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ORIGINAL ARTICLE

Follow-up of fatty acid β-oxidation disorders in expanded newborn screening era

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Abstract

Fatty acid β-oxidation (FAO) disorders have a wide variety of symptoms, not usually evident between episodes of acute decompensations. Cardiac involvement is frequent, and severe ventricular arrhythmias are suspected of causing sudden death. Expanded newborn screening (ENS) for these disorders, hopefully, contribute to prevent potentially acute life-threatening events. In order to characterize acute decompensations observed in FAO-deficient cases identified by ENS, a retrospective analysis was performed, covering a period of 9 years. Demographic data, number/type of acute decompensations, treatment, and follow-up were considered. Eighty-three clinical charts, including 66 medium-chain acyl-CoA dehydrogenase deficiency (MCADD), 5 carnitine-uptake deficiency (CUD), 3 carnitine palmitoyltransferase I and II (CPT I/II) deficiency, 5 very long-chain acyl-CoA dehydrogenase deficiency (VLCADD), and 4 multiple acyl-CoA dehydrogenase deficiency (MADD) cases were reviewed. Nineteen patients had acute decompensations (1 CPT I, 1 CPT II, 3 MADD, 14 MCADD). Six patients developed symptoms previously to ENS diagnosis. Severe clinical manifestations included multiple organ failure, liver failure, heart failure, and sudden death. Long-chain FAO disorders had the highest number of decompensations *per* patient.

Conclusion: Despite earlier diagnosis by ENS, sudden deaths were not avoided and acute decompensations with severe clinical manifestations still occur as well.

What is Known:
- *Severe ventricular arrhythmias are suspected to cause unexpected death in FAO disorders.*
- *Neonatal screening intends to reduce the incidence of severe metabolic crisis and death.*

What is New:
- *Acute severe decompensations occurred in FAO disorders diagnosed through neonatal screening.*
- *Sudden deaths were not avoided by starting treatment precociously.*

Keywords Fatty acid ß-oxidation disorders · Acute decompensations · Sudden death

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Abbreviations

CK	Creatine kinase
CK-MB	Creatine kinase muscle and brain subunits
CPT I	Carnitine palmitoyltransferase I
CPT II	Carnitine palmitoyltransferase II
CUD	Carnitine-uptake deficiency
DBS	Dry blood spot
DMD	Duchenne muscular dystrophy
ENS	Expanded newborn screening
FAO	Fatty acid β-oxidation
LC-FAO	Long-chain fatty acid oxidation disorders
MADD	Multiple acyl-CoA dehydrogenase deficiency
MCADD	Medium-chain acyl-CoA dehydrogenase deficiency
R.V.	Refference values
VLCADD	Very long-chain acyl-CoA dehydrogenase deficiency

Introduction

Mitochondrial fatty acid β-oxidation is one of the most important processes for cellular energy production [1]. Twenty-five enzymes and specific transport proteins comprise this pathway. Deficiencies in 18 of these proteins have been demonstrated to cause disease in humans. So far, all defects identified are inherited in an autosomal recessive trait, although obligate heterozygotes have been found to have intermediate enzyme activity levels [2]. Fatty acid β-oxidation disorders (FAO disorders) show different severity, age of onset, and a wide variety of clinical manifestations, mostly related to the compromise of high metabolic demanding organs such as liver, skeletal muscle, and heart. The heart relies mainly on FAO for energy production after birth, and it is considered that energy deprivation contributes to the development and progression of metabolic cardiomyopathy [3–5]. In the case of long-chain FAO disorders (LC-FAO), the accumulation of toxic metabolites, such as acyl-CoAs and acylcarnitines, contribute to the pathogenesis of the disorders. Evidence for a heartbeat disorder has been found in the very-long-chain acyl-CoA dehydrogenase knockout (VLCAD-KO) mouse which can develop polymorphic ventricular tachycardia and display a prolonged rate-corrected QT (QTc) interval under all conditions examined [6]. In fact, long-chain acylcarnitines are thought to be arrhythmogenic because they may change membrane properties and integral proteins such as the sarcolemmal Na/K-ATPase [3, 4]. This potentially lethal kind of arrhythmias is not attributable only to LC-FAO, Wiles and colleagues [7] described an MCAD-deficient patient who presented at 3 days of age with poor feeding, lethargy, hypoglycemia, metabolic acidosis, hypocalcemia, and prolonged QTc interval that normalized after correction of the metabolic imbalances. Severe ventricular arrhythmias are suspected to be the cause of sudden infant death syndrome or unexpected deaths in young children [4, 8]. Liver manifestations such as fatty liver, hepatomegaly, and Reye-like syndrome can also occur combined with the cardiac manifestations comprising the most severe phenotype. A myopathic phenotype can also be present with muscle weakness or pain and severe rhabdomyolysis, usually at a later onset [9]. Situations of increased energy demand such as prolonged fasting, infections, physical exercise, and exposure to cold or a fat-rich diet may trigger a metabolic decompensation. Between these episodes, patients may be completely asymptomatic [2, 9, 10].

