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3 Tables, 1 Figure + 2 supplementary tables.

Keywords

Triheptanoin; LC-FAOD; metabolic disorder

Abstract

Introduction: Triheptanoin provides long-chain fatty acid oxidation disorder (LC-FAOD) patients with an alternative to medium-even-chain triglycerides therapy.

Material-methods: Retrospective analysis of 18 French LC-FAOD patients benefiting from early access to triheptanoin treatment.

Results: Eight female and 10 male patients with LC-FAOD (VLCAD, LCHAD, CACT, CPTII and MTP) were treated with triheptanoin for a median duration of 22 months (range: 9–228 months). At last consultation, triheptanoin accounted for 15–35% of their daily caloric intake. In the year following the introduction of triheptanoin, patients reported a reduction of intermittent snacking and nocturnal meals. Three patients, including 1 adult, became free of severe hypoglycaemic events. Ten of 12 paediatric patients and 4 of 6 adult patients reported reduced fatigue with reductions in the number and severity of episodes of myalgia. Of 6 patients, including 1 adult, that had required the use of a wheelchair in the year prior to triheptanoin, all but one no longer required its use. The number of emergency hospitalizations decreased, and none were recorded for paediatric patients during these 12 months. Cumulative annual days of emergency domiciliary care were reduced from 286 to 51 days in the year before and after initiation, respectively, and 13 patients required no such interventions. Adverse events were limited to digestive issues that dissipated over time.

Conclusions: Our case-series suggests that long-term treatment of LC-FAOD paediatric and adult patients with triheptanoin is safe and leads to marked improvement of symptoms and an improved quality of life.

Synopsis

This case series documents the successful long-term use of triheptanoin therapy for the treatment of 18 French LC-FAOD patients.

1. Introduction

Long-chain fatty acid (LC-FA) oxidation into medium- and short-chain intermediates provides cells an alternative source of reducing equivalents produced during times of fasting and physiologic stress to allow synthesis of adenosine triphosphate (ATP) by oxidative phosphorylation. A group of autosomal recessive metabolic diseases, LC-FA oxidation disorders (LC-FAOD), disrupt these processes, provoking acute cellular energy deficits (Knottnerus et al 2018). While LC-FAOD may be classified by genotype (Longo et al 2016; Knottnerus et al 2018), clinical manifestations vary in severity and age of onset among patients of each subtype. Presentation in neonates or infants may include cardiomyopathy, hepatic encephalopathy or severe hypoketotic-hypoglycaemia that require urgent care and may lead to sudden death (Spiekerkoetter et al 2009). Similar symptoms may be triggered in late-onset cases by stresses including fever, fasting or prolonged physical exertion, along with myalgia and during severe episodes, rhabdomyolysis (Knottnerus et al 2018). Peripheral neuropathy and retinopathy may occur in some subtypes (Merritt et al 2018).

Both paediatric and adult LC-FAOD patients suffer from severe energy deficiency and life-threatening acute episodes of metabolic decompensation, leading to premature mortality or frequent hospitalizations and a substantial, lifelong impact on daily function. Mitochondrial dysfunction results in a heterogeneous set of clinical manifestations that primarily affect systems reliant upon fatty acid oxidation as an energy source, in particular the heart, skeletal muscle and liver (Wajner and Amaral 2015). Prognosis for patients presenting symptoms at an early age is poor, reports of premature mortality range from 60 to 90% (Baruteau et al 2014). In a 107 patient series, mortality ranged from 30% (first week of life mortality) to 69% (<1-year mortality) (Baruteau et al 2014). Even with careful management, including avoiding fasting and a low fat-high carbohydrate diet, a medium-even-chain triglycerides (MCT) rich diet, or a combination of these, patients continue to suffer from cardiomyopathy, hypoglycaemia, liver disease, rhabdomyolysis, exercise intolerance, and muscle weakness (Vockley et al. 2020; Roe et al. 2016). Likewise, conventional diet therapy has not reduced mortality for LC-FAOD patients (Spiekerkoetter et al. 2009, Saudubray et al. 1999, Baruteau et al 2013).

At present, most LC-FAOD complications are surmised to be due to a paucity of Krebs cycle intermediates compromising ATP production. Beyond diet modifications, LC-FAOD can be effectively and safely treated with an anaplerotic drug such as triheptanoin, that was associated with a reduction in chronic cardiomyopathy, rhabdomyolysis and muscle weakness in patients (Roe et al 2002). Upon ingestion, triheptanoin is rapidly metabolized into a 7-carbon heptanoate, capable of diffusing directly into cells and across the mitochondrial membrane and provides both acetyl-CoA and propionyl-CoA. Propionyl-CoA is converted to succinyl-CoA, an intermediate of the Krebs cycle, and thus increases the intermediate pool size (Roe and Mochel 2006).

