by the range observed in normal controls, and the values is also expressed as standard deviations (*Z*-score) of the log transformed values of controls which are normally distributed. Activities that are reduced are highlighted in bold.

Activity	Patient	Controls	Z-score in SD
Complex I	**117**	145–396	**−2.2**
Complex II	549	297–863	−0.1
Complex III	57	19–65	+1.3
Complex II-III	377	131–376	+1.4
Complex IV	**5**	6–23	**−2.2**

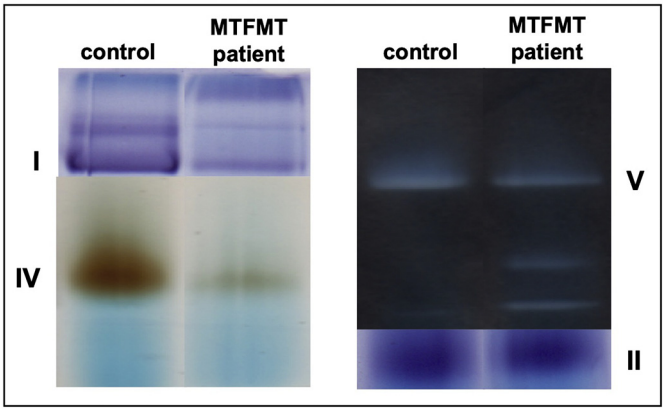

Fig. 6. Respiratory chain enzyme complexes evaluated by blue native polyacrylamide (BN-PAGE) with in-gel activity staining. Blue native PAGE with in-gel activity staining revealed the presence of subunits of lower molecular weight for complex V in fibroblasts, and decreased staining intensity for complexes I and IV.

have now been described [7,19,14,15,16,20–24]. Twenty six of 28 patients who had muscle biopsies performed had respiratory chain deficiencies with complex I activity being the most affected but complex III, IV and V are also known to be affected. Of the 34 patients with available data at last follow-up, nine were deceased. Lactic acidosis, developmental delay and regression were present in 27 patients, six had seizures, 10 had feeding problems, and 17 had cardiac abnormalities [14]. Cardiac issues included aortic valve regurgitation, ventricular septal defect requiring surgical closure, mild thickening of the ventricular septum, mild ventricular hypertrophy, and/or left ventricular noncompaction cardiomyopathy. Previously, co-enzyme Q10, riboflavin, carnitine, and/or a fat-enriched diet were used as a treatment strategy on 11 patients, but this only resulted in minimal success [15]. None of these treatments were used in our patient because our focus in the acute setting was the immediate reduction of elevated blood lactate and acidosis.

In the cases described in the literature, eight had homozygous mutations, [14] and 30 cases demonstrated compound heterozygous mutations. The c.994C > T, p.(Arg332*) mutation present in our patient was found 11 other times in the compound heterozygous form and once in the homozygous form. This patient had similarities with our case, including developmental delay, lactic acidosis, complex I and IV deficiencies, hypotonia, and dysmorphic features, but passed away at 22 months of age. Cardiomyopathy was not mentioned in regards to this patient.

In our case, treatment with DCA was an effective strategy resulting in the reduction of high lactate levels and correction of the secondary metabolic acidosis. With respect to the use of thiamine and biotin, there is no specific reason to suspect their efficacy in treating MTFMT deficiency. Thiamine and biotin were used in our patient because our routine protocol with primary congenital lactic acidosis includes starting with thiamine to treat a number of possible inborn errors of metabolism [25,26]. Biotin was started since newborn screening had not been performed at day 1 of life, and the response to thiamine was minimal. We add biotin as part of our protocol with congenital lactic acidosis considering the possibility of holocarboxylase/multiple carboxylase synthetase deficiency [27]. Biotinidase testing was subsequently normal and the exome analysis did not identify another defect in a biotin-containing pathway. Both thiamine and biotin have been continued in our patient because she is healthy and a clinical decision was made not to alter the treatment cocktail; although, it is possible that the thiamine and biotin are not necessary.

There were attempts to wean the DCA once the diagnosis of MTFMT deficiency was made, as there was no precedence for using DCA. However, each attempt to wean the DCA resulted in an increase in our patient's lactate levels, with normalization linked to DCA readministration. As she has gained weight, we noted from trial and error that the optimal dose of DCA appeared to be 30 mg/kg/day, below which we see a rise in blood lactate levels.

We also reviewed additional data in the MITO-FIND exome analysis which revealed two variants in the *GSTZ1* (glutathione S-transferase Z1) gene with a *GSTZ1A* genotype (c.94G > A, c.245 T > C), with pharmacogenomic analysis indicating slow metabolizer status of dichloroacetate [11]. However, we have not performed specific pharmacologic studies in our patient to validate this. The *GSTZ1A* genotype was not reported in the data from the clinical laboratory.

With the use of DCA, our patient's left ventricular hypertrophy also showed significant improvement. A key feature in some patients with mitochondrial disease is hypertrophic cardiomyopathy [28]. High levels of lactate specifically reduces cardiac contractility and exacerbates hyporesponsiveness to vasopressors. Further, lactic acidosis changes the calcium transient of action potentials, which has clinical consequences for cardiac arrhythmias. Low blood pH is also detrimental for hemodynamics [29]. High lactate levels are strongly correlated with mortality, and therefore, our patient's case was an emergency situation. The immediate goal was to reduce her lactate levels quickly, to avoid exacerbating cardiomyopathic and hemodynamic dysfunction, which could ultimately result in death. It is not clear how the DCA impacted the hypertrophic cardiomyopathy in this patient, but the use of DCA was associated with favourable left ventricular remodeling over several months as the patient remained clinically stable. This pattern is similar to another case with a mutation in *FBXL4* that we described previously, [30] suggesting that DCA favorably impacts the cardiomyopathy caused by some mitochondrial defects.

3. Conclusions

We conclude that DCA may have some utility in helping control the lactic acidosis in patients with *MTFMT* deficiency. Since this is a case report and not a study using controls, further evaluation will be necessary before general recommendations on the use of DCA can be made.

Informed consent was obtained for enrolment by the patient's guardians. This work is part of the MITO-FIND project sponsored by MitoCanada, and consent was obtained following standard procedures through the University of Calgary Conjoint Research Ethics Board protocol REB 13–0753. All patients gave written informed consent in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Author contributions

Aneal: project design, design of laboratory testing, organization, manuscript writing and editing, principal investigator.

Jenni: Writing – original draft; Writing – review & editing.

Dustin: design of mitochondrial sequencing and interpretation, reviewing and editing manuscript.

Marina: design of exome sequencing and interpretation, reviewing and editing manuscript.

Steven: design and review of cardiac data, reviewing and editing manuscript.

Marisa Friederich and Johan Van Hove: mitochondrial functional assays, review and editing of manuscript.

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Declaration of Competing Interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Aneal Khan currently serves on the scientific advisory board for MitoCanada.

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