In the Expanded Newborn Screening (ENS) era, a greater number of patients have been identified, suggesting a higher prevalence of these disorders than previously suspected. In Portugal, according to the national report, between 2004 and 2016, the prevalence of β-oxidation disorders was 1: 5849 newborns [11]. ENS was initiated based on the belief that presymptomatic diagnosis could prevent acute, potentially life-threatening events by prompting to the avoidance of prolonged fasting, and the treatment of affected infants and children, during acute illness. Nevertheless, it also lead to the identification of a great number of mildly affected patients who may never develop clinical symptoms throughout life [5, 9, 12–14].

In order to evaluate the effects of the ENS on the outcome of FAO disorder patients, the authors performed a retrospective analysis of the clinical charts of 83 patients with FAO disorders followed over a period of 9 years at the Lisbon University Sta Maria Hospital, Pediatric Metabolic Disease Unit.

Materials and methods

The authors performed a retrospective analysis covering a period of 9 years of FAO-deficient cases identified by ENS, including demographic data, obstetric and neonatal background, number/type of acute decompensations, treatment, and follow-up.

The majority of the patients (96.4%) included in this study were identified by the established National Neonatal Screening program; for details, see Vilarinho L. et al. [15]. The Portuguese Neonatal Screening Program is performed over the whole country and in a single laboratory that performs routine MS/MS neonatal screening. The newborn blood spot is collected between the third and the sixth day of life on Whatman 903 filter paper, after 48 h of full enteric feeding regarding gestational age and weight. For preterms (below 30 weeks of gestational age) and very low birth weight (below 1500 g), two samples are collected on the 3rd and 15th day of life. The result is communicated to one of the five national reference centres for the treatment of inborn errors of metabolism, closest to the patient living area. The patient's family is then informed by the pediatrician from the national reference center, and a hospital visit is immediately scheduled. On the first outpatient visit, blood samples are collected for

confirmation of the altered biomarkers and for further molecular DNA studies. A urine sample for organic acids evaluation is also collected. If necessary, and according to the laboratory protocol, specific samples are collected for enzymatic assay.

Descriptive statistics were performed using excel 2010 version. Rank correlation tests, Mann-Whitney *U* test, survival Kaplan Maier curve and Log rank (Mantel Cox) were performed using SPSS version 21. Statistically significant *p* value was considered below 0.05.

Results

A total of 83 clinical charts were reviewed, including 66 medium-chain acyl-CoA dehydrogenase-deficient (MCADD), five carnitine-uptake-deficient (CUD), two carnitine palmitoyltransferase I-deficient (CPT I), one CPT II-deficient, five very long-chain acyl-CoA dehydrogenase-deficient (VLCADD), and four multiple acyl-CoA dehydrogenase-deficient (MADD) patients.

The female-to-male ratio was 1.5. The current median age was 4.7 years (range 0.24–8.5 years). Pregnancy and delivery history were essentially unremarkable in all cases except for one MCADD patient with an episode of pre-eclampsia described during pregnancy. All index cases (96.4% total cases) were detected by the ENS. Two MCADD cases were family members of index cases.