Studies have described LC-FAOD treatment using a highly purified triheptanoin (Vockley et al 2015; Vockley et al 2016; Vockley et al 2017), and it has been shown to be superior to even-chained medium-length triglycerides in a randomized controlled trial (Gillingham et al 2017). In a single-arm Phase 2 study, 29 patients received triheptanoin as a replacement for 25-35% of their daily calory intake (DCI) for a period of 78 weeks: hospitalization events were reduced for these patients (Vockley et al 2018). Most recently, long-term use of triheptanion has been found to be well supported in a group of American patients (Vockley et al 2020).

Here, we report a retrospective case series of 18 FAOD patients with 5 different genotypic diagnoses and variable age of onset, disrupting carnitine transport or mitochondrial LC-FA oxidation, all benefiting from the French early access program for treatment with triheptanoin.

2. Materials and methods

Triheptanoin received a temporary authorization for use ("ATU" or early access program) in France, in September 2018. This retrospective case series presents observational data of 18 patients benefiting from this ATU, collected in December 2019. Access to the ATU was reviewed by the French national authorities (Agence Nationale de Sécurité du Médicament et des produits de santé – ANSM) separately for each patient, with ongoing treatment subject to a review of patient progress every 3months in December 2019 were included in this case series.

All procedures followed were in accordance with the ethical standards described in the 1975 Helsinki Declaration, revised in 2000. All patients provided verbal informed consent to their physician, permitting anonymous data from their medical history to be published as part of this report, as per local legislation. Local ethics committee approval of the retrospective analysis of these data was obtained.

Patient heights and weights were monitored and compared to local growth charts, noting the number of standard deviations (or Z-score) from the national norms. The median, mean and standard deviation (SD) are presented for certain measures, (e.g., annual counts of emergency hospitalisations). For myalgia, each patient's physician provided a subjective score of 0 (no symptoms) to 3 (severe symptoms).

3. Results

Table 1 lists the characteristics of the 18 LC-FAOD patients, 8 females and 10 males. These included 5 cases of very long-chain acyl-CoA dehydrogenase deficiency (VLCAD), 5 long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD), 3 carnitine-acylcarnitine translocase (CACT), 3 carnitine palmitoyl transferase II (CPTII), and 2 mitochondrial trifunctional protein (MTP) deficiency cases.

3.1 Initial presentation

Neonatal manifestations were recorded for 9 patients, symptoms included hypotonia (8 patients), hepatic alterations (8 patients), malaise and consciousness disturbances (8 patients) leading to coma for 2 patients, cardiac arrhythmias with bradycardia and supraventricular tachycardia (8 patients), renal insufficiency (3 patients) and hypothermia (3 patients). Biological abnormalities included elevated creatine kinase (CK) levels (7 patients), metabolic acidosis with hyperammonaemia (7 patients), hyperlactatemia (6 patients), hypoglycaemia (6 patients), hypocalcaemia and hyperkalaemia (both in 5 patients). All patients with neonatal manifestations were diagnosed during their first week of life, with the exception of one whose initial symptoms were less severe (malaise at 2 days) and was diagnosed 2 months later (outlined in Table 1).

The initial symptoms in the 5 infants (1 month–2 years) were cardiomyopathy (2 patients), exercise intolerance with recurrent rhabdomyolysis (2 patients), hypotonia (2 patients), feeding difficulties with failure to thrive (1 patient), recurrent malaise (1 patient), hypoglycaemic coma (1 patient), neuropathy and retinopathy (1 patient). Biological symptoms included hypoglycaemia (4 patients), hepatic disorders (3 patients), elevated CK (2 patients), hyperlactatemia (2 patients), and hyperammonaemia (1 patient).

Among the 3 patients who presented their first symptoms as children (2–12 years), 2 presented with exercise intolerance and elevated CK, associated in 1 case with neuropathy and retinopathy, and the third presented with isolated retinopathy during childhood. In these children, biological status was normal except for elevated CK after exercise in 2 patients. Diagnosis of MTP deficiency was made for 1 patient during adolescence, diagnosis of LCHAD was made during adulthood following signs of cardiomyopathy in 1 case, and during childhood following rhabdomyolysis in the other.

One patient presented with exercise intolerance and rhabdomyolysis crisis as an adolescent and was diagnosed with VLCAD deficiency as an adult, following signs of cardiomyopathy.

