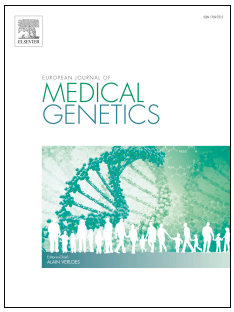

Cardiovascular involvement in later-onset malonyl-CoA decarboxylase deficiency: Case studies and literature review

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Title: Cardiovascular involvement in later-onset malonyl-CoA decarboxylase deficiency: case studies and literature review

Short Title: Later-onset MLYCDD

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Abstract:

Background: Malonyl-CoA decarboxylase deficiency (MLYCDD) is an ultra-rare inherited metabolic disorder, characterized by multi-organ involvement manifesting during the first few months of life. Our aim was to describe the clinical, biochemical, and genetic characteristics of patients with later-onset malonyl-CoA decarboxylase deficiency.

Methods Clinical and biochemical characteristics of two patients aged 48 and 29 years with a confirmed molecular diagnosis of MLYCDD were examined. A systematic review of published studies describing the characteristics of cardiovascular involvement of patients with MLYCDD was performed.

Results: Two patients diagnosed with MLYCDD during adulthood were identified. The first presented with hypertrophic cardiomyopathy and ventricular pre-excitation and the second with dilated cardiomyopathy (DCM) and mild-to-moderate left ventricular (LV) systolic dysfunction. No other clinical manifestation typical of MLYCDD was observed. Both patients showed slight increase in malonylcarnitine in their plasma acylcarnitine profile, and a reduction in malonyl-CoA decarboxylase activity. During follow-up, no deterioration of LV systolic function was observed. The systematic review identified 33 individuals with a genetic diagnosis of MLYCDD (median age 6 months [IQR 1-12], 22 males [67%]). Cardiovascular involvement was observed in 64% of cases, with DCM the most common phenotype. A modified diet combined with levocarnitine supplementation resulted in the improvement of LV systolic function in most cases. After a median follow-up of 8 months, 3 patients died (two heart failure-related and one arrhythmic death).

Conclusions: For the first time this study describes a later-onset phenotype of MLYCDD patients, characterized by single-organ involvement, mildly reduced enzyme activity, and a benign clinical course.

Keywords: malonyl-CoA decarboxylase deficiency; dilated cardiomyopathy; hypertrophic cardiomyopathy; prognosis.

1. Introduction

Malonyl-CoA decarboxylase deficiency (MLYCDD, OMIM #248360) is a very rare inherited metabolic disorder caused by bi-allelic variants in *MLYCD,* which encodes for the malonyl-CoA decarboxylase enzyme (EC 4.1.1.9)[1]. Malonyl-CoA plays an important role in regulating mitochondrial long-chain fatty acid beta-oxidation in cardiac and skeletal muscle[2]. Accumulation of malonyl-CoA caused by MLYCDD inhibits carnitine palmitoyltransferase 1, which is the rate-limiting enzyme in fatty acid beta-oxidation in mitochondria and peroxisomes[2] **(Figure 1)**.

MLYCDD is characterized by multi-organ involvement, presenting with neurological and gastrointestinal manifestations, metabolic acidosis, hypoglycaemia, failure to thrive and cardiomyopathy[3,4]. The diagnosis is established by identifying increased levels of malonic acid in urine and malonylcarnitine in blood and confirmed by the presence of bi-allelic disease-causing variants in *MLYCD*[1,3].

Cardiac involvement usually manifesting with a dilated cardiomyopathy (DCM) phenotype is frequent in MLYCDD and is the leading cause of morbidity and mortality[3,5]. The clinical course is variable and ranges from asymptomatic cases to patients with reduced left ventricular systolic function and premature death[3–7]. Of note, a modified diet (high carbohydrate, low fat) with levocarnitine supplementation, can lead to normalization of LV systolic function[1,3,8–13].

In most cases, the clinical manifestations of MLYCDD become apparent during the first months of life[3,4]. Anecdotal cases with later-onset presentation during childhood have been described[14] but data on the clinical characteristics and clinical course of patients with later-onset MLYCDD are currently limited.

This study aims to describe the clinical, biochemical, and genetic characteristics of two adult patients diagnosed with later-onset MLYCDD. We also perform a systematic review of the literature focusing on cardiac involvement in MLYCDD.

2. Methods

This study was a collaboration between a dedicated cardiomyopathy clinic (St Bartholomew's Centre for Inherited Cardiovascular Diseases, St Bartholomew's Hospital, London, UK) and a specialized centre for inherited metabolic diseases (Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, London, UK).

An observational, longitudinal, retrospective case series design was used. The description of the cases was performed according to the case report (CARE) guidelines[15]. The study complies with the principle of Good Clinical Practice and the Declaration of Helsinki. Written informed consent for genetic investigation was obtained from all participants.

2.1. Study population

Two patients with a diagnosis of MLYCDD aged ≥16 years evaluated from January 1990 to March 2023 were identified. The genetic diagnosis was based on demonstration of a pathogenic or likely pathogenic variant in both alleles of *MLYCD*. The biochemical diagnosis was based on the demonstration of reduced enzyme activity in skin fibroblasts.

2.2. Data collection

Anonymized clinical data were collected, including non-identifiable demographics, family history, detailed information about clinical and biochemical presentation, genetic testing results, treatment, and long-term outcomes. Data were collected from the baseline evaluation to the last clinical review using hospital attendance records.

2.3. Enzymatic activity and genetic testing

Malonyl-CoA decarboxylase activity was assayed in cultured fibroblasts from a skin biopsy. Enzyme activity was measured at the Laboratory for Genetic and Metabolic Disease, Amsterdam University Medical Centres, the Netherlands. Genetic testing was performed using a next-generation sequencing (NGS) panel. The pathogenicity of reported variants was reviewed and reclassified by the authors according to the American College of Medical Genetic (ACMG) classification[16].

2.4. Systematic literature review

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[17].