The median age at ENS was 5 days (range 2–60 days). The treatment started at 18 days (range 9–70 days). For all cases, the diagnosis was confirmed through further metabolic studies, namely urine organic acid analysis, enzymatic tests (in the case of VLCADD patients), and molecular genetic characterization, which was achieved in 79.5% of the cases (Table 1). A high prevalence of gipsy ancestry (95.5%) and consanguinity (77.3%) was observed among the MCADD patients. Interestingly, almost all of MCADD with molecular characterization ($n = 54$) had the classical genotype (c.985A > G/c.985A > G). Only one, non-gipsy, MCADD patient harbor other sequence variants, showing compound heterozygosity for the common mutation and other rare mutation (c.1205G > T). One of the patients was referred to our Metabolic Diseases Unit at 16 months of age due to poor weight growth, developmental delay, and hypotonia. The biochemical investigation revealed slight hyperammonemia (124 μM: R.V. < 85) and a urinary organic acid profile indicative of mild MADD. Riboflavin supplementation was then initiated, the clinical status improved, and the organic acid profile normalized. The genetic study revealed homozygosity for c.461C > T mutation in the *ETFB* gene. The same genetic pattern was present in his father but, so far, without any clinical symptoms or organic acid profile alterations. The variant was also found in heterozygosity in his mother. The variant was considered to be a polymorphism. Riboflavin supplementation was stopped and surprisingly, a moderate excretion of some MADD's urinary biomarkers was detected. Therefore, overall beta-oxidation activity in fibroblasts was performed and did not reveal abnormalities. Although, mild phenotypes may have a normal result in fibroblasts. Therefore, to clarify, the evaluation of the specific enzyme activity is ongoing.

Acute metabolic decompensations, requiring hospital admissions, occurred in 22.9% of the studied patients (19/83), including 14 MCADD, 3 MADD, 1 CPT I-deficient, and 1 CPT II-deficient patients. The clinical signs and symptoms observed are presented in Table 2. Among these patients, with a median age of 2 days (range 2–7 days), six individuals (3 MCADD; 2 MADD; 1 CPT I-deficient patients) developed clinical manifestations previous to the return of the ENS results; similar observation was also reported by others [16]. Documented hypoglycemia was observed in four of the six patients, liver failure in one CPT I-deficient patient and multiple organ failure and death at day 7 in one MADD patient.

There was no difference related to gender (0.9 female to male rate). The median age of the first decompensation was 4 months (2 days – 35 months), and the median number of decompensations *per* patient was one episode (1–5 episodes).

If we consider the VLCAD, CPT I, CPT II, and MADD as part of the long-chain fatty acid oxidation disorders (LC-FAO) group, and then compare this group, as a whole, with the MCADD group, we can see that, although not statistically significant, the LC-FAO group had a poor survival outcome than the MCADD group ($p = 0.101$) with a higher rate of events throughout time (42 vs 21% events, respectively); see Fig. 1. Moreover, the individuals with LC-FAO disorders had the highest number of decompensations (median of 3 episodes per patient ± 1.3 SD) when compared to MCADD (median of 1 episodes ± 1.1 SD) [Mann-Whitney test $p = 0.011$]. It is also evident from Fig. 1 that metabolic crisis occurred very early in patients' life-time. After acute decompensation, the great majority of patients (84.2%) recovered completely. However, three deaths occurred involving two MADD and one MCADD patients. One of the MADD patients died at the seventh day of life due to multiorgan failure during an acute decompensation (see Table 2). The other MADD patient, 2 years old, was found dead during sleep, without clinical identified reason for this occurrence. The MCADD patient died suddenly at 2 months of age, with a cardiopulmonary arrest. Interestingly, this patient had been exclusively breastfed and lost more than 10% of birth weight in the neonatal period.

Comparing the group of patients who suffer from any acute metabolic decompensation with the group of asymptomatic patients, there were no differences regarding median ENS age (6 days ± 1.5 SD versus 5 days ± 7.9 SD; $p = 0.665$; independent samples Mann-Whitney *U* test) or treatment start (18.5 days ± 9.2 SD versus 18 days ± 11.5 SD; $p = 0.768$; independent samples Mann-Whitney *U* test).