3.2 MCT supplementation

With the exception of 1 patient who was treated directly with triheptanoin, all other cases of neonatal onset were treated with MCT supplementation and nocturnal feeding during 23–204 months (median: 126 months) following diagnosis. All patients diagnosed during infancy and childhood received MCT supplementation (range: 9–176 months, median: 120 months), while among the 3 patients diagnosed as teens or adults, all were treated for less than 1 year (2.5–8 months). Prior to triheptanoin therapy, the dose of MCT ranged from 0.2–2.6 g/kg/day, or 6–42% of DCI.

3.3 Triheptanoin treatment and safety

Tables 2 and 3, as well as Supplementary Tables 1 and 2 all show patients grouped by their age at initiation of triheptanoin, which included 1 neonate, 1 infant, 6 children, 4 adolescents and 6 adults. Patients received a median of 22 months of triheptanoin treatment (n=18, range: 9–228 months, Supplementary Table 1). Other concomitant treatments are shown in Supplementary Table 2. Triheptanoin doses is described at 3 time points: at initiation, at 1 year of treatment, and at the last recorded consultation (Supplementary Table 1). Although triheptanoin was generally well tolerated, dose adjustments over the course of treatment were made. For 2 patients, t-his was linked to management of the most commonly recorded adverse effects for two patients, which included transitory diarrhoea or loose stools and abdominal pain. All of the patients have been able to continue triheptanoin treatment to date, free of gastrointestinal complaints.

At the last recorded consultation, median dosages of triheptanoin were 1.05 g/kg/day and 21% DCI (range: 0.78–1.7 g/kg/day, 15–25% DCI) for children (n=6), 1.08 g/kg/day and 27% DCI (range: 0.96–1.5 g/kg/day, 22–32% DCI) for adolescents (n=4), and 1.08 g/kg/day and 25.5% DCI (range: 0.77–1.5 g/kg/day, 25–35% DCI) for adults (n=6).

As patients adjusted to their new dietary regimen, 2 aged between 12–18 years reported improvement in appetite and a reduced need for intermittent snacking. Of the 9 patients who required enteral/nocturnal feeding prior to initiating triheptanoin treatment, 1 patient who had initiated treatment at 17 years of age, no longer required enteral/nocturnal feeding the following year. An adult patient with low BMI reported gaining weight (from 47 to 54 kg, height 163 cm) and a reduction in gastrointestinal complaints. The weight and height of all patients were compared to the standard growth charts for the French population to follow this evolution (Supplementary Table 1; National (Auxologie).

3.3.1 Muscular symptomatology

In the year following the introduction of triheptanoin, 10 of 12 paediatric patients and 4 of 6 adult patients reported a marked reduction in fatigue and weakness, leading to improved activity levels. The intensity of myalgia also decreased for 8 of the 12 paediatric patients and 3 of the 6 adult patients (Table 2). Compared to the year before, the median score of myalgia intensity from 2 to 1 in the year after triheptanoin initiation (Figure 1a). It should also be noted that among those patients that reported ongoing myalgia, in at least 3 cases these episodes were transient and occurred following increased physical activity that would otherwise not have been feasible prior to treatment.

Episodes of rhabdomyolysis reduced for 8 of the 12 paediatric patients and for 3 adult patients (Table 2, Figure 1b; mean: 2.59 *vs* 1.22; median: 2 *vs* 1; ranges: [0–8] *vs* [0–5]; for the years before and after triheptanoin initiation, respectively). Lower peak CK levels during rhabdomyolysis were observed in 6 patients (data not shown). Most strikingly, of 6 patients, including 1 adult, that had required the use of a wheelchair in the year prior to triheptanoin initiation, all but one no longer require its use.

3.3.2 Liver and hypoglycaemia symptoms

Three patients, including 1 adult, had reported severe hypoglycaemic events during the year prior to receiving triheptanoin; no such events were reported during the year following triheptanoin initiation. The patient with 5 severe Reye-like syndrome decompensations during the year prior to triheptanoin presented only 1 mild episode during the year following triheptanoin initiation.

3.3.3 Emergency hospitalizations and home care

During the year before the introduction of triheptanoin, patients had a mean of 1.12 (SD: 1.50) emergency hospital care visits (median: 1; range [0–5]). This diminished during both the first (mean: 0.17; SD: 0.38; median: 0; range: [0–1] and second years following triheptanoin initiation (Table 3; Figure 1c). Moreover, for paediatric patients such hospitalizations were altogether eliminated after the introduction of triheptanoin.

