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Qualitative evaluation of the symptoms and quality of life impacts of long-chain fatty acid oxidation disorders

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Abstract

Background: Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of rare autosomal-recessive genetic disorders characterized by metabolic deficiencies in which the body is unable to convert long-chain fatty acids into energy. To date, however, there is limited understanding of the patient experience of LC-FAOD.

Methods: The symptoms, observable signs, and quality of life (QoL) impacts associated with LC-FAOD were explored via a focus group ($n = 8$) and semi-structured interviews ($n = 6$) with patients and caregivers of patients with LC-FAOD, and interviews ($n = 4$) with expert clinicians. Data were analyzed via thematic analysis and summarized in a conceptual model.

Results: Participants reported a wide range of signs and symptoms associated with LC-FAOD, broadly categorized as musculoskeletal, endocrine/nutritional/metabolic, neurological, gastrointestinal/digestive, sensory, cardiovascular, respiratory, urological, and constitutional. LC-FAOD were reported to have a significant impact on various aspects of patients' lives including physical functioning, participation in daily activities, emotional/psychological wellbeing, and social functioning. Lifestyle modifications (such as diet and exercise restrictions) were necessary because of the condition. Symptoms were typically episodic in presentation often arising or exacerbated during catabolic conditions such as prolonged exercise, fasting, physiological stress, and illness/infection. Symptoms were also commonly reported to lead to emergency room visits, hospitalization, and clinical complications.

Conclusion: LC-FAOD have a considerable impact on patients' lives. There is a high degree of concordance in the signs, symptoms, and impacts of LC-FAOD reported by patients, caregivers, and clinicians; however, there were many symptoms and impacts that were only reported by patients and caregivers, thus demonstrating that insights from patient/caregiver experience data are integral for informing medical product development and facilitating patient-centered care.

Keywords: long-chain-fatty acid oxidation disorders, multi-method, multi-perspective, patient experience, qualitative, quality of life, symptoms

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Introduction

Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of rare autosomal recessive genetic disorders characterized by metabolic deficiencies in which the body is unable to convert fatty acids into energy. Historically diagnosed any time from infancy through to adulthood,[1] the introduction of newborn screening (NBS) programs in the 1990s has led to earlier identification, diagnosis, and treatment of LC-FAOD.[2–4] The estimated combined incidence of all FAOD is 1:9,300 births based on NBS in the United

States (US), Australia, and Germany, with lower rates in individual LC-FAOD types (1:85,000–200,000).[5] The most common LC-FAOD types include long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD), very-long-chain acyl-CoA dehydrogenase (VLCAD), carnitine palmitoyltransferase 2 (or CPT-II), and trifunctional protein (TFP) deficiencies. Carnitine palmitoyltransferase 1 (CPT-I) and carnitine-acylcarnitine translocase (CACT) are less common.

LC-FAOD are characterized clinically by episodic crises of metabolism and severe energy deficiency, particularly during (but not limited to) periods of exercise, fasting, physiological stress, or illness/infection. Clinical presentations of LC-FAOD include involvement of the liver, skeletal muscle, and/or heart with key signs and symptoms across types including rhabdomyolysis, muscle pain and weakness, hypotonia, hypoglycemia, cardiomyopathy, exercise intolerance, and fatigue.[1,6,7] The pattern and severity of organ involvement is typically unpredictable.[8–11] Symptom presentation is often punctuated by episodes of acute, life-threatening, unpredictable, and precipitous decompensation, regardless of current disease status, age, or type, and can have a detrimental impact on patients' quality of life (QoL).[12]

Traditionally, management of LC-FAOD includes the avoidance of fasting and the use of low-fat/high carbohydrate diets, carnitine supplementation, and/or medium-chain triglyceride oil.[13–17] However, even with compliance rates of $> 80\%$,[15,18] dietary management and supplementation is only partially successful in alleviating the symptoms of LC-FAOD; thus, the impact and burden of disease is persistent.

Triheptanoin (Dojolvi™), an odd carbon, medium-chain triglyceride is the first and only treatment for LC-FAOD approved in the US, Canada, and Brazil (between June 2020 and August 2021).[19–24] While the new treatment could help reduce the frequency and duration of hospitalizations and major metabolic and decompensation clinical events, as well as improve exercise endurance and tolerance for pediatric and adult patients,[25,26] clinical data regarding its longitudinal effects on symptoms, QoL, morbidities, and overall mortality is unknown.

Many of the features of LC-FAOD are often clinician-read signs, symptoms, and complications (e.g. rhabdomyolysis, hypoglycemia, and cardiomyopathy).[11,27,28] As experts in their disease, there is increasing recognition of the value of patient experience data among stakeholders such as clinicians, pharmaceutical companies, researchers, and regulators for facilitating the understanding of a disease, condition, and treatment, and informing clinical trial measurement strategies and clinical decision-making.[29–33] However, the population of patients with LC-FAOD is limited in size, widely dispersed geographically, and includes pediatric patients who may be unable to reliably self-report. This coupled with the fact that published research largely focuses on the clinical presentation, pathophysiology, and treatment of LC-FAOD only, in-depth qualitative research can provide insight into the patient experience of LC-FAOD. This study aimed to conduct qualitative research with patients, caregivers, and clinicians to explore the symptom and QoL impact of LC-FAOD.