As we could expect during acute decompensation episodes, glycemia median levels were significantly low (median =

Table 1 Molecular characterization for each group of patients

Genotype		Percent*	*N***
MCADD	c.985A > G (p.K329E)/c.985A > G (p.K329E)	80,3%	53
	c.985A > G (p.K329E)/c.1205G > T (p.G402 V)	1.5%	1
VLCADD	c.991G > C (p.E331Q)/c.1944delCT (p.L648Lfs*2)	20%	1
	c.664G > A (p.G222R)/c.478-20delCA	20%	1
	c.848C > T (p.V283A)/c.1322G > C (p.G441A)	20%	1
CUD	c.844C > T (p.R282*)/c.844C > T (p.R282*)	60%	3
CPT I	c.1456_1458 + 1del GAGg/c.1456_1458 + 1del GAGg	50%	1
	c.1907C > T (p.A636V)/c.1907C > T (p.A636V)	50%	1
CPT II	c.680C > T (p.P227L)/c.1106A > G (p.H369R)	100%	1
MADD	c.405 + 3A > T/c.1601C > T (p.P534L) – ETFDH	25%	1
	c.461C > T (p.T154 M)/c.461C > T (p.T154 M) – ETFB	25%	1
	c.35 + 5G > C/c.1601C > T (p.P534L) – ETFDH	25%	1

[a] Percentage of patients with molecular characterization for each individual disease group

[b] Total patient number ($n = 66$) with molecular characterization

2.7 mmol/L, range 1.1–3.7 mmol/L; R.V. 3.9–6.1 mmol/L), uric acid median levels were high (median = 660.3 μmol/L, range 333.1–1314.6 μmol/L; R.V.: 184.39–463.94 μmol/L), and ammonia median levels were slightly elevated (median = 83 μmol/L, range 46–342 μmol/L; R.V. 11–32 μmol/L).

Regarding the follow-up, 41% of the patients had poor compliance to therapy and 26.5% abandoned follow-up. Most of the patients (68.7%) remained completely asymptomatic during follow-up (47 MCADD; 5 CUD; 4 VLCAD; 1 CPT I deficiency) presenting no decompensation or disease manifestation. Along the follow-up, five patients revealed altered biochemical parameters or clinical symptoms, namely persistent elevated aminotransferase levels in one VLCAD patient; developmental delay was observed in two MADD cases, curiously in the patient with the homozygosity for c.461C > T mutation and in the one that suffer an acute episode at day 2 of life. Interestingly, two of the MCADD patients presented in Table 2 showed persistent extremely elevated aminotransferases and creatine kinase (CK) levels despite complete clinical recovery after an acute crisis. Therefore, these two patients were enrolled in further investigation for the clarification of the situation. Additionally, the diagnoses of sacrogycanopathie (SGCG gene mutation c.848G > A p.Cys283Tyr in homozygosity) and that of Duchenne muscular dystrophy (deletion in the exon 48 of dystrophin (DMD) gene) were confirmed in each case, respectively.

Routine biochemical tests, performed during asymptomatic periods of follow-up, revealed altered creatine kinase muscle and brain subunit (CK-MB) levels. The two MCADD cases with an additional neuromuscular disorder were excluded. The mean values of CK-MB in long-chain FAO disorders (6.2 ± 3.9 μg/L) were higher than in MCADD group (4.2 μg/L ± 2.2 μg/L) [Mann-Whitney test $p = 0.025$]. Despite showing creatine kinase, troponin, glycemia, ammonia, and uric acid levels within the normal reference ranges, four patients—three MCADD and one VLCAD—revealed very high levels of CK-MB. All patients had a complete routine cardiac evaluation, which included electrocardiography and echocardiography exams, without reports of cardiac abnormalities.

Along the follow-up period, comparing decompensated patients´ asymptomatic periods with the full asymptomatic group of patients, no differences in CK-MB, CK, troponin, uric acid, glycemia, and ammonia levels were observed.