The cumulative annual number of days of emergency home care was reduced from a total of 286 days to 51 days, post-triheptanoin (Table 3; Figure 1d). The mean number of emergency home care events diminished from 16.82 (SD: 30.60; median: 1; range [0–104]) during the year prior to treatment to 2.83 (SD: 5.97; median: 0; range [0–24]) and 0.81 (SD: 1.64; median: 0; range [0–5]) during each year following triheptanoin initiation. Among individual patients, a reduction or complete absence of such interventions was observed for 6 children, 3 adolescents and 4 adults.

3.3.4 Cardiac symptoms

One adult patient was diagnosed with LCHAD following cardiac decompensation. Exams revealed an aggravation of a restrictive and dilated hypokinetic heart disease (left ventricle at the limit of hypertrophy, with an ejection fraction of 27%). After adjusting the patient's cardiac medications (Supplementary Table 2) and the initiation of triheptanoin and 3-hydroxybutyrate, the patient's clinical presentation was objectively improved: the left ventricular ejection fraction was 45%. Due to this, planning for heart transplantation was suspended.

3.3.5 Quality of Life

After 1 year, 8 out of 12 paediatric patients and 3 out 6 adult patients reported a marked improvement in academic or professional activity. A reduction in absenteeism allowed them to participate more fully in these activities. A majority of paediatric patients (10/12) reported improved physical activity, which included participation in social activities and sport. Four out of 6 patients aged 2–12 years achieved a significant change from being physically inactive to being able to run, cycle, skate and swim, with 1 patient commenting that her 'life had changed' since undertaking the treatment. Similar reactions to the treatment were recorded for all 4 adolescent patients (12–18 years) whose reports at their last consultation included mention of being able to dance, cycle, play football and swim compared to having been physically inactive prior to triheptanoin initiation. Among 6 adult patients, 3 reported improvement in activity, with 2 patients being able to achieve autonomy in their daily life. The patient that had been envisaged for heart transplantation was able to return to work.

4. Discussion

In our group of 18 French LC-FAOD patients, with 5 different LC-FAOD, all benefited from triheptanoin therapy. Benefits included striking reductions in fatigue and weakness, myalgia, episodes of rhabdomyolysis, episodes of hypoglycaemia, days of emergency hospitalizations, together with marked improvements in academic or professional activity.

Triheptanoin was introduced gradually to limit digestive difficulties, which appear to have dissipated over time. At initiation, triheptanoin provided patients on average with 18% DCI, in line with the mean 16% DCI observed during the 16-week study of Gillingham *et al.* (Gillingham et al 2017). Over time, patients spontaneously adjusted their dietary intake in line with their treatment, and the urge to eat between meals diminished. Adolescent patients, in particular, ate less frequently at night, reporting that they were no longer awakened by hunger. As overall caloric intake was reduced while triheptanoin doses were maintained stable, the mean last reported dose increased to 24% DCI. Although this is less than the 27.5% and 30% mean DCI observed in 2 longer term studies conducted in the USA (Vockley et al 2017; Vockley et al 2018), the majority of patients nonetheless received the recommended dose (25–35% DCI).

Having established triheptanoin as the cornerstone of their diet, clear clinical benefits were observed as patients required fewer days of emergency care. This had a further impact on their quality of life; those who initiated treatment during childhood (2–12 years old) all improved attendance at school, or were able to participate in a wider range of activities. Among the 4 patients who initiated treatment as adolescents, all benefited from increased mobility or capacity for physical activity. This translated into an improved social life, with 1 patient able to undertake a professional internship, and another adolescent now envisaging pursuing a university education. These results are consistent with a series of 20 patients with various LC-FAOD treated with triheptanoin, as part of a compassionate use protocol, who experienced a significant reduction (67%) in mean hospital days per year (Vockley et al 2017; Vockley et al 2018) as well as a recently published retrospective study in 12 LC-FAOD children (Zoggeler et al 2021). Triheptanoin was also associated with the near elimination of hospitalizations for hypoglycaemic events and a reduction in hypoglycaemia event rates (Vockley et al 2017; Vockley et al 2018).