We performed a systematic review of published studies (from 1971 to 2023) by searching the Pubmed and EMBASE databases on February 13, 2023, with the following keywords: ('malonic aciduria' OR 'malonyl coenzyme a decarboxylase'/exp OR 'malonyl coenzyme a decarboxylase' OR 'malonyl coa decarboxylase'/exp OR 'malonyl coa decarboxylase' OR 'malonyl-coa decarboxylase'/exp OR 'malonyl-coa decarboxylase' OR ‘MLYCD’).

Criteria for inclusion were: 1) observational full-length original article, research letter, case series, and case report describing paediatric and/or adult individuals with genetic confirmation of MLYCCD; 2) reporting clinical characteristics of patients with MLYCCD; 3) reporting DNA analyses and specific *MLYCD* mutations; 4) English language studies. Studies published as abstract, review, or preclinical study were excluded. Reference lists of the articles included in the review were manually screened to identify additional studies.

For each reported study, the following information was collected: first author; date of publication; number of patients; sex; age at diagnosis and at cardiomyopathy presentation; presence and phenotype of the cardiomyopathy; treatment; response to treatment; follow-up; outcome.
The *MLYCD* variants described were re-evaluated on February 14, 2023, for their pathogenicity according to the ACMG criteria[16] using the Varsome database (https://varsome.com/), and were classified as pathogenic (P), likely pathogenic (LP), unknown significant, likely benign (LB) or benign (B). Diagnosis of MLYCDD was defined in the presence of a bi-allelic P/LP variant in *MLYCD*.

3. Results

3.1. Description of MLYCDD cases

3.2.Case 1

The first case was a 48-year-old woman with history of mild LV hypertrophy **(Figure 2)**. She was first seen by a cardiologist 5 years before complaining of frequent palpitations. An electrocardiogram (ECG) showed sinus rhythm with ventricular pre-excitation and transthoracic echocardiography revealed asymmetric LV hypertrophy. At that time, she also underwent a computerized tomography (CT) coronary angiogram, which was unremarkable.
Two years later, she underwent an electrophysiological study which confirmed the presence of a mid-septal accessory pathway, but ablation was unsuccessful. Given the proximity to the atrioventricular node, further attempts were abandoned.

At her first visit to the outpatient clinic, she reported exertional dyspnoea and palpitations. She had additional comorbidities, including asthma, obstructive sleep apnoea, obesity, bilateral carpal tunnel syndrome, dyslipidaemia, and glaucoma.

There was no family history of sudden cardiac death or cardiomyopathy. Her parents were first cousins. Clinical examination was unremarkable. Ventricular pre-excitation was evident on her

ECG and the transthoracic echocardiogram confirmed the presence of LV hypertrophy (with a LV maximal wall thickness of 18 mm) with LV outflow tract obstruction, and revealed the presence of mild aortic regurgitation and left atrial enlargement. A 24-hour ECG Holter monitor showed sinus rhythm with first-degree atrioventricular block alternating with intermittent pre-excitation pattern and occasional supraventricular and ventricular premature complexes. She was claustrophobic and did not undergo cardiac magnetic resonance (CMR) imaging.
Routine laboratory tests (including full blood cell count, glucose, renal function, creatine phosphokinase, liver function tests, and lactic acid) were normal, except for mildly raised N-terminal pro B-type natriuretic peptide and troponin T values.

A NGS panel for genes associated with hypertrophic cardiomyopathy (HCM) was performed and identified homozygous likely pathogenic variants in the *MLYCD* gene (c.8G>A, p.Gly3Asp) and a variant of uncertain significance in the *MYL2* gene (c.308T>G, p.Phe103Cys). The plasma acylcarnitine profile showed normal total and free carnitine concentrations but C3DC (malonyl) carnitine was increased at 0.98 µmol/L (normal reference < 0.09 µmol/L), while the urinary organic acid profile showed a marginally raised malonate, with normal methylmalonate concentration. Malonyl-CoA decarboxylase activity was assayed in skin fibroblasts, showing reduction (3.7 nmol/[hour.mg protein]) compared to reference values (21.0 ±6.7 nmol/[hour.mg protein]).
She was followed up for eight years with repeat cardiovascular evaluation every 6-12 months, showing no increases in LV hypertrophy or deterioration of LV ejection fraction (LVEF).

3.3. Case 2

A 29-year-old woman was referred one month after giving birth due to a recent history of peripartum cardiomyopathy **(Figure 3)**. She had an unclear previous cardiac history for which she was under follow-up from 4 months up to the age of 4 years. She had a statement of educational support at school and had one-to-one support with a special needs teacher. There was no family history of sudden cardiac death or cardiomyopathy. When she reached 18 years of age, she was re-referred to her local cardiology service and was diagnosed with mild LV systolic dysfunction for which she received treatment with lisinopril and bisoprolol. A routine check-up during pregnancy at 37 weeks showed LV dilatation and moderate LV systolic dysfunction with an LVEF of 35-40%. She delivered by Caesarean section with no complications.

When reviewed in clinic she reported exertional dyspnoea and fatigue. On examination, she had normal blood pressure (115/70 mmHg) and a regular heart rate (75 bpm). A systolic murmur was

noted. The ECG showed sinus rhythm with normal atrioventricular and intraventricular conduction and no evidence of abnormal repolarization pattern. The transthoracic echocardiogram confirmed evidence of LV dilatation with moderate systolic dysfunction (LVEF 40%) and moderate mitral regurgitation. She underwent CMR that confirmed the diagnosis of DCM and showed LV dilatation (LV end-diastolic volume index 99 mL/m2) and mild systolic impairment (LVEF 53%), with normal native T1 values and no evidence of late gadolinium enhancement. Routine laboratory tests were normal.

An NGS panel identified homozygous pathogenic variants in *MLYCD* (c.721delT, p.Ser241Leufs*17). The plasma acylcarnitine profile showed normal total and free carnitine concentrations, but C3DC (malonyl) carnitine was increased at 0.83 µmol/L (normal reference < 0.09) while the urinary organic acid profile showed a mildly increased malonic acid. The malonyl-CoA decarboxylase activity was assayed in skin fibroblasts, showing a significant reduction (6.5 nmol/[hour.mg protein]) compared to reference values (21.0 ±6.7 nmol/[hour.mg protein]).