Methods

In this non-interventional, cross-sectional qualitative study, the patient experience of LC-FAOD was explored from the patient, caregiver, and clinician perspective via the conduct of a focus group and semi-structured interviews. This research was approved by Copernicus Independent Review Board (Approval reference: ADE1-16-560). All participants provided written informed consent before their participation and the conduct of any research-related activities.

Focus group with patients and caregivers

A focus group was conducted with eight participants including patients with LC-FAOD ($n = 4$) and caregivers ($n = 4$) in the US to explore the symptoms and QoL impacts associated with LC-FAOD. Participants were identified via healthcare providers and patient advocacy organizations. Eligible participants were required to be English-speaking, aged ≥ 18 years, and either a patient with LC-FAOD or a caregiver of a patient (of any age) with LC-FAOD. Participants were excluded from the study if they were participating in an Ultragenyx Pharmaceutical Inc or another clinical trial at the time of recruitment. The focus group took place in Scottsdale, Arizona in April 2016 and was 2 h, 20 min in duration. The focus group was conducted by trained moderators and a semi-structured guide was followed to ensure that all topics of interest were explored.

Patient, caregiver, and clinician interviews

Nine participants (independent of those in the focus group), including patients with LC-FAOD ($n = 4$), caregivers ($n = 1$), and clinicians ($n = 4$) were recruited for the concept elicitation (CE) interviews. CE is the process of collecting relevant concepts (e.g. symptoms and impacts) that are important to the population of interest from relevant stakeholder perspectives.[34]

Patients and caregivers were identified via healthcare providers, patient advocacy organizations, and a recruitment advert posted on the Ultragenyx Pharmaceutical Inc. website. Clinicians were identified by Ultragenyx Pharmaceutical Inc. Participants were required to be English-speaking, and either a patient with LC-FAOD (aged $\geqslant 12$ years), a caregiver of a patient with LC-FAOD (of any age), or a clinician specializing in/experienced in managing patients with LC-FAOD.

Interviews (1 h in duration) were conducted by trained qualitative interviewers via telephone. Semi-structured interview guides (one for each respondent type) were followed. Interviews were exploratory in nature and conducted one-to-one. This permitted the collection of detailed and individualized insights, uninfluenced by the experiences or behaviors of other participants; a noted limitation of focus groups.[34,35] Discussions comprised open-ended questions to facilitate spontaneous discussions of the signs, symptoms, and impacts experienced by individuals with LC-FAOD. More focused questions were also asked to probe participants on key topics of interest or statements that required additional clarification. All interviews were conducted between January 2017 and January 2018.

Data analysis

The focus group and interviews were audio-recorded, transcribed verbatim, and entered into ATLAS.ti; a software package designed to facilitate the storage, coding, and analysis of qualitative data.[36] Transcripts were analyzed by trained qualitative researchers using thematic analysis methods which involved identifying, organizing, and reporting emerging patterns or themes within the data.[37] Participant quotes pertaining to the main research objectives (i.e. the symptom and QoL experience of patients with LC-FAOD) were highlighted and assigned corresponding concept codes. Findings were combined to develop a conceptual model; a visual framework of the signs, symptoms, and QoL impacts associated with LC-FAOD.[30]

Results

Focus group and patient/caregiver interviews

The focus group included four patients with LC-FAOD and four caregivers of individuals with various LC-FAOD including VLCAD ($n = 4$), LCHAD ($n = 1$), and CPT-II ($n = 3$). Patients were aged 21–60 years and there was an equal distribution of males ($n = 2$; 50.0%) and females. Caregivers were all mothers (aged 28–55 years) of adults (aged 22 and 23 years) and children (aged 4 and 11 years) with LC-FAOD.

Interviews were conducted with four patients (aged 15–59 years) and one mother of a two-year-old boy with various LC-FAOD including VLCAD ($n = 2$), LCHAD ($n = 2$), and CPT-II ($n = 1$). Most patients with LC-FAOD were female ($n = 3$; 80.0%). All participants who provided their race were White/Caucasian ($n = 4/4$; 100%). Table 1 summarizes the demographic and clinical characteristics of the study participants.

A range of symptoms were discussed during the focus group and patient/caregiver interviews by participants using a combination of layperson and medical terminology. This demonstrated that many patients and caregivers of patients with LC-FAOD and rare diseases more generally, are experts in their disease and can have a high level of clinical understanding of their condition (Table 2; Figure 1). The signs and symptoms reported by participants in the focus group and interviews can be categorized into nine domains including constitutional ($n = 12$), musculoskeletal ($n = 11$), sensory ($n = 11$), gastrointestinal/digestive ($n = 9$), endocrine/nutritional/metabolic ($n = 7$), cardiovascular ($n = 5$), neurological ($n = 5$), urological ($n = 4$), and respiratory ($n = 3$). In addition, observable signs and clinical manifestations of the disease that may typically be clinician-reported were also reported by patients and caregivers including muscle breakdown/rhabdomyolysis ($n = 7$), low blood sugar/hypoglycemia ($n = 6$), liver complications ($n = 5$), and cardiac complications ($n = 3$).

Participants discussed symptoms occurring episodically and referred to them as ‘metabolic crises’ or ‘acute symptom episodes’. Typically, participants

Table 1. Demographic characteristics of patients with LC-FAOD obtained from patients and caregivers who participated in the focus group/interviews.