Discussion

In the expanded newborn screening era, FAO disorders are being increasingly identified. After Portugal's expansion of newborn screening in 2006, MCADD became the most prevalent inborn error of metabolism in the country with a birth incidence of 1:7632, higher than phenylketonuria (1:10,646) during the same period of time [11].

In our MCADD patients studied, a high prevalence of asymptomatic cases was observed.

Regarding treatment strategy, long fasting avoidance and lipid/carbohydrate dietary recommendations were prescribed according to the specific FAO disorder. Patients diagnosed with CUD, CPT II deficiency, and MCADD received L-carnitine supplementation according to their free carnitine plasma levels and, in the case of MADD patients, riboflavin supplementation was also prescribed.

In spite of the precocious diagnosis by ENS and the concomitant implementation of the therapeutic measures, acute decompensations with severe clinical manifestations occurred in all types of fatty acid β-oxidation defects included in this report, independent of being long or medium-chain FAO-associated defects.

Vomiting was the major finding in decompensated patients and should lead to prompt medical attention. Acute neonatal

Table 2 Patient manifestations in acute crisis ($n = 19$)

Current age/sex	FAO disorder	Genotype	Gestational age (weeks)	Birth weight	Hypotermia	Time screen collected	Initial feeding method	Poor weight gain (neonatal)	Acute episodes	Age at 1st crisis	Symptomatic before NBS	Clinical manifestations during decompensation	
												Vomiting	Rhabdomyolisis
8 Y/F	MCADD	Homozygous c.985A > G	40	3420 g	No	3 D	Formula	Yes	5	23 M	No		
4 Y/F	MCADD	?	39	3320 g	No	3 D	Breast	No	1	2 Y	No	+	
6 Y/M	MCADD	Homozygous c.985A > G	?	?	No	5 D	Breast	No	1	18 M	No	+	
2 Y/F	MCADD	Homozygous c.985A > G	35	2820 g	No	6 D	Breast + formula	No	1	2 D	Yes		
4 Y/M	MCADD	Homozygous c.985A > G	39	3415 g	No	7 D	Formula	No	1	2 Y	No	+	
7 Y/M	MCADD	Homozygous c.985A > G	39	3190 g	No	5 D	Formula	No	1	2 D	Yes		
7 Y/M	MCADD	Homozygous c.985A > G	40	3210 g	No	5 D	Breast	No	1	4 D	Yes		
5 Y/M	MCADD	Homozygous c.985A > G	39	3085 g	No	6 D	Breast	No	1	34 M	No	+	
4 Y/F	MCADD	Homozygous c.985A > G	37	2660 g	No	9 D	Breast + formula	No	1	15 M	No	+	
7 Y/F	MCADD	Homozygous c.985A > G	39	2665 g	No	8 D	Breast	No	2	6 M	No	+	
8 Y/F	MCADD	Homozygous c.985A > G	39	3720 g	No	6 D	Breast	No	1	8 M	No	+	
7 Y/F	MCADD	Homozygous c.985A > G	35	2360 g	No	4 D	?	No	2	2 Y	No		+
−/F	MCADD	Homozygous c.985A > G	36	3050 g	No	6 D	Breast	Yes[b]	1	2 M	No		
2 Y/M	MCADD	Homozygous c.985A > G	37	2520 g	No	7 D	Breast	No	1	1 M	No		+
8 Y/M	CPT I	Homozygous c.1456–1458 + 1delG-AGg	39	3840 g	No	4 D	Breast + formula	No	3	2 D	Yes		
4 Y/M	CPT II	c.680C > T; c.1106A > G	39	3295 g	No	6 D	Breast	No	4	6 M	No		
−/F	MADD	c.34 + 5G > C; c.1601C > T	40	?	No	6 D	Breast	?	2	22 M	No	+	
4 Y/M	MADD	c.405 + 3A > T; c.1106C > T	38	2690 g	No	5 D	Breast	No	4	2 D	Yes		
−/M	MADD	–[c]	40	2760 g	Yes	5 D	Breast	No	1	7 D	Yes		