Empagliflozin was commenced in addition to lisinopril and bisoprolol. She was followed up for two years with repeated cardiovascular evaluation every 6-12 months, showing no deterioration of LVEF.

3.4. Systematic literature review

We identified 457 studies through electronic searches, and 21 studies met the inclusion criteria[1,3–14,18–26] **(Supplemental Figure 1)**, providing data for 42 patients with genetically confirmed MLYCDD. However, after *MLYCD* variant re-evaluation, it was found that eight patients carried a bi-allelic VUS (ID04.4; ID04.6; ID04.8; ID06; ID09; ID11; ID13.6; ID13.8) and one patient a bi-allelic benign variant (ID07) **(Supplemental Table 1)**. These patients were excluded from the analyses.

The final population of MLYCDD patients with bi-allelic P/LP variants in *MLYCD* was composed of 33 individuals (median age 6 months [IQR 1-12], 22 males [67%]) **(Figure 4)**. Cardiovascular involvement was described in 21 patients (64%)[1,3–13,22,25], with DCM representing the most common phenotype (n=14, 67%)[1,3–6,9,13,22,25], followed by left ventricular non-compaction (n=4, 19%)[3,8,10,11], and HCM (n=3, 14%)[4,7,12]. The median age at cardiomyopathy presentation was 5 months (IQR 1-7 months).

Among patients with cardiomyopathy, 16 (76%) were started on a high carbohydrate and low fat diet combined with medium chain triglyceride (MCT) and levocarnitine supplementation[1,3–5,8–13,22,25]. A few months after the diet and supplementation initiation, most patients (n = 12) showed a significant improvement in systolic function with normalization of LVEF and reversal of the cardiac phenotype[1,3,8–13,25]. In two cases, LVEF was stabilized[4,22] while in 2 patients with severely LVEF reduction, progressive deterioration of the cardiac function was observed, leading to death after 1-month and 8-months of follow-up, respectively[3,5].

Overall, among patients with cardiomyopathy and documented follow-up information[1,3–5,7–13,22,25], (with a median follow-up of 8 months [IQR 7-57 months]), 3 patients died (the two previously mentioned cases with heart failure-related death[3,5] and one patient with HCM who had a cardiac arrest one month after the diagnosis during a surgical procedure[7]).

No patient diagnosed during adulthood was reported. However, two patients showed a later-onset presentation during childhood (aged 9 years old[14] [ID06] and 13 years old[4] [ID13.1], respectively). Both patients exhibited mild neurodevelopmental delay and no signs of cardiovascular involvement.

4. Discussion

This comprehensive literature review of cardiovascular involvement in MLYCDD demonstrated that patients generally present during the first months of life with DCM the most common cardiac phenotype. We present the first report of the clinical, biochemical, and genetic characteristics of MLYCDD patients presenting during adulthood. In both cases, the cardiovascular involvement was the only clinical manifestation of MLYCDD.

4.1.Cardiovascular disease in MLYCDD

Inherited metabolic disorders account for less than 5% of patients with cardiomyopathy and, in most cases, present during infancy or childhood with severe multi-systemic manifestations[27]. MLYCDD is a rare cause of cardiomyopathy, with less than 35 cases with genetic confirmation described. In almost all cases, the phenotype was evident during the first months or years of life, with severe multi-systemic manifestations. The two older MLYCDD patients identified previously were a 9-year-old girl[14] and a 13-year-old boy[4] both presenting with mild neurodevelopmental delay. Neither individual showed evidence of cardiovascular involvement or other severe clinical manifestations at the time of the diagnosis. However, the 9-year-old girl carried a *MLYCD* variant that was classified as a variant of uncertain significance and malonyl-CoA decarboxylase activity

was not determined, leaving the diagnosis of MLYCDD questionable. Moreover, there is no further information regarding the clinical follow-up of these patients.

Cardiovascular involvement was evident in nearly two-thirds of affected patients with early-onset MLYCDD. DCM was the most common phenotype and exhibited a variable range of LV dilatation and systolic dysfunction. However, rare cases of patients with HCM have been described. Untreated, DCM presenting during the first months of life with congestive heart failure is associated with adverse outcomes. In contrast, most patients that are treated with a specific diet (high-carbohydrate low-fat diet with MCT) combined with levo-carnitine supplementation, in addition to standard heart failure medications, show a significant improvement of LV systolic function and complete reversal of the phenotype.

The underlying pathophysiology leading to DCM is most likely related to the accumulated metabolites, which inhibit acyl-CoA metabolism, lower cellular pH, and promote oxidization of mitochondrial components **(Figure 1)**. LV hypertrophy may result from an adaptive cardiac response to inefficient contraction, which is also described in other conditions associated with inborn errors of metabolism.

4.2. *MLYCDD in adulthood*

The biochemical findings in the two adults described in this study were subtle and much less obvious than in previously reported affected children, requiring the measurement of reduced malonyl-CoA decarboxylase activity in fibroblasts to confirm the diagnosis.
The first patient showed HCM with ventricular pre-excitation, a clinical phenotype similar to that seen in mitochondrial disease or glycogen storage disorders[28], while the second patient had DCM with mild-to-moderate systolic dysfunction. Both patients were counselled to follow a low-fat diet, but a high carbohydrate diet, MCT and levo-carnitine supplementation were not implemented. Neither patient has shown deterioration in LV function or adverse events during long-term follow-up.

4.3. Clinical Implications

The case studies suggests that patients with later-onset MLYCDD may have near-normal plasma carnitine profile and urinary organic acid profiles with only subtle abnormalities requiring biochemical confirmation of reduced enzyme activity for a definitive diagnosis **(Figure 5)**. The diagnosis was only suspected following the demonstration of bi-allelic variants in *MLYCD*,

suggesting that rare metabolic causes of cardiomyopathy should be sought when standard diagnostic gene panels fail to reveal a definite cause of disease.