Overall, muscular symptoms were a large part of the clinical presentation of LC-FAOD in this group of patients. Every incident of myalgia and rhabdomyolysis was counted and presented herein, but a broader qualitative view of the patients' increased capabilities must also be taken when interpreting these data. One individual, patient 14, did indeed suffer an additional episode of rhabdomyolysis in the year following triheptanoin initiation. However, this patient benefited from a great improvement in quality of life and was able to eventually return to full time employment, walking to her workplace. Another individual, patient 10, continues to use a wheelchair, but its use is limited to occasions when a great deal of walking would be required. Two adolescents are now able to regularly participate in sport, with patient 9 training with a competitive football club for 2 hours at a time, 4 times per week, and patient 10 cycling regularly. In general, as individuals improved, they undertook more physical activity which in some cases led to incidents of myalgia, however such episodes were less severe and of a shorter duration than those experienced during the year prior. Notably, the only patient from our series presenting with a cardiomyopathy also improved with triheptanoin. This is in line with a case series of 10 patients with LC-FAOD and acute heart failure for whom triheptanoin led to normal ejection fractions within 3 weeks of initiation (Vockley et al. 2016). Furthermore, our series included 3 CACT patients, all of whom presented symptoms as neonates but are surviving to this day, with 1 patient now over 12 years of age. This is in sharp contrast with the 14 CACT patients described in (Baruteau et al 2013) who experienced a 92% mortality rate under conventional diet therapy (patient ages unknown).

5. Conclusions

Despite its retrospective nature, our case series supports previously published studies by providing further evidence of long-term treatment of LC-FAOD with triheptanoin. Both paediatric and adult patients supported triheptanoin treatment well, and it has led to marked improvements of symptoms, disabilities and quality of life.

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Figure legend

Figure 1: (a) Median myalgia scores for patients the year before and year after triheptanoin initiation; (b) mean (blue) and median (orange) annual number of rhabdomyolysis episodes for patients before and after triheptanoin initiation. (c) Line graphs depicting mean annual emergency hospitalizations for each patient for the year before and for the two years after initiation. (d) Line graph visualizing the annual number of days of emergency home care for each patient (d). The line colour corresponds to the genetic form of LC-FAOD (legend top right).