Patient/Caregiver	Age *Age of caregiver; age of patient	Sex assigned at birth *Sex of caregiver; sex of patient	Diagnosis
Focus group (*n* = 8)			
Patient (01)	21	Male	LCHAD
Patient (02)	60	Female	CPT-II
Patient (03)	22	Female	VLCAD
Patient (04)	47	Male	CPT-II
Caregiver (01)	55; 22*	Female; Female*	VLCAD
Caregiver (02)	48; 23*	Female; Female*	VLCAD
Caregiver (03)	37; 4*	Female; Male*	VLCAD
Caregiver (04)	28; 11*	Female; Male*	CPT-II
Interviews (*n* = 5)			
Patient (01)	59	Female	CPT-II
Patient (03)	15	Male	LCHAD
Patient (04)	36	Female	VLCAD
Patient (05)	24	Female	VLCAD
Caregiver (01)	39; 2*	Female; Male*	LCHAD

CPT-II, carnitine palmitoyltransferase 2; LC-FAOD, Long-chain fatty acid oxidation disorders; LCHAD, long-chain 3-hydroxy-acyl-CoA dehydrogenase; VLCAD, very-long-chain acyl-CoA dehydrogenase.
*Indicates that the data are showing the age of the caregiver followed by the age of the patient.

reported that these episodes occurred once or twice per year and for some, these resulted in emergency room visits and/or periods of hospitalization. Participants reported numerous perceived triggers of these episodes (Figure 1) such as prolonged exercise, fasting, period of acute illness such as colds and viruses, temperatures too hot/cold, sleep deprivation, dehydration, stress, hormonal changes, and menstruation; however, for some patients, triggers were unknown. Participants had good knowledge and understanding of what improved or worsened LC-FAOD and all patients took precautions and used management strategies to avoid symptom worsening and effectively manage exposure to triggers (e.g. limiting exercise duration/distance, fasting duration, and time spent in the sun or cold).

Participants explained that LC-FAOD are associated with significant impacts that require many lifestyle modifications for disease management, even though metabolic crises may not be experienced for months at a time. QoL concepts reported by patients and caregivers during the focus group and interviews were categorized into eight domains (Table 3). Participants reported impacts to patient's medical care/intervention ($n = 12$), social functioning ($n = 11$), physical functioning ($n = 10$), work/school ($n = 10$) impacts, overall lifestyle inclusive of modifications due to LC-FAOD ($n = 9$), emotional/psychological wellbeing ($n = 9$), daily activities ($n = 7$), and sleep ($n = 5$).

Clinician interviews

Four clinicians who treat patients with LC-FAOD were also interviewed as part of the study. The clinicians held the following roles: pediatrician specializing in metabolic disorders ($n = 1$), metabolic physician ($n = 1$), and geneticist with a focus on a