5. Conclusions

Patients with later-onset MLYCDD present with predominant cardiovascular involvement, mildly reduced malonyl-CoA activity, and a relatively benign clinical course. The demonstration of reduced enzyme activity combined with bi-allelic variants in *MLYCD* is required for the diagnosis.

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Data availability: The data that support the findings of the study are available from the corresponding author upon reasonable request.

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Figure legends

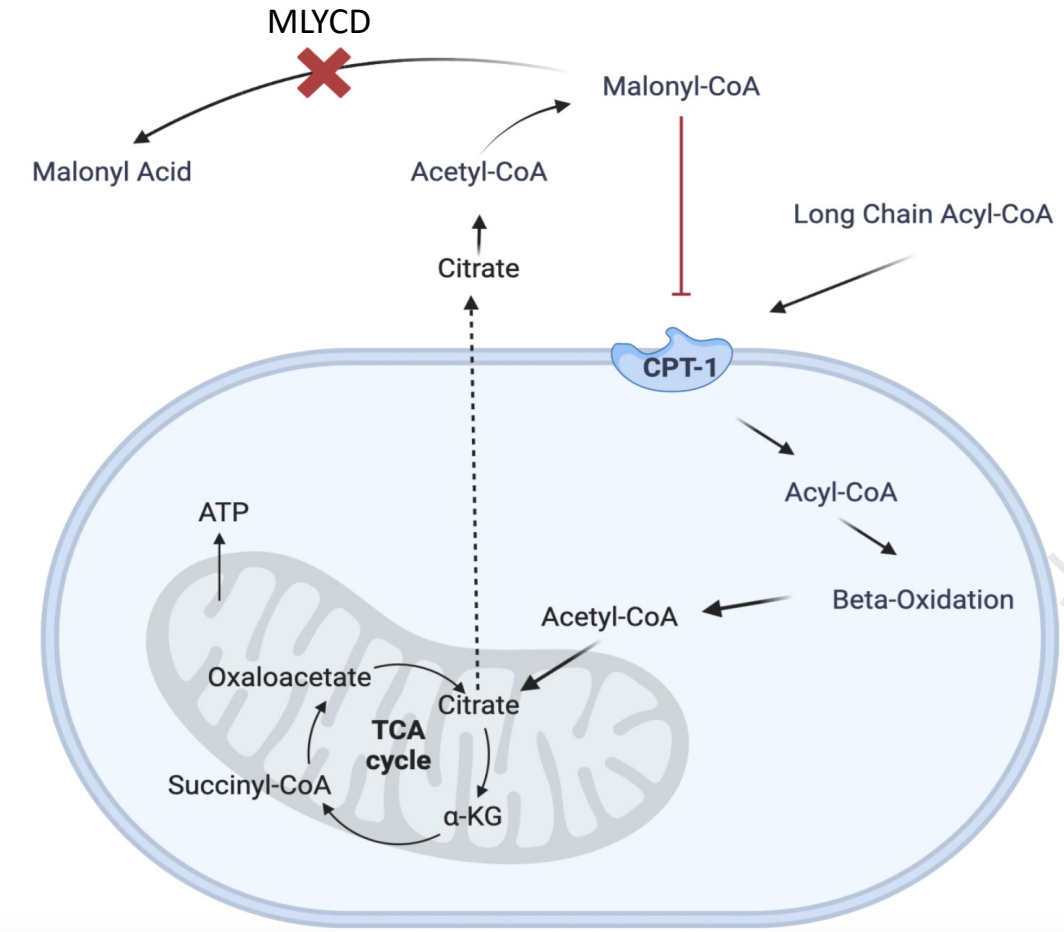
Figure 1. The accumulation of malonyl-CoA caused by MLYCDD inhibits carnitine palmitoyltransferase 1, which is the rate-limiting enzyme in fatty acid beta-oxidation in mitochondria and peroxisome. The underlying pathophysiology leading to a dilated cardiomyopathy phenotype is most likely related to the accumulated metabolites, which inhibit acyl-CoA metabolism, lower cellular pH, and promote oxidization of mitochondrial components.

Figure 2. Clinical characteristics of the first patient: A) The 12-lead ECG shows sinus rhythm with ventricular pre-excitation; B) The 24-hour ECG Holter monitoring shows sinus rhythm first-degree atrioventricular block alternated with intermittent ventricular pre-excitation; C) The transthoracic echocardiography shows severe left ventricular hypertrophy (long-axis view on the left, apical 4-chamber view on the right).

Figure 3. Clinical characteristics of the second patient: A) The 12-lead ECG shows sinus rhythm, low voltages in peripheral leads, and negative T-waves in lateral leads; B) The transthoracic echocardiography shows left ventricular dilation (long-axis view on the left, apical 4-chamber view on the right); C) The cardiac magnetic resonance shows left ventricular dilation with prominent trabeculations.

Figure 4. Summary of the results of the systematic review of published MLYCDD cases. *Abbreviations:* LV, left ventricular.

Figure 5. Comparison between clinical and biochemical characteristic between early-onset and later-onset MLYCDD patients.