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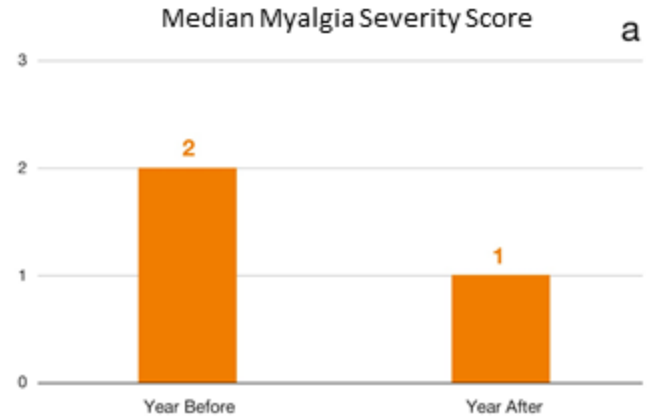
Median Myalgia Severity Score
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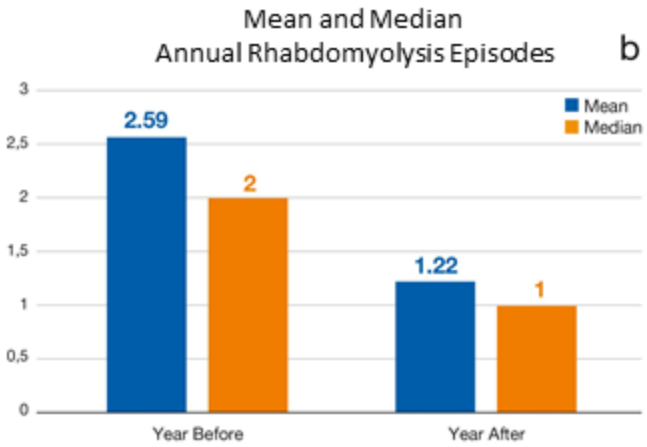
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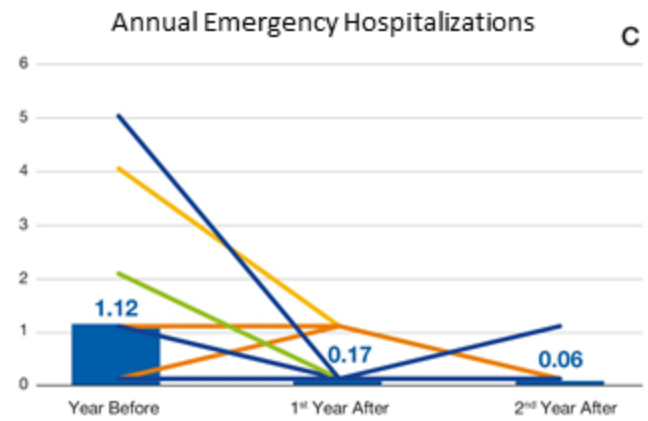
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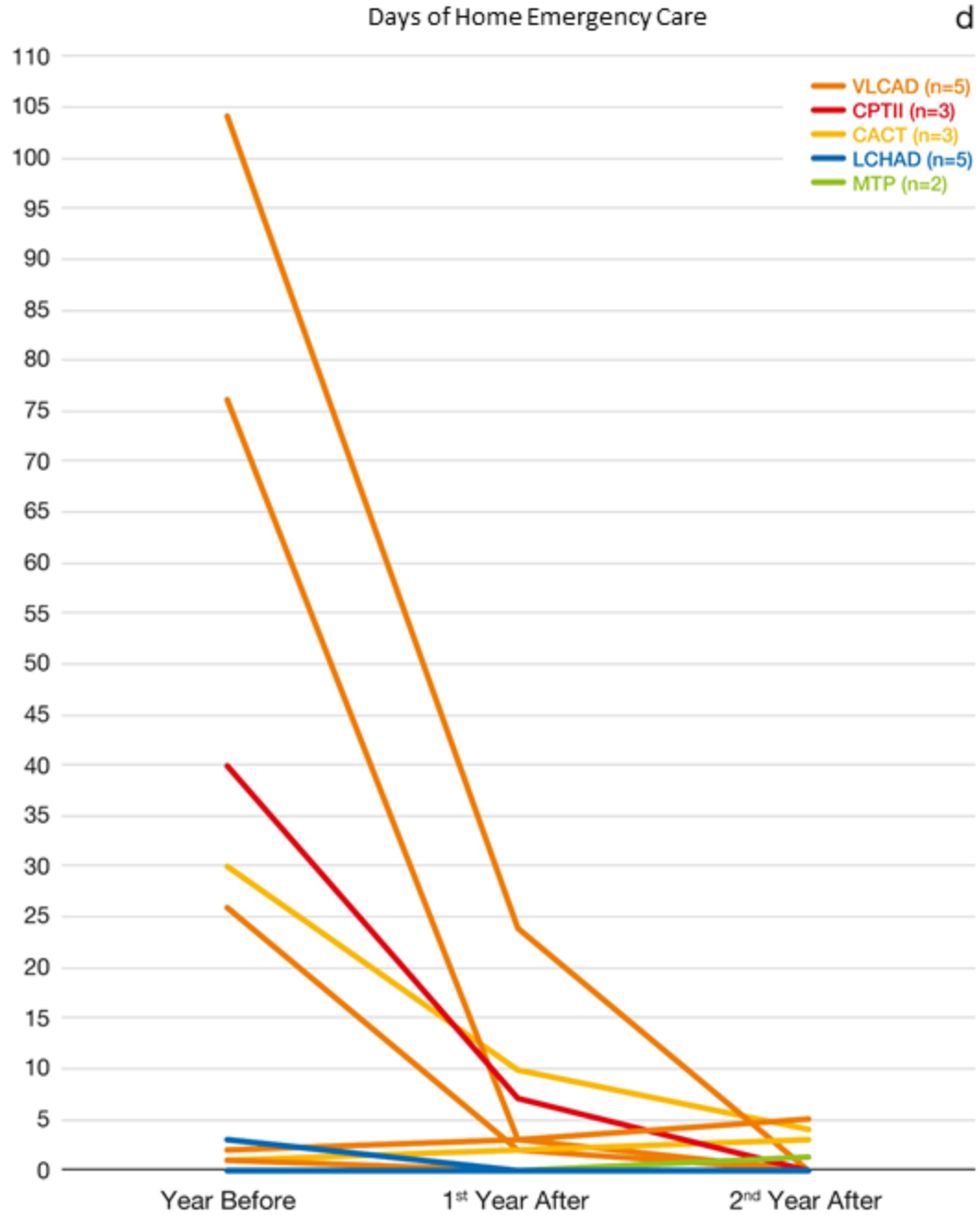
Days of Home Emergency Care
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VLCAD (n=5)
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CACT (n=3)
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Table 1 - Characteristics of patients at initiation of triheptanoin