Current age/sex	Clinical manifestations during decompensation									Clinical recovery
	Liver failure	Heart failure	Lethargy	Seizures	Multiple organ failure	Sudden death	Hypoglycemia	Metabolic acidosis	Other	
8 Y/F			+				+		Respiratory infection	+
4 Y/F							+			+
6 Y/M									Hyperuricemia	+
2 Y/F							+		Cyanosis (IVC, PAS)	+
4 Y/M							+	+	Hyperuricemia	+
7 Y/M			+				+			+
7 Y/M							+			+
5 Y/M										+
4 Y/F							+		Hyperuricemia	+

Table 2 (continued)

7 Y/F							+			+
8 Y/F									Hyperammonemia	+
7 Y/F							+		Hypotonia	+
–/F						+				[a]
2 Y/M										+
8 Y/M	+						+		Hyperammonemia	+
4 Y/M	+	+						+	Hyperammonemia	+
–/F							+		Hyperammonemia	[a]
4 Y/M			+					+	Hepatomegaly, fatty liver	+
–/M			+	+	+					[a]

+ complete recovery, *IVC* interventricular communication, *PAS* pulmonary artery stenosis, *NBS* newborn screening

[a] Deceased

[b] Loss more than 10% of birth weight in neonatal period

[c] Molecular study not available

distress was also frequent, and it is usually precipitated by infectious illness or fasting [6, 8]. Acute illnesses have been implicated as triggers of metabolic decompensation by intolerance to prolonged fasting and lack of energy production [17]. In fact, the impaired mitochondrial FAO activity causes a shortage of energy, particularly in circumstances of increased reliance on fatty acids as the main energy substrate, such as during the immediate postnatal period [6, 8]. We noted, like others [16], that in our studied patient group, clinical manifestations during the neonatal period occurred very early, even before the availability of the ENS results, thereby enabling clinical care anticipation.

A high prevalence of the severe genotype (c.985A > G/ c.985A > G), is observed among the MCADD Portuguese population [18]. This is in line with previous reports referred in the literature, especially in symptomatic cases [9, 12, 16, 19, 20]. The residual activity of the *ACADM* gene product and hence its impact on cell metabolism and patient clinical presentation depend on a series of factors, including MCAD protein misfolding, which lead to tetramer instability, and thermosensitivity of the variant protein. Febrile episodes may negatively impact the disease outcome, especially when the mutant protein is thermosensitive, which is the case for the most common MCAD protein variant [20, 21]. Patients with this variant have not only to face increased energy demands but also the sudden lowering of fatty acid oxidation-derived energy production, secondary to a drop in residual MCAD activity. This might explain why one quarter of the patients with classical MCADD do not survive their first life-threatening episode and why it is also related to sudden infant death syndrome [16, 19]. Interestingly, as observed by others [16], the MCADD patient that was found dead in bed during the night, at the age of 2 months, was not gaining sufficient weight being exclusive breastfeeding. Later, the autopsy exam pointed out the occurrence of cardiopulmonary arrest. This is in accordance with the findings of Ahrens-Nicklas and colleagues [16] that 11 (44%) of the exclusive breastfeeding neonates with MCADD had signs of metabolic decompensation during the neonatal period; 4 of them died or survived sudden cardiac arrest, whereas none of the 19 neonates who received formula became ill.

Long-chain FAO disorders showed a higher number of decompensations per patient and, although not statistically significant, poor survival rates when compared to the MCADD group.

Sudden death during sleep was observed in one MADD patient. The exact underlying mechanism to the sudden death is unclear, but as reported already by others, acute arrhythmia may account for these unexplained deaths [5, 8]. There is evidence regarding pro-arrhythmic effects of lipid metabolites, dependent on fatty acid chain length that may account for acute arrhythmias and unexpected deaths [4–6].

In our study, long and medium FAO disorders showed CK-MB mean values above the normal range, during asymptomatic periods, despite a normal routine cardiac evaluation.