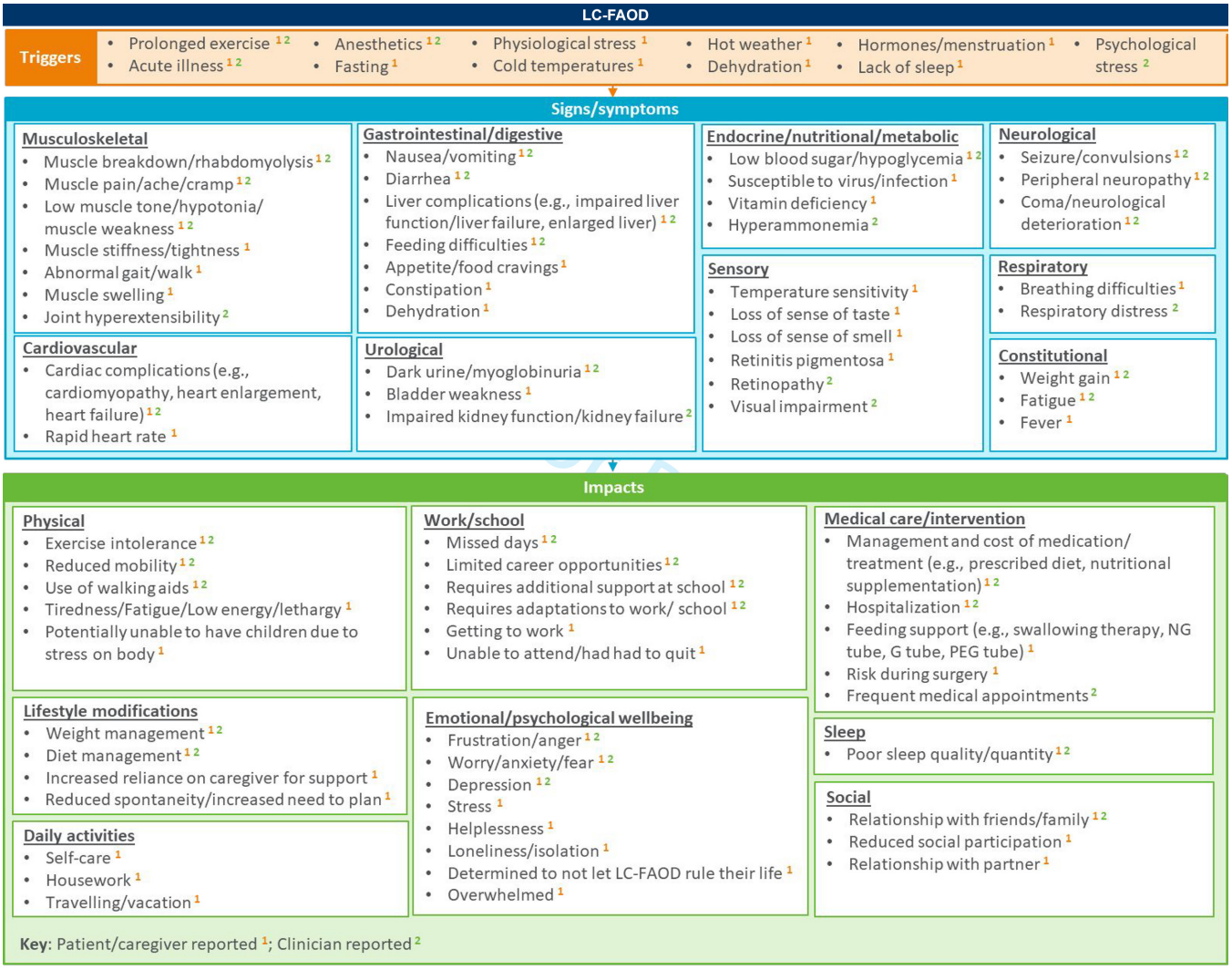

Figure 1. Conceptual model of LC-FAOD. Conceptual model detailing the signs/symptoms and impact concepts in LC-FAOD as reported by patients/caregivers and clinicians.

combination of clinical care and research ($n = 2$). Clinicians were based in the US ($n = 2$), Netherlands ($n = 1$), and France ($n = 1$). Three clinicians managed between three to 100 patients with LC-FAOD; one clinician provided input to the management of all patients with LC-FAOD identified through their country's NBS program. All four clinicians reported seeing their patients with LC-FAOD every 3 to 12 months, or more frequently, for pediatric patients.

All four clinicians reported signs and symptoms of LC-FAOD that aligned with the eight patient-reported domains (Table 2). Clinicians reported that rhabdomyolysis, muscle pain, and hypoglycemia are acute or episodic symptoms. Several signs and symptoms were identified by clinicians to be serious and or signifying severe disease as they can lead to decompensation events, hospitalizations, and increased morbidities and mortality. For example, symptoms such as cardiomyopathy, hypoglycemia, and rhabdomyolysis can lead to complications including, but not limited to, heart failure, renal dysfunction/failure, liver dysfunction/failure, coma, bone marrow edema, and seizures. Clinicians reported exercise intolerance and impaired mobility as the key functional limitations of LC-FAOD. Additional impacts reported by clinicians were also consistent with participant-reported QoL impacts (Figure 1).

Table 2. Signs and symptoms of LC-FAOD reported by patients, caregivers, and clinicians in the focus groups and interviews.

Sign/symptom domain (Patients, caregivers, clinicians)	Symptom	Patients *N* = 8	Caregivers *N* = 5	Clinicians *N* = 4	Example patient and caregiver quotes[a]
Constitutional *N* = 16 (8, 4, 4)	Fatigue	4	2	4	*". . .I would get up and feel fine, and then a couple of hours of being up, I'd just be to the point where I was sitting on the sofa and I literally could feel my eyes just shutting and then I'd sort of wake up again and then I said to my husband, 'I really feel like I just need to go to sleep."* I-P04-VLCAD
	Weight gain	5	3	0	
	Fever	1	0	0	
Musculoskeletal *N* = 15 (8, 3, 4)	Muscle pain/ache/cramp	8	2	4	*"[It's an] extreme muscle fatigue. . .when I'm having the severe muscle pain. Burning, aching, off the charts pain.* I-P01-CPTII *" After an episode or experience of the muscle breakdown or the high CK levels, it could be up to a week later that I would . . . it wasn't necessarily painful, just an overall weakness."* FG-P03-VLCAD *"He toe walks significantly, which we think is probably related to LCHAD."* I-CG01-LCHAD
	Low muscle tone/hypotonia/ muscle weakness	6	3	4	
	Muscle breakdown/ rhabdomyolysis	6	1	4	
	Muscle swelling	3	1	0	
	Muscle stiffness/tightness	3	1	0	
	Abnormal gait/walk	3	2	0	
	Joint stiffness/pain	1	2	2	
Sensory *N* = 15 (8, 3, 4)	Temperature sensitivity	7	3	4	*"I. . .just prefer not to be cold. Not to be hot either, but cold is worse for me. And because if I am cold, I'm going to get an episode quicker."* FG-P04-CPT-II *"I have bad taste buds. I don't know if that has anything to do with it, but they said it, my doctor said it might be because I was force-fed as a child because I had to eat so much. But they say that I never really truly developed my taste buds."* FG-P01-LCHAD

(Continued)

Table 2. (Continued)

