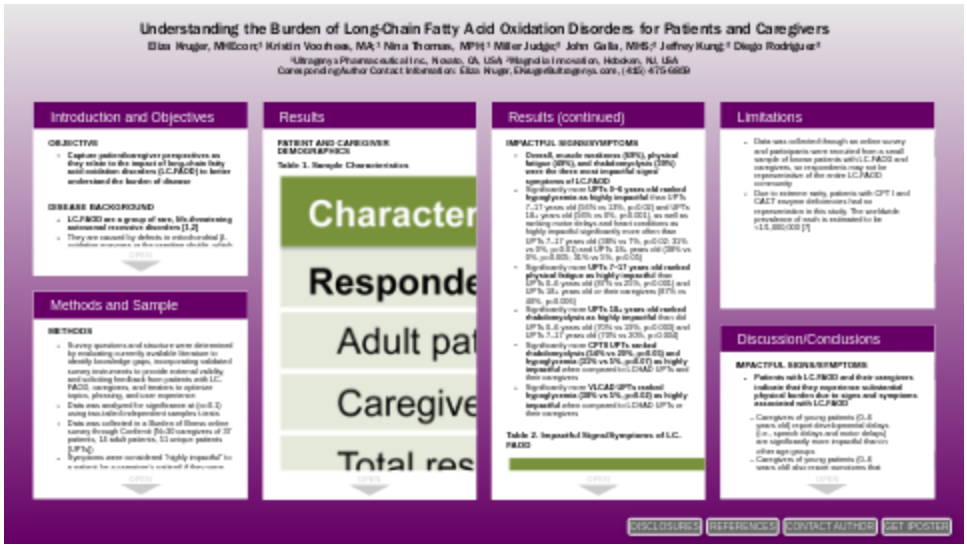
Understanding the Burden of Long-Chain Fatty Acid Oxidation Disorders for Patients and Caregivers



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INTRODUCTION AND OBJECTIVES

OBJECTIVE

- **Capture patient/caregiver perspectives as they relate to the impact of long-chain fatty acid oxidation disorders (LC-FAOD) to better understand the burden of disease**

DISEASE BACKGROUND

- **LC-FAOD are a group of rare, life-threatening autosomal recessive disorders [1,2]**
- They are caused by defects in mitochondrial β-oxidation enzymes or the carnitine shuttle, which are components of the metabolic pathway by which long-chain fatty acids are converted to energy [3,4]
- There are 6 main enzyme deficiencies associated with LC-FAOD [5]:
  - Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
  - Long-chain L-3 hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
  - Carnitine palmitoyltransferase I (CPT I) deficiency
  - Carnitine palmitoyltransferase II (CPT II) deficiency
  - Trifunctional protein (TFP) deficiency
  - Carnitine-acylcarnitine translocase (CACT) deficiency
- LC-FAOD is characterized by chronic energy deficiency as well as acute metabolic crises during times of increased energy demand; these metabolic crises can result in hypoglycemia, rhabdomyolysis, or cardiomyopathy
- Toxic metabolite build-up as a result of LC-FAOD can lead to complications in a wide range of organs, that may affect the heart (cardiomyopathy), eyes (retinopathy), and nervous system (neuropathy) [1,6]
- The symptoms experienced by patients with LC-FAOD are understood to have a substantial negative impact on the lives of patients and their caregivers, but to date, this impact has not been quantified in a rigorous study
- This poster describes the results of a Burden of Illness online survey of patients with LC-FAOD and caregivers of patients with LC-FAOD, stratified by age groups and types of LC-FAOD

METHODS AND SAMPLE

METHODS

- Survey questions and structure were determined by evaluating currently available literature to identify knowledge gaps, incorporating validated survey instruments to provide external validity, and soliciting feedback from patients with LC-FAOD, caregivers, and treaters to optimize topics, phrasing, and user experience
- Data was analyzed for significance at (α=0.1) using two-tailed independent samples t-tests
- Data was collected in a Burden of Illness online survey through Confirmit (N=30 caregivers of 37 patients, 14 adult patients, 51 unique patients [UPTs])
- Symptoms were considered “highly impactful” to a patient (or a caregiver’s patient) if they were ranked in the top 3 of 12 symptoms
- Analysis of “rest or relaxation time spent recuperating from LC-FAOD” was performed by looking at the percentage of patients and caregivers of patients who reported being affected “most” or “all” of the time