↑Malonyl-CoA Concentration
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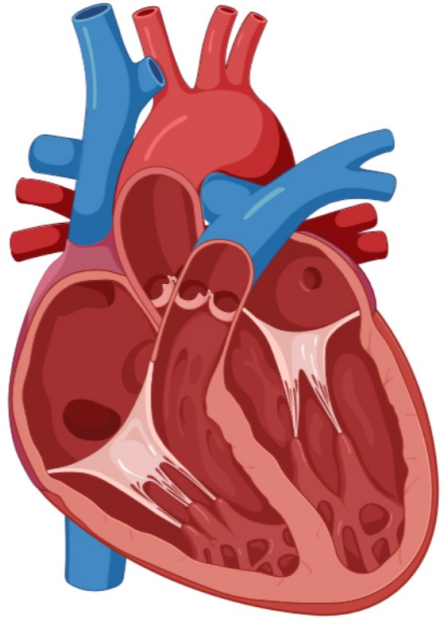
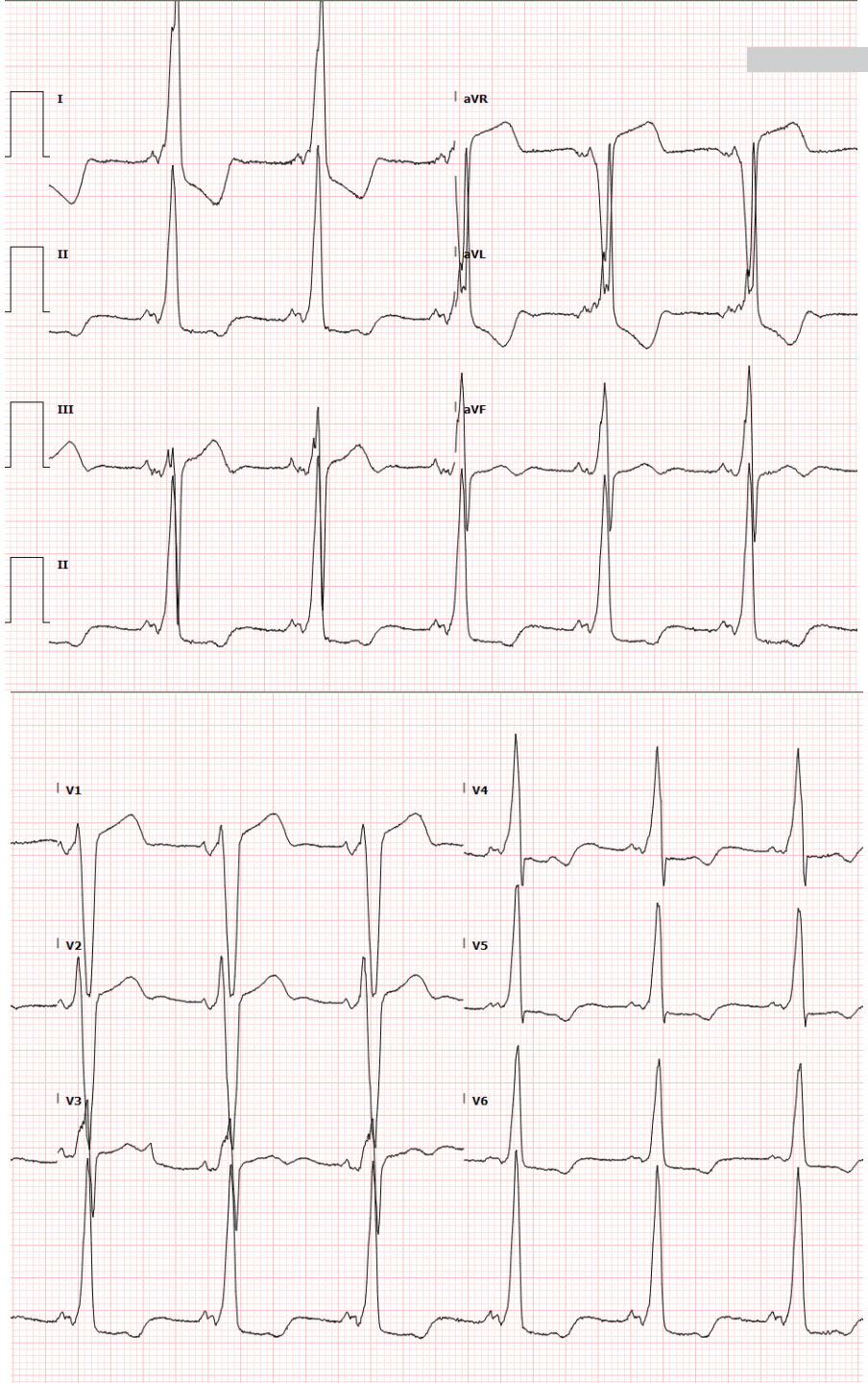
↓ Cellular pH
↑ Oxidative Stress