Case	Sex	Deficit type	Gene (gene locus)	Nucleotide change (protein change)	Age at initial presentation	Age at diagnosis	Initial presentation at diagnosis	Prior MCT treatment duration (months)
1	M	CPTII	*CPT2* (NM_000098)	c.452G>A / c.233+2T>A (p.Arg151Gln / p.?*)	Neonate	Neonate	Malaise with hypoglycaemia, followed by cardiac arrhythmia, hepatocellular insufficiency with cytolysis, renal failure, metabolic acidosis, hyperammonaemia, elevated CK.	0
2	M	CACT	*SLC25A20* (NM_000387)	c.110G>C / c.110G>C (p.Arg37Pro / p.Arg37Pro)	Neonate	Neonate	Hypotonia, convulsions, coma, hyperammonaemia, hepatocellular insufficiency.	23
3	M	CACT	*SLC25A20* (NM_000387)	c.327_417del/ c.327_417del (p.Ser109Argfs*50 / p.Ser109Argfs*50)	Neonate	Neonate	Cardiac arrest, arrhythmia, coma, convulsions, cytolysis, hypotonia, metabolic acidosis, hyperammonaemia, hypocalcaemia, hyperkalaemia, renal failure, hyperlactatemia, elevated CK.	32
4	M	CACT	*SLC25A20* (NM_000387)	c.533G>A / c.533G>A (p.Arg178Gln / p.Arg178Gln)	Neonate	Neonate	Malaise with hypoglycaemia, hypotonia followed by cardiac arrhythmia, cardiac arrest, hepatomegaly, hepatocellular insufficiency, hyperammonaemia,	132

							hypocalcaemia, hyperkalaemia, hyperlactacidaemia, elevated CK.	
5	M	VLCAD	*ACADVL* (NM_000018)	c.541C>T / c.541C>T (p.His181Tyr / p.His181Tyr)	Neonate	Neonate	Hypotonia, elevated CK, also of note: the death of an elder brother (malaise, cardia arrhythmia).	126
6	F	VLCAD	*ACADVL* (NM_000018)	c.364A>G / c.1616C>A (p.Asn122Asp / p.Ala539Asp)	Neonate	Neonate	Hypoglycaemia followed by hypotonia and cardiac arrhythmia, hyperammonaemia, hypocalcaemia, hyperkalaemia, renal failure, cytolysis, hyperlactatemia, elevated CK.	108
7	F	VLCAD	*ACADVL* (NM_000018)	c.541C>T / c.541C>T (p.His181Tyr / p.His181Tyr)	Neonate	Neonate	Feeding difficulties, hypotonia, malaise with hypoglycaemia, then cardiac arrhythmia, convulsions, hepatocellular insufficiency with cytolysis, metabolic acidosis, hyperammonaemia, hypocalcaemia, hyperkalaemia, hyperlactatemia, elevated CK.	132
8	F	CPTII	*CPT2* (NM_000098)	c.1301T>C / c.1301T>C (p.Phe434Ser / p.Phe434Ser)	Neonate	1m - 2 years	Malaises with hypotonia then cardiac arrhythmia, hypothermia, hepatic cytolysis, elevated CK; also of note, a brother's sudden death, unexplained at 4 months old.	120
9	M	VLCAD	*ACADVL* (NM_000018)	c.899T>C / c.899T>C (p.Met300Thr / p.Met300Thr)	1m - 2 years	2 - 12 years	Hypotonia at 9 months old, then 3 episodes of malaises with	36

							somnolence (aged 1-4 years), hypoglycaemia, hepatic cytolysis, vomiting, followed by the development of exercise intolerance with myalgia, asthenia, elevated CK.	
10	M	LCHAD	*HADHA* (NM_000182)	c.1528G>C / c.1528G>C (p.Glu510Gln / p.Glu510Gln)	1m - 2 years	1m - 2 years	Feeding difficulties with failure to thrive, hypotonia, hepatomegaly, hypertrophic cardiomyopathy, hypoglycaemia, hepatic cytolysis, anaemia, hyperlactatemia.	176
11	M	CPTII	*CPT2* (NM_000098)	c.1511C>T / c.1547T>C (p.Pro504Leu / p.Phe516Ser)	Neonate	Neonate	Malaises with hypoglycaemia, followed by cardiac arrhythmia and 2 cardiac arrests, cardiomegaly, hepatic insufficiency with cytolysis, hypotonia, hyperammonaemia, hypocalcaemia, hyperkalaemia, hyperlactacidemia.	204
12	M	LCHAD	*HADHA* (NM_000182)	c.1058_1059delinsT / c.1528G>C (p.Lys353Ilefs*19 / p.Glu510Gln)	1m - 2 years	2 - 12 years	Hypoglycaemic episodes, peripheral neuropathy, retinopathy, exercise intolerance with rhabdomyolysis episodes, elevated CK.	9
13	F	MTP	*HADHB* (NM_000183)	c.1165A>G / c.1165A>G (p.Asn389Asp / p.Asn389Asp)	1m - 2 years	1m - 2 years	Persistent diarrhoea, hepatomegaly, hepatocellular insufficiency, myalgia with	120