Key Screening Criteria

- Adult patients must have LC-FAOD
- Caregivers must care for a patient with LC-FAOD and must not be compensated for their care or be a healthcare provider caring for the patient
- Adult patients and patients of caregivers must currently receive care from an LC-FAOD treating endocrinologist, geneticist / metabolic specialist, or dietitian / nutritionist

RESULTS

PATIENT AND CAREGIVER DEMOGRAPHICS

Table 1. Sample Characteristics

Characteristics	
Respondent types (# respondents)	
Adult patients*	14
Caregivers†	30
Total respondents	44
Unique patient reports (# unique patients [UPTs])	
Adult patients*	14
Patients of caregivers‡	37
Total unique patients	51
Sex of UPTs (%, #)	
Male	55%, 28
Female	45%, 23
Age of all UPTs (N=51)	
Mean	16.25 years
Median	14.0 years
Range	8 months–67 years

Age of adult patient respondents (N=14)	
Mean	31.63 years
Median	25.5 years
Range	19 years–67 years
Age of patients of caregivers (N=37)	
Mean	10.48 years
Median	9.0 years
Range	8 months–27 years
UPT age groups (%, n)	
UPTs 0– 6 years old	31.4%, 16
UPTs 7– 17 years old	29.4%, 15
UPTs 18+ years old	39.2%, 20
Enzyme deficiencies (%, n)	
LCHAD	39.2%, 20
VLCAD	31.4%, 16
CPT II	25.5%, 13
TFP§	3.9%, 2

Time since diagnosis	
All UPTs (N=51)	5.87 years
Adult patients (N=14)	17.48 years
Patients of caregivers (N=37)	1.48 years
UPTs diagnosed via NBS ¶ (%, n)	
Diagnosed via NBS	45%, 23
Not diagnosed via NBS	55%, 28
Experience with triheptanoin (C7/Dojolvi#) or MCT products (%, n)	
Only triheptanoin/C7/Dojolvi	11%, 5
Only MCT products	66%, 34
Both triheptanoin/C7/Dojolvi and MCT products	24%, 12
Neither triheptanoin/C7/Dojolvi nor MCT products	0%, 0

NBS = newborn screening; UPTs = unique patients.

*Patients with LC-FAOD, 18+ years old.

†Caregivers of at least 1 child with LC-FAOD.

‡Patients with LC-FAOD of any age, survey responses entered by a caregiver.

§TFP patients have been excluded from analysis by enzyme deficiency due to small sample size, but are included in analysis of the full sample.

¶Adult patients were assumed to not be diagnosed via NBS.

#Dojolvi® (triheptanoin) is the only FDA-approved treatment for pediatric and adult patients with molecularly confirmed LC-FAOD. [8]

RESULTS (CONTINUED)