Sign/symptom domain (Patients, caregivers, clinicians)	Symptom	Patients $N = 8$	Caregivers $N = 5$	Clinicians $N = 4$	Example patient and caregiver quotes[a]
	Loss of sense of smell	2	1	0	
	Loss of sense of taste	1	0	0	
	Retinitis pigmentosa	1	0	0	
Gastrointestinal/ digestive $N = 12$ (7, 2, 3)	Liver complications (e.g., impaired liver function/liver failure, enlarged liver)	5	0	3	*"I went once without eating beforehand and, and I felt very um nauseous, which, I mean that could be a problem in general, just not eating before exercise. But I felt very nauseous um, exercising and not having eating."* FG-P03-VLCAD *"When I was younger... I did have some gastrointestinal problems. I kind of suffered from like diarrhea, constipation. . . those have seemed to have gotten better as I've got older. . .I still have a sensitive stomach and it's usually due to what I eat."* I-P05-VLCAD
	Nausea/ vomiting	3	2	2	
	Appetite/ food cravings	3	1	0	
	Diarrhea	2	0	0	
	Feeding difficulties	1	0	2	
	Constipation	1	1	0	
	Dehydration	1	0	0	
Endocrine/nutritional/ metabolic $N = 11$ (5, 2, 4)	Low blood sugar/ hypoglycemia	4	2	4	*"If I start to get low blood sugar, I definitely get lethargic. I get a low energy."* FG-P01-LCHAD *"I have young kids, so they're always coming home from school with terrible viruses. And literally I have to be in the same room with them for one day, and then within 48 hours, I've gone down with the same thing."* I-P04-VLCAD *"You can become antisocial in that aspect to prevent um, things like that [illnesses]."* FG-P03-VLCAD
	Susceptible to virus/infection	3	1	0	
	Vitamin deficiency	1	0	0	

(Continued)

Table 2. (Continued)

Sign/symptom domain (Patients, caregivers, clinicians)	Symptom	Patients *N* = 8	Caregivers *N* = 5	Clinicians *N* = 4	Example patient and caregiver quotes[a]
Cardiovascular *N* = 9 (4, 1, 4)	Cardiac complications (e.g., cardiomyopathy, enlarged heart, heart failure)	1	0	4	*"In the past have had issues with cardiomyopathy. . .I'm still getting checked on a yearly basis to make sure it's not returning or during illness that it's not enlarging my heart. . . [once] they discovered that my heart was enlarged like five times the normal size. . .it couldn't break down the fat, so there was fat building up around it."* I-P05-VLCAD
	Rapid heart rate	2	0	0	
Neurological *N* = 9 (3, 2, 4)	Seizure/convulsions	1	2	3	*"Oh, yes, my daughter had a hypoglycemic seizure. . .right before she was diagnosed."* FG-CG02-VLCAD *"During a crisis I would just have to say that my skin just feels weird. Like tingly. Like my legs, my lower legs, um, I just don't even want to move or breath or anything."* FG-P02-CPT-II
	Peripheral neuropathy	2	0	4	
	Coma/neurological deterioration	0	1	3	
Urological *N* = 8 (3, 1, 4)	Dark urine/myoglobinuria	3	1	0	*". . .very dark urine that's like very abnormal, like not just like concentrated, but like, like a bad abnormal, like almost blood color."* I-P05-VLCAD
	Bladder weakness	1	0	0	
Respiratory *N* = 7 (2, 1, 4)	Breathing difficulties	2	1	0	*"During a crisis, your muscles and your ribs get like stiff, so you can't breathe. You feel like you can't breathe."* FG-P02-CPT-II

CPT-II, carnitine palmitoyltransferase 2; LC-FAOD, Long-chain fatty acid oxidation disorders; LCHAD, long-chain 3-hydroxy-acyl-CoA dehydrogenase; VLCAD, very-long-chain acyl-CoA dehydrogenase.

[a]Participant IDs distinguish whether participant quotes were elicited from the interview (I) or focus group (FG), if the concept was reported by a patient (P) or caregiver (CG), the order in which participants were recruited (e.g. 01, 02), and the LC-FAOD type (e.g. LCHAD) of the patient either participating in the study or being reported on by a caregiver. Concepts reported by clinicians only are not included in the table but can be found in Figure 1.

Table 3. Impacts of LC-FAOD reported by patients and caregivers of individuals with LC-FAOD reported in the focus groups and interviews.

Impact domain (Patient, caregiver)	Impact	Patients *N* = 8	Caregivers *N* = 5	Example patient and caregiver quotes[a]
Medical care/ intervention *N* = 12 (8, 4)	Management and cost of medication/ treatment (e.g., prescribed diet, nutritional supplementation)	8	3	*"Well once he went to the hospital after that low blood sugar episode, they did an IV. . .. Two days after his release from the hospital, he was crawling. And so, I think before that, probably he was at a low blood sugar [level] and just didn't have the energy to develop like a normal, you know, infant."* FG-CG04-CPT-II [Reflecting on a time the patient had surgery] *"It's dangerous going under general anesthesia. . .Because of LCHAD. They can't use any inhalant medication. It would cause muscle breakdown. They have to check my blood sugar a lot during surgery and I need special IV with sugar in it."* I-P03-LCHAD
	Hospitalization	5	3	
	Feeding support (e.g., swallowing therapy, NG tube, G tube, PEG tube)	1	2	
	Risk during surgery	2	0	
Social *N* = 11 (8, 3)	Relationship with friends/family	6	3	*"It definitely affected my socialization like as a child or a teenager. . .my life is a little different than most people my age. A lot of my friends say – I hibernate They don't see me, because I usually need to keep in and keep warm."* I-P05-VLCAD *"She was bullied when she was in middle school, just terribly"* FG-CG02-VLCAD *"I would be very active and involved in church and things, but during the flu or you know, strep season or whatever you may call it, there would be weeks that I would not go, period. You can become antisocial in that aspect to prevent things like that [that may trigger metabolic crises]."* FG-P03-VLCAD
	Reduced social participation	6	1	
	Relationship with partner	1	0	
Physical *N* = 10 (8, 2)	Exercise intolerance	8	2	*"I, I feel like my exercise tolerance has gone down over the years. Like I used to be able to exercise more and when I did exercise within my comfort level before, I felt better, and I felt like- and you know I used to be able to walk forty-five minutes. It felt actually good, you know, and I like doing it and I wanted to do more. Um, but nowadays not so much."* FG-P04-CPT-II *"I was able to walk about 100 yards, but I used my son's push-chair. . . [for] a bit of support. . . I went into a really. . .bad metabolic crisis. . .when I came out of hospital a week later. . .there was just no muscle sort of power at all. . .I couldn't even get from one room to the other."* I-P04-VLCAD