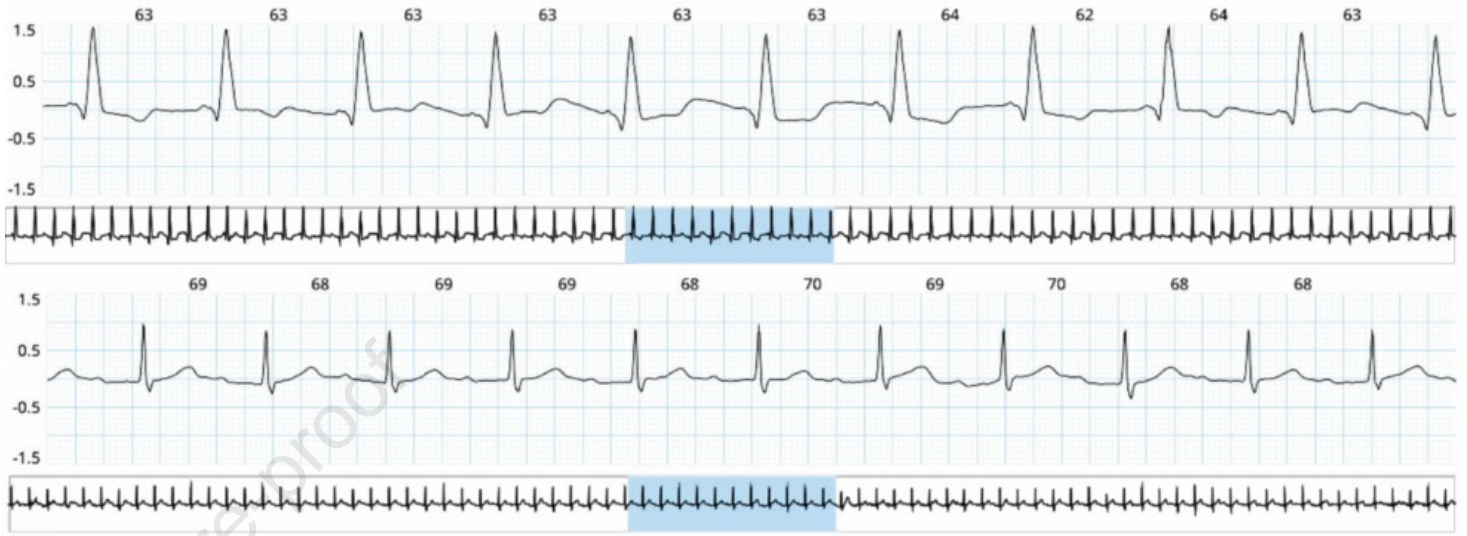


Left Ventricular
Function Impairment

A



B



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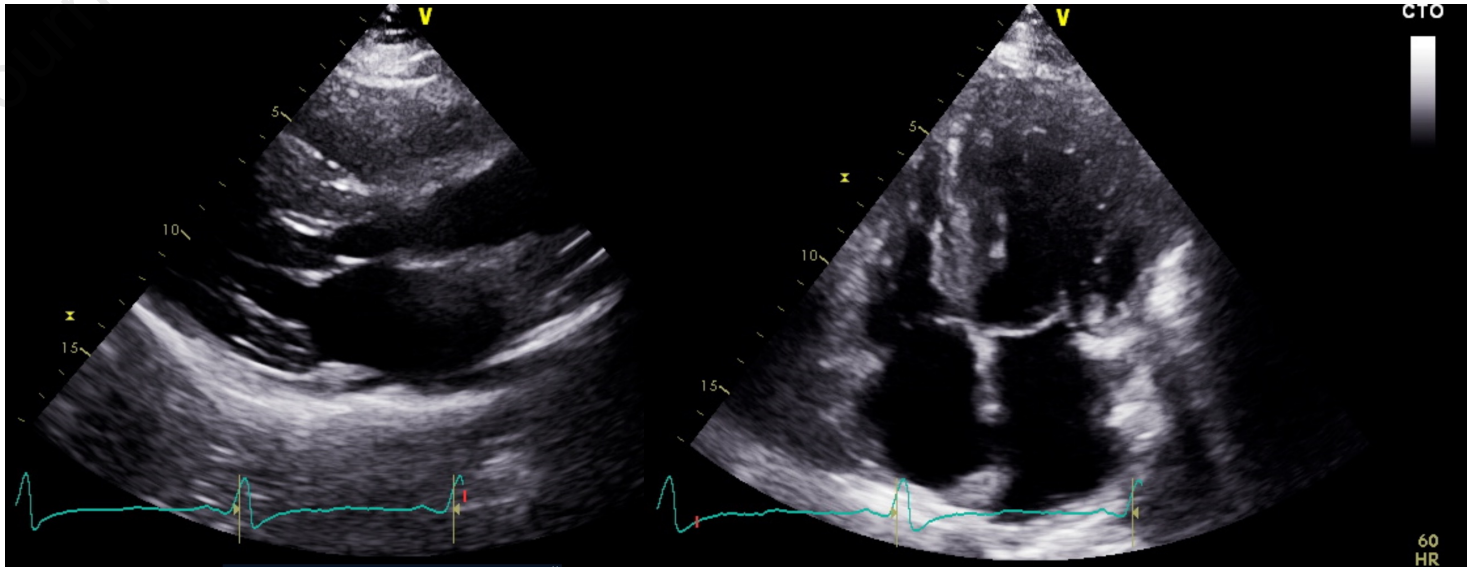
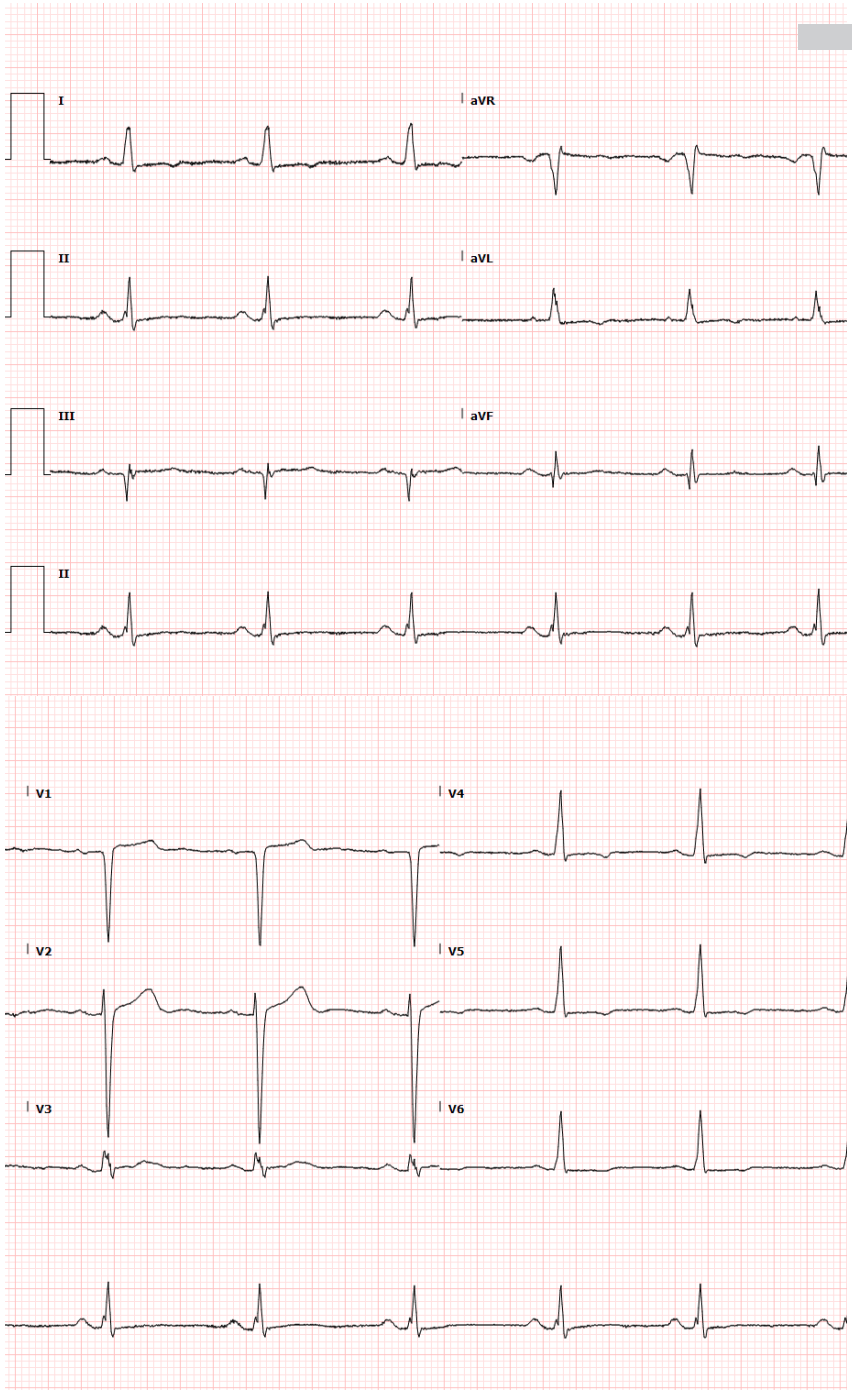