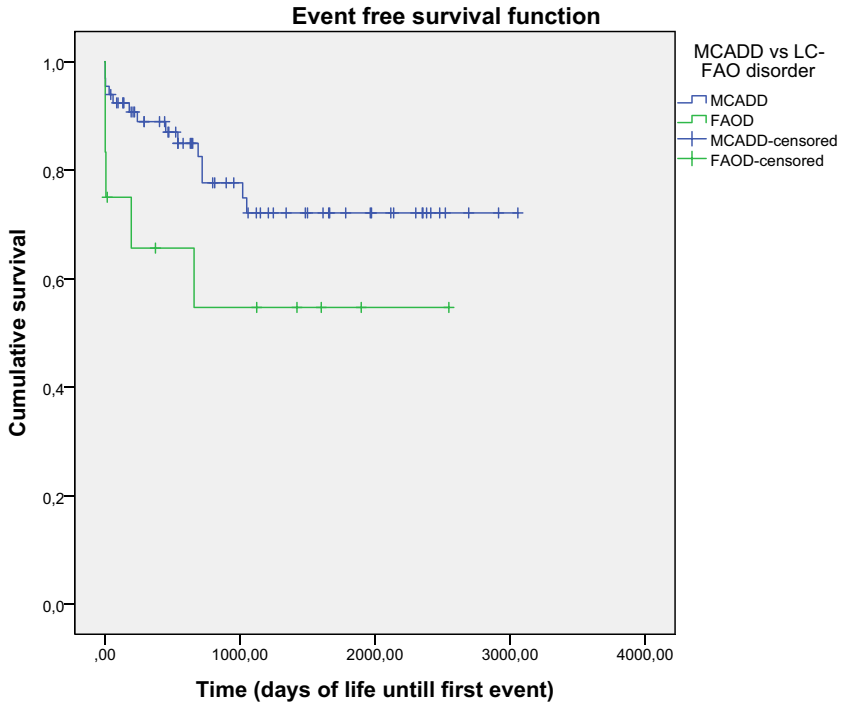

Fig. 1 Event-free survival Kaplan-Maier curve showing the days of life until the first event of metabolic decompensation. Log rank (Mantel Cox) p value 0.101. Long-chain fatty acid disorders group of patients (LC-FAOD) had a higher percentage of decompensation events (42%) compared to medium-chain acyl-CoA deficiency disorders (MCADD) group (21%)

Taking into account mean CK-MB values of each group, LC-FAO disorders displayed CK-MB mean values higher than the MCADD group. To better understand these findings, a further heart evaluation, such as 24 h monitoring of the heart rhythm, may be helpful.

Several studies show that early identification of FAO disorders, through neonatal screening, reduces the incidence of severe metabolic crisis and death since treatment focuses on avoiding periods of fasting, preventing hypoketotic hypoglycemia episodes [9, 10, 14, 17, 22, 23]. Nevertheless, in our population of patients, and as reported by others [16, 24], acute manifestations in the newborn period occurred very early and sudden deaths were not avoided by starting treatment precociously.

In summary, early identification of FAO disorders through ENS is an important tool for anticipating the treatment of these diseases, although in some cases, it was not sufficient to prevent very early and severe manifestations. It is important to alert the clinicians that take care of newborn infants for the precocious manifestations of FAO disorders. Regardless of the highly prevalent classic homozygous MCADD genotype (c.985A > G), there was a huge diversity of clinical manifestations, with a high percentage of asymptomatic patients and a poor outcome in some patients. Febrile episodes and poor weight gain are important factors that may negatively impact the disease outcome. The long-chain FAO disorder group of patients had higher number of decompensations, higher CK-MB levels during asymptomatic periods, and although not statistically significant, poor survival outcome. More studies are needed to better understand the pathophysiology of these diseases and the underlying mechanisms of clinical decompensations, in order to develop better biomarkers that can help us to identify patients at risk for acute decompensation and also develop more efficacious treatments that can improve the outcome of these patients.

Authors' Contributions The planning, carrying out, and reporting of the work was done by Patrícia Janeiro with guidance from Isabel Tavares de Almeida. Rita Jotta had a major contribution in data collection. Ruben Ramos and Fátima Ventura contributed with biochemical and molecular studies. Laura Vilarinho provided neonatal screening data. Ana Gaspar provided clinical outcome data and contributed in the article review process.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, formal consent is not required.

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