(Continued)

Table 3. (Continued)

Impact domain (Patient, caregiver)	Impact	Patients $N = 8$	Caregivers $N = 5$	Example patient and caregiver quotes[a]
	Tiredness/fatigue/low energy/ lethargy	7	1	
	Reduced mobility	3	1	
	Use of walking aids	2	0	
	Potentially unable to have children due to stress on body	1	0	
Work/school $N = 10$ (7, 3)	Unable to attend/had to quit	4	1	*"Between myself and the GP practice that I worked for, as a practice nurse, we said it would be best if I retired on ill health grounds"* I-P04-VLCAD *"he was saying he wanted to go into the military, well they're not going to take him with that medical condition in the military and that kind of thing, so we're limited by certain options."* FG-P03-VLCAD *"it's very hard for me to even like walk around. . .get to work, get home."* I-P05-VLCAD *"If I'm not feeling good then I definitely can't go to school. . .I miss a lot of school because of doctor's appointments."* I-P03-LCHAD
	Requires additional support at school	2	2	
	Limited career opportunities	2	0	
	Requires adaptations to work/school	2	1	
	Missed days	2	0	
	Getting to work	1	0	
Lifestyle modifications $N = 9$ (7, 2)	Diet management	7	2	*"I'm learning here, how important diet is and I'm sure I was told, but I haven't been very good about it, so, I mean I eat a lot of carbs for sure, but also, haven't been all that careful about fat. . .I plan to do better."* FG-P04-CPT-II *"I'm always having to plan ahead. I have to plan where I'm going to put medicine or if I were to have a sort of metabolic situation kind of what would I do. . .what hospitals are close by? You know, can I get access to the Gatorade and things like that that I need? Um, so it's kind of just like always having to think about the web of resources that I need available to me. . .it's just time consuming. . .there's very few things I can kind of just do spontaneously without thinking about my disorder or how it might be impacted or what I need to do to make sure I don't get sick."* I-P05-VLCAD *"My husband is my main carer, so he helps me with my day to day living. . . he gets me ready most days."*I-P04-VLCAD
	Reduced spontaneity/ increased need to plan	3	0	

(Continued)

Table 3. (Continued)

Impact domain (Patient, caregiver)	Impact	Patients $N = 8$	Caregivers $N = 5$	Example patient and caregiver quotes[a]
	Weight management	2	0	
	Increased reliance on caregiver for support	1	1	
Emotional/ psychological wellbeing $N = 9$ (7, 2)	Depression	4	1	*"And then stress, um, it's just overwhelming and then you kind of, at least for myself, if I start a crisis, then I get mad at myself that I'm sick. Or I get, I get frustrated with myself that I'm going through this or the consequences of the crisis. And it's just become more stressful. And then the stress doesn't help it. It just adds to it."* FG-P01-LCHAD *"I said I could not give the CPT-II power over my life"* I-P01-CPTII "I mean he's starting to realize that he can't eat what his sister can and. . .you know, he gets mad at his sister." I-CG01-LCHAD
	Stress	3	0	
	Frustration/anger	2	1	
	Worry/anxiety/fear	2	0	
	Determined to not let LC-FAOD rule their life	1	0	
	Overwhelmed	1	0	
	Loneliness/isolation	1	0	
	Helplessness	1	0	
Daily activities $N = 7$ (7, 0)	Self-care	5	0	*". . .I'll sit with the door open, of the dishwasher. My son would pass me the stuff and then I would load it in. . .the same with the tumble dryer."* I-P04-VLCAD *". . .when it acts up. There would be times that it would be hard to take a shower or things like that because my muscles would just be very weak."* I-P02-VLCAD
	Housework	3	0	
	Traveling/vacation	3	0	
Sleep $N = 5$ (4, 1)	Poor sleep quality/quantity	4	1	*"Well if you're suffering with an episode, it's difficult to sleep because you're in a lot of pain, it's very hard to get comfortable..."* FG-P01-LCHAD

CPT-II, carnitine palmitoyltransferase 2; LC-FAOD, Long-chain fatty acid oxidation disorders; LCHAD, long-chain 3-hydroxy-acyl-CoA dehydrogenase; VLCAD, very-long-chain acyl-CoA dehydrogenase.
[a]Participant IDs distinguish whether participant quotes were elicited from the interview (I) or focus group (FG), if the concept was reported by a patient (P) or caregiver (CG), the order in which participants were recruited (e.g. 01, 02), and the patients LC-FAOD type (e.g. LCHAD) of the patient either participating in the study or being reported on by a caregiver.

Conceptual model

Findings from the focus group, patient, caregiver, and clinician interviews were used to develop a conceptual model outlining the reported signs, symptoms, and QoL impacts of LC-FAOD (Figure 1).