A



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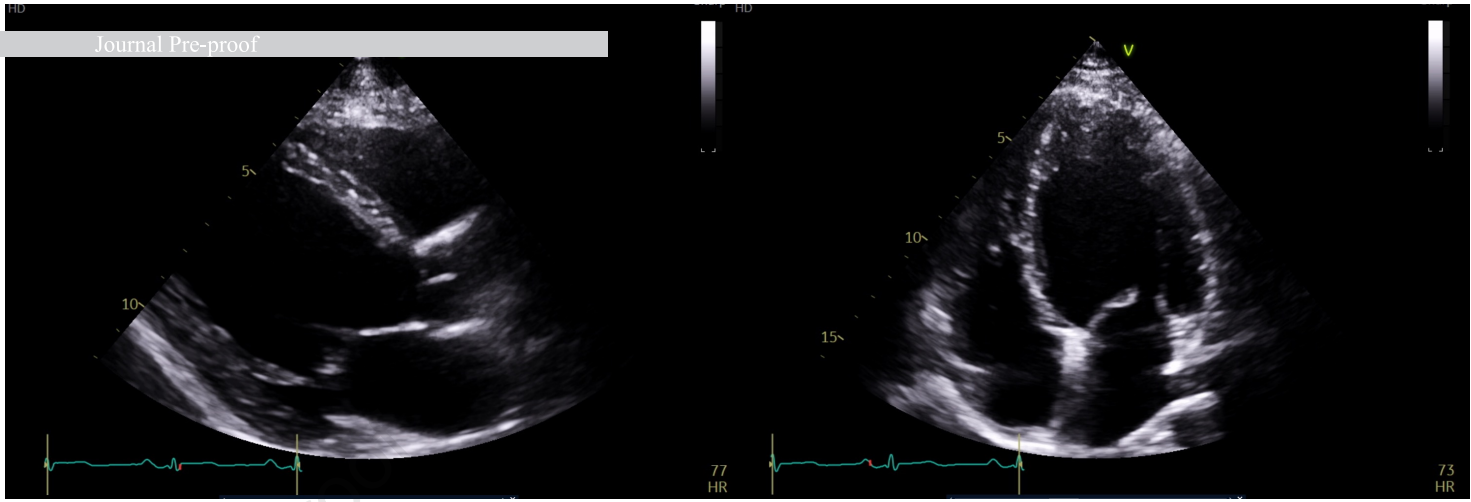