							rhabdomyolysis episodes, elevated CK.	
14	F	VLCAD	*ACADVL* (NM_000018)	c.399del / c.1838G>A (p.Trp133Cysfs*84/ p.Arg613Gln)	12-18 years	≥18 years	Exercise intolerance with rhabdomyolysis episodes, elevated CK.	8
15	F	MTP	*HADHB* (NM_000183)	c.575_676del102 / c.575_676del102 (p.Met192_Ser226delinsThr/ p.Met192_Ser226delinsThr)	2 - 12 years	12 - 18 years	Exercise intolerance with rhabdomyolysis episodes and elevated CK, peripheral neuropathy.	6
16	F	LCHAD	*HADHA* (NM_000182)	c.1195C>T / c.1528G>C (p.Arg399X / p.Glu510Gln)	1m - 2 years	1m - 2 years	Coma, hypoglycaemia, hyperammonaemia, hyperlactatemia, followed by cardiomyopathy.	>144
17	M	LCHAD	*HADHA* (NM_000182)	c.1108G>A / c.1528G>C (p.Gly370Arg / p.Glu510Gln)	2 - 12 years	≥18 years	Retinopathy during childhood, cardiac failure as an adult.	2.5
18	F	LCHAD	*HADHA* (NM_000182)	c.914T>A / c.1528G>C (p.Ile305Asn / p.Glu510Gln)	2 - 12 years	2 - 12 years	Asthenia, myalgia and rhabdomyolysis episodes, elevated CK.	84

*Splice mutation

Table 2 - Myalgia symptoms and rhabdomyolysis episodes before and after triheptanoin

		Myalgia		**Rhabdomyolysis episodes**	
Patient	**Age at triheptanoin initiation**	**Year before triheptanoin**	**First year on Triheptanoin**	**Year before triheptanoin**	**First year on Triheptanoin**
1	Neonate	NA	0	NA	0
2	1m - 2 years	0	0	0	1
3	2 - 12 years	0	0	5	1
4	2 - 12 years	3	1	1	0
5	2 - 12 years	3	2	3	2
6	2 - 12 years	3	2	6	4
7	2 - 12 years	3	2	6	2
8	2 - 12 years	3	2	3	1
9	12 - 18 years	2	0	1	1
10	12 - 18 years	3	0	2	0
11	12 - 18 years	3	2	8	5
12*	12 - 18 years	1	1	1	2
13	≥18 years	2	1	3	0
14*	≥18 years	3	1	2[&]	3[&]
15*	≥18 years	1	1	1	0
16	≥18 years	2	0	2	0
17*	≥18 years	0	0	0	0
18	≥18 years	1	2	0	0
Mean		-	-	2.59	1.22
Median		2	1	2	1
SD		-	-	2.37	1.52

NA: not applicable, patient had no prior MCT treatment, receiving triheptanoin as a neonate.
SD: Standard Deviation
*: patient received less than 1 year of MCT treatment prior to triheptanoin
[&] mild episodes while being treated with triheptanoin in the context of marked increased physical activity compared to 2 severe episodes in the context of minimal activity the year prior to triheptanoin

Table 3 - Description of hospitalization and emergency home care

Patient #	**Age at triheptanoin initiation**	**Hospitalizations linked to an acute episode of the disease**			**Number of days under emergency home care**		
		Year before triheptanoin	1st year on triheptanoin	During last 1 year on triheptanoin	Year before triheptanoin	1st year on triheptanoin	During last 1 year on triheptanoin
1	Neonate	NA	0	0	NA	0	0
2	1m - 2 years	4	1	0	0	0	0
3	2 - 12 years	2	0	0	30	10	4
4	2 - 12 years	0	0	0	0	0	0
5	2 - 12 years	1	1	0	76	3	0
6	2 - 12 years	2	0	0	104	24	0
7	2 - 12 years	1	0	0	26	2	0
8	2 - 12 years	1	0	0	1	2	3
9	12 - 18 years	0	1	NA	1	0	NA
10	12 - 18 years	0	0	NA	0	0	NA
11	12 - 18 years	0	0	0	40	7	0
12	12 - 18 years	1	0	0	0	0	0
13	≥18 years	2	0	0	3	0	0
14	≥18 years	0	0	0	2	3[&]	5[&]
15	≥18 years	0	0	0	0	0	1
16	≥18 years	5	0	0	3	0	0
17	≥18 years	0	0	1	0	0	0
18	≥18 years	0	0	0	0	0	0
Mean		1.12	0.17	0.06	16.82	2.83	0.81
Median		1	0	0	1	0	0
SD		1.50	0.38	0.25	30.60	5.97	1.64

[&] mild episodes in the context of marked increased physical activity
SD: Standard Deviation
NA: Not available