Within the conceptual model, the key denotes the reporter(s) of each concept (i.e. patient/caregiver reported and/or clinician-reported). Both patients/caregivers and clinicians reported at least one sign or symptom within each of the sign/symptom domains, except for the sensory and respiratory domains, the sub-concepts of which were predominately reported by patients/caregivers only. Patients/caregivers reported several signs/symptoms that were not reported by clinicians including muscle stiffness/tightness, muscle swelling, abnormal gait/walk, (musculoskeletal), rapid heart rate (cardiovascular), increased appetite/food cravings, constipation, and dehydration (gastrointestinal/digestive), bladder weakness (urological), increased susceptibility to viruses and infections and vitamin deficiency (endocrine/nutritional/metabolic), temperature sensitivity, loss of taste and smell, and retinitis pigmentosa (sensory), and breathing difficulties (respiratory). Fewer signs/symptoms were reported by clinicians only and are detailed in Figure 1. These included joint hyperextensibility (musculoskeletal), hyperammonemia (endocrine/nutritional/metabolic), impaired kidney function/kidney failure (urological), retinopathy and visual impairment (sensory), respiratory distress (respiratory), and fever (constitutional).

Both patients/caregivers and clinicians reported a range of QoL impacts experienced by patients with LC-FAOD. The greatest concordance between patient/caregiver and clinician reports was seen for impacts within the physical and work/school impact domains. Clinicians were able to identify additional QoL impacts experienced by patients with LC-FAOD, including impacts to relationships with friends/family (social), diet and weight management (lifestyle modifications), and taking time out of their day to attend medical appointments (medical care/intervention). As expected, clinicians were less able to comment on the detail of more distal impacts relevant to the patient experience of LC-FAOD such as emotional/psychological wellbeing. A greater number of impacts were, however, reported by patients/caregivers only which included (but were not limited to) having reduced spontaneity and an increased need to plan their day/events around their diet and symptom management and an increased reliance on a caregiver for support (lifestyle modifications), reduced social participation and affected relationships with their partner (social), impacts to self-care activities, housework, and traveling/vacations (daily activities), and feeling stressed, helpless, and lonely/isolated (emotional/psychological wellbeing). The full presentation of impacts can be seen in Figure 1.

Discussion

Primary data collection with patients is not always practical or feasible in rare disease populations. Therefore, obtaining input from a range of stakeholders and leveraging existing research to support study goals is recommended.[38,39] Taking a holistic, multi-method approach, the current study provides unique insights into the signs, symptoms, and associated QoL impacts of LC-FAOD from the perspective of patients, caregivers, and clinicians.

Findings are consistent with what limited research has been conducted in this area[40] and highlight that LC-FAOD are serious, life-threatening conditions with substantial impacts on the functioning and QoL of affected individuals. For example, across all domains, both patients/caregivers and clinicians reported signs/symptoms of LC-FAOD which included muscle breakdown/rhabdomyolysis, cardiac and liver complications, dark urine/myoglobinuria, and low blood sugar/hypoglycemia. The concordance of some clinical signs of LC-FAOD reported by patients/caregivers and clinicians, particularly the observable symptoms indicative of clinical signs (i.e. dark urine denoting the presence of rhabdomyolysis), support the notion that patients and caregivers often have an in-depth knowledge of the clinical and biochemical presentation of conditions. Typically, this information may be reserved for clinician reports and assessment only, but findings support that patients' can monitor their condition outside of a clinical setting.[31,41]

Some key symptoms, including (but not limited to) muscle swelling and stiffness/tightness, were reported by patients and caregivers only. Overall, the number of signs/symptoms reported by patients only exceeds the number of signs/symptoms that were reported by clinicians only. This highlights the added value and importance of patient- and caregiver-reported data in obtaining

a comprehensive understanding of health conditions beyond that obtained from clinicians alone.

While the impacts of a condition are always best reported directly by patients or caregivers close to the daily experience of the condition, clinicians also demonstrated knowledge of the QoL impacts associated with LC-FAOD, particularly impacts within the physical and work/school impact domains.

A conceptual model summarizing the clinical signs, symptoms, triggers, and impacts of LC-FAOD has been developed based on qualitative data generated from multiple stakeholders as part of this study. The conceptual model includes both layperson and medical terminology as both patients/caregivers and clinicians each used a combination of the two and therefore, overlap may exist in the labeling of some domain sub-concepts. Such models are valuable in terms of identifying key measurement concepts that can be used to demonstrate treatment benefit, providing insight into how best to measure these particular concepts, and providing a contextual basis for interpreting study findings.[42] As documented within the conceptual model, LC-FAOD are associated with a vast array of serious signs and symptoms affecting multiple organ systems. The most chronic symptoms of LC-FAOD typically include muscle pain, muscle weakness, and fatigue that arise or are exacerbated during catabolic situations such as fasting, illness, and endurance exercise. These chronic symptoms are punctuated by acute and recurrent episodes of severe rhabdomyolysis and in some cases cardiomyopathy and arrhythmias, hypoglycemia, and liver dysfunction. Patients may also experience musculoskeletal, neurological, endocrinological/nutritional/metabolic, gastrointestinal/digestive, sensory, cardiovascular, respiratory, urological, and constitutional signs/symptoms.