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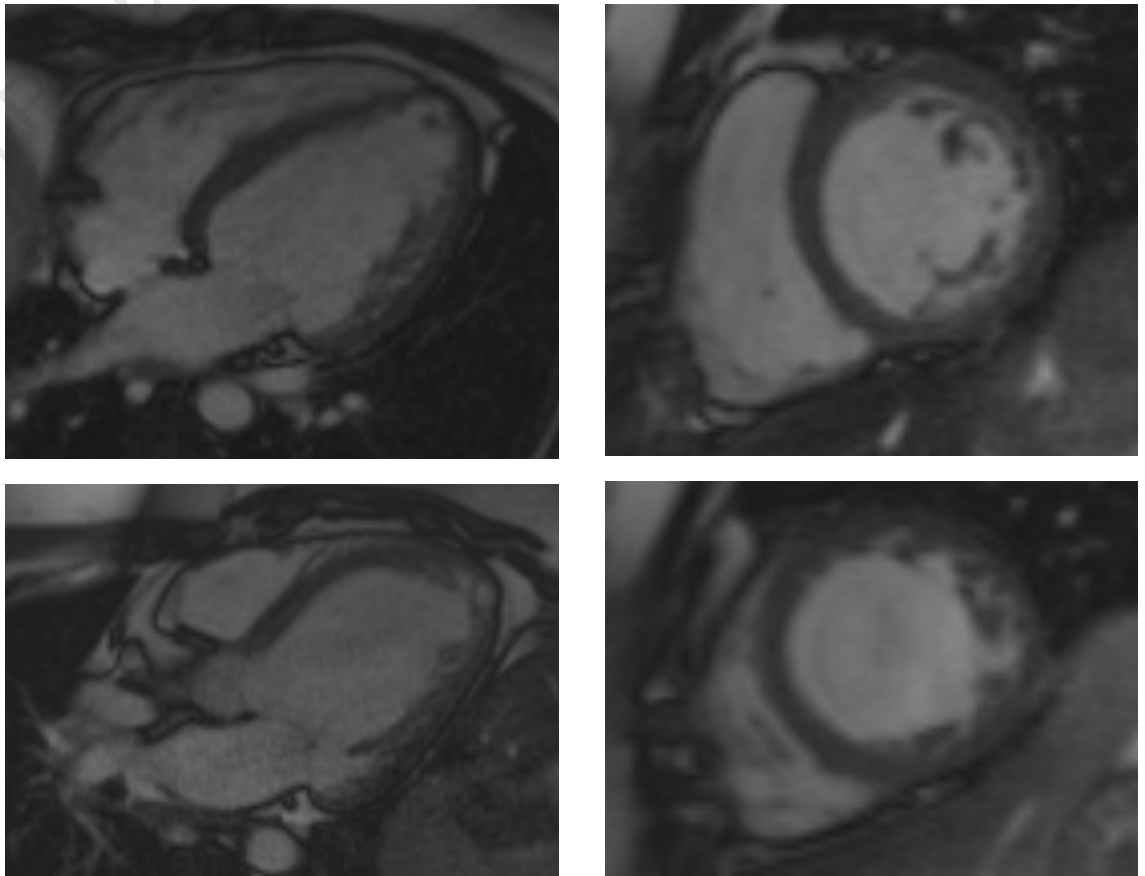
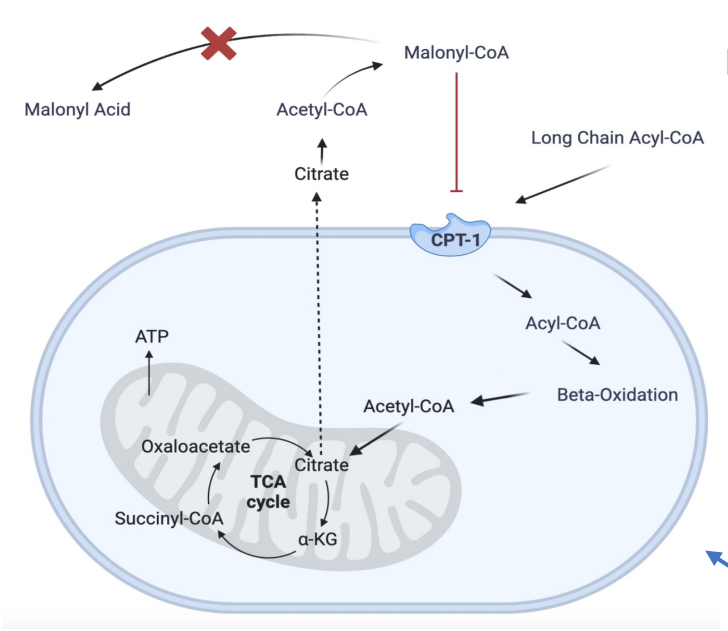


Articles Identified from EMBASE and Medline
(n = 457)

Articles Fulfilling the Inclusion Criteria
(n = 22)

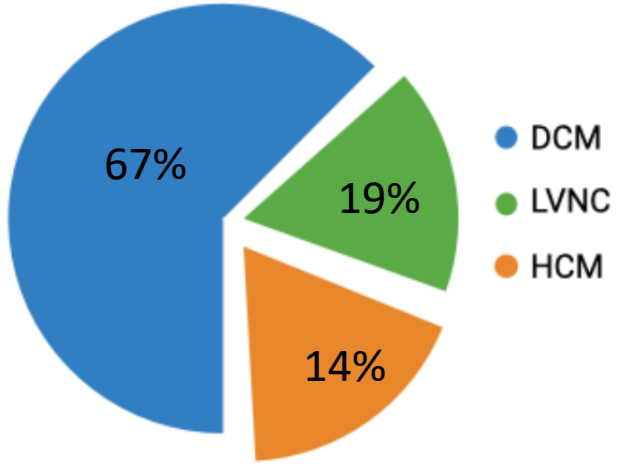
Patients with Genetic Diagnosis of MLYCDD
(n = 33)

Presence of cardiac involvement
(n = 21, 64%)



PATHOPHYSIOLOGY

Age of Cardiomyopathy Presentation
Median 8 months (IQR 7-57 months)



CARDIOMYOPATHY

TREATMENT

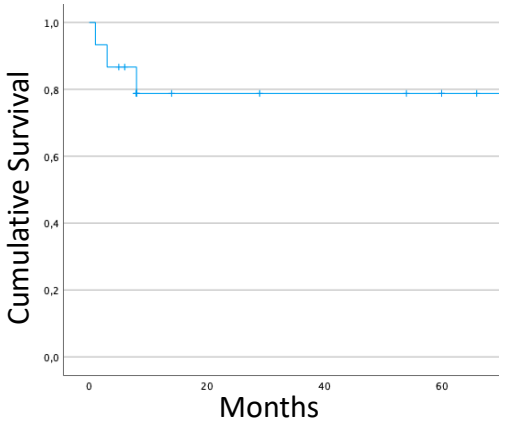
High-Carbohydrate / Low-Fat Diet
± Levocarnitine
(n = 16)

- LV Function Normalization (n = 12, 75%)
- LV Function Stabilization (n = 2, 12%)
- No Response to Therapy (n = 2, 12%)

FOLLOW-UP

Follow-up Available
(n = 15)

Median 8 months (IQR 7-57)



Patients Experienced Death
(n = 3)

- HF-Related Death (n = 2)
- Death During Surgery (n = 1)

	Early-onset MLYCDD	Later-onset MLYCDD
Age at presentation	First months of life	Adulthood
Clinical features	Severe phenotype with multiorgan involvement	Mild phenotype with single organ involvement
Biochemical profile	- Elevated levels of malonylcarnitine in blood acylcarnitine profile - Elevated levels of malonic acid in the urine organic acid profile	- Mildly elevated levels of malonylcarnitine in blood acylcarnitine profile - Mildly elevated levels of malonic acid in the urine organic acid profile
Malonic-CoA decarboxylase activity	Very low or absent residual enzyme activity	Low residual enzyme activity
Diagnosis	Biochemical profile + Bi-allelic mutation in *MLYCD*	Bi-allelic mutation in *MLYCD* + Demonstration of reduced enzyme activity