Patients with LC-FAOD experience significant negative impacts on physical, emotional/psychological, and social functioning, as well as sleep, ability to perform daily activities, and work/school attendance or performance. Specifically, patients experienced fatigue/exercise intolerance which restricted performance in daily activities such as self-care activities and housework. Reduced social participation was also commonly experienced by patients along with impacts on relationships with friends, family, and partners. Uncertainty and fear surrounding LC-FAOD, the future, and its long-term impacts can have a detrimental effect on a patient's emotional and psychological well-being; patients reported feelings of frustration/anger, stress, worry/anxiety/fear, depression, helplessness, and loneliness/isolation. Patients were also required to make significant lifestyle modifications to monitor their diet and weight, periods of fasting and associated energy levels, signs and symptoms of decompensation, and attempts to avoid triggers of episodic crises. For some patients, these lifestyle modifications led to reduced spontaneity and an increased need for them to plan their lives and daily activities around symptom monitoring and implementation of prescribed diets. Patients experienced impacts regarding the strict management and costs of medication/treatment for their condition such as the implementation of a prescribed diet and nutritional supplements. For some patients, feeding support was required such as swallowing therapy and the use of surgically inserted feeding tubes. Acute symptoms commonly led to hospitalizations and emergency treatment interventions for some patients. LC-FAOD were even more unpredictable and challenging to manage for patients who were unable to identify the triggers and exacerbated features of their condition.

The limitations of this research should be noted. LC-FAOD present with heterogeneous clinical phenotypes of differing severity and at various ages of onset (from neonate to adulthood). Due to the small sample sizes involved in this study, the conceptual model does not permit distinct connections to be made between individual LC-FAOD types and their associated signs, symptoms, and impacts. Furthermore, due to the opportunity sampling methods employed to recruit participants, no patients or caregivers of patients with CACT, CPT-I, or TFP deficiencies participated in the focus group or semi-structured interviews and therefore insights from these populations are lacking. It should also be noted that insights from the current study pertain largely to adult patients with LC-FAOD, with only limited information available for pediatric patients as reported by participating caregivers. In addition, the collection of detailed information regarding patients' clinical history (e.g. LC-FAOD type, age of disease onset, method of diagnosis (NBS or not), frequency of metabolic attacks, and coping strategies/treatments) that may be used to predict disease severity, was not feasible as part of this study. Therefore, any trends in symptoms/impact

presentation by disease severity and age both within and between LC-FAOD types could not be explored.

There may be appreciable differences in the presentation of LC-FAOD in childhood compared to adulthood and among patients with differing severity of LC-FAOD.[7,43] Furthermore, advances in the diagnosis and identification of LC-FAOD may also mean that there are fundamental differences based on the method and age of diagnosis. For example, the patient experience of LC-FAOD may differ considerably for those diagnosed via NBS, who either may never present with clinical symptoms or have received appropriate clinical management from an early age, compared to those with later-onset, exercise-induced myopathic symptoms characteristic of LC-FAOD.[44] Further, little is known about the natural history of LC-FAOD throughout childhood (a period characterized by considerable physiological, psychological, and social changes) and adulthood (particularly the pathologies and associated impacts that may emerge in older adults).[45]

To build on this current work and overcome the limitations of this study, it would be beneficial to conduct further qualitative interviews with a larger and more demographically and clinically diverse group of LC-FAOD patients. Specifically, this would help facilitate the conduct of additional subgroup analyses and sampling stratification, and greater exploration of the similarities and differences in the patient experience of LC-FAOD based upon their demographic and clinical characteristics.

Conclusion

This study provides unique insights into the signs, symptoms, and associated QoL impacts of LC-FAOD from the perspective of patients, caregivers, and clinicians. The conceptual model illustrates the sign/symptom (nine domains), impact (eight domains), and trigger (11 triggers) concepts reported by participants. Findings support that LC-FAOD are associated with a broad variety of serious signs and symptoms, such as muscle breakdown/rhabdomyolysis, low blood sugar/hypoglycemia, and cardiac and liver complications. Patients also experience significant QoL impacts that affect all aspects of life from physical functioning, work/school, and sleep which are intensified by their monitoring of symptoms, diet, and exercise in attempts to avoid triggering and/or exacerbating symptoms. Future research should aim to explore the patient experience of LC-FAOD in a more demographically and clinically diverse sample and in response to novel treatments such as triheptanoin. This may further generate an understanding of the unmet needs and considerations for the ongoing management of LC-FAOD, in addition to their longitudinal effects on patients' symptoms, QoL, and mortality.

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Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Rebecca Williams-Hall, Katie Tinsley, and Adam Gater are all employees of Adelphi Values, a health outcomes research agency commissioned by Ultragenyx Pharmaceutical Inc. to conduct the research outlined in this manuscript. Chloe Johnson was an employee of Adelphi Values at the time this research was conducted. Eliza Kruger and Tricia Cimms are employees and shareholders of Ultragenyx Pharmaceutical Inc. Alexandra Bowden was an employee and shareholder of Ultragenyx at the time this research was conducted.

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Ethics statement

This research was conducted in accordance with the Declaration of Helsinki 1964 and its later amendments and was approved by an Independent Review Board in the US (Copernicus Group Independent Review Board-Approval references ADE1-16-560 and ADE1-17-423).

Patient consent statement

Written informed consent was obtained from all study participants before taking part in this research.

Data availability

All data reported in this study are owned by Ultragenyx Pharmaceutical Inc. and are not publicly available. Due to the rarity of LC-FAOD and the small number of subjects in this trial, individual patient data will not be shared in order to safeguard patient privacy, consistent with the data sharing policy listed on Ultragenyx.com.

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