IMPACTFUL SIGNS/SYMPTOMS

- **Overall, muscle weakness (69%), physical fatigue (49%), and rhabdomyolysis (39%) were the three most impactful signs/ symptoms of LC-FAOD**
- Significantly more **UPTs 0–6 years old ranked hypoglycemia as highly impactful** than UPTs 7–17 years old (56% vs 13%, p=0.02) and UPTs 18+ years old (56% vs 0%, p<0.001), as well as ranking motor delays and heart conditions as highly impactful significantly more often than UPTs 7–17 years old (38% vs 7%, p=0.02; 31% vs 0%, p=0.01) and UPTs 18+ years old (38% vs 0%, p=0.005; 31% vs 5%, p=0.05)
- Significantly more **UPTs 7–17 years old ranked physical fatigue as highly impactful** than UPTs 0–6 years old (87% vs 25%, p<0.001) and UPTs 18+ years old or their caregivers (87% vs 40%, p=0.006)
- Significantly more **UPTs 18+ years old ranked rhabdomyolysis as highly impactful** than did UPTs 0–6 years old (70% vs 19%, p=0.003) and UPTs 7–17 years old (70% vs 20%, p=0.004)
- Significantly more **CPTII UPTs ranked rhabdomyolysis (54% vs 20%, p=0.05) and hypoglycemia (31% vs 5%, p=0.07) as highly impactful** when compared to LCHAD UPTs and their caregivers
- Significantly more **VLCAD UPTs ranked hypoglycemia (38% vs 5%, p=0.02) as highly impactful** when compared to LCHAD UPTs or their caregivers

Table 2. Impactful Signs/Symptoms of LC-FAOD

	UPTs						
	All (N=51) (%, n)	0–6 yrs. (N=16) (%, n)[a]	7–17 yrs. (N=15) (%, n)[b]	18+ yrs. (N=20) (%, n)[c]	LCHAD (N=20) (%, n)[a]	VLCAD (N=16) (%, n)[b]	CPTII (N=13) (%, n)[c]
Muscle weakness	69%, 35	56%, 9	73%, 11	75%, 15	70%, 14	63%, 10	77%, 10
Physical fatigue	49%, 25	25%, 4	87%[ac], 13	40%, 8	55%, 11	50%, 8	39%, 5
Rhabdomyolysis	39%, 20	19%, 3	20%, 3	70%[ab], 14	20%, 4	44%, 7	54%[a], 7
Exercise intolerance	31%, 16	19%, 3	33%, 5	40%, 8	30%, 6	25%, 4	39%, 5
Hypoglycemia	22%, 11	56%[bc], 9	13%, 2	0%, 0	5%, 1	38%[a], 6	31%[a], 4
Mental fatigue	16%, 8	6%, 1	20%, 3	20%, 4	25%, 5	13%, 2	8%, 1
Speech delays	16%, 8	25%[c], 4	20%, 3	5%, 1	20%, 4	13%, 2	15%, 2
Motor delays	14%, 7	38%[bc], 6	7%, 1	0%, 0	15%, 3	6%, 1	23%, 3
Heart conditions	12%, 6	31%[bc], 5	0%, 0	5%, 1	10%, 2	19%, 3	8%, 1
Eye conditions	12%, 6	6%, 1	13%, 2	15%, 3	20%[c], 4	13%, 2	0%, 0
Cognitive delays	12%, 6	6%, 1	13%, 2	15%, 3	15%, 3	13%, 2	8%, 1
Peripheral neuropathy	10%, 5	13%, 2	0%, 0	15%[b], 3	15%[c], 3	6%, 1	0%, 0

[a,b,c]Indicates statistical significance between indicated groups of each analysis at $\alpha = 0.10$.

REQUIRING ACCOMMODATION FOR SOCIAL EVENTS

- **31% of UPTs require special accommodations for social events most or all of the time**
- When split by enzyme deficiency, significantly fewer CPTII UPTs require special accommodations for social events most or all of the time than did LCHAD UPTs or their caregivers (15% vs 45%, p=0.08)

REST/RELAXATION TIME SPENT RECOVERING FROM LC-FAOD

- **22% of UPTs spend most or all rest/relaxation time recovering from LC-FAOD**
- UPTs 18+ years old and their caregivers reported directionally higher rates than did both caregivers of UPTs 0–6 years old and caregivers of UPTs 7–17 years old, but these differences were not significant

Table 3. Special Accommodation Required for Social Events and Rest/Relaxation Time Spent Recovering From LC-FAOD

	UPTs						
	All (N=51) (%, n)	0–6 yrs. (N=16) (%, n)[a]	7–17 yrs. (N=15) (%, n)[b]	18+ yrs. (N=20) (%, n)[c]	LCHAD (N=20) (%, n)[a]	VLCAD (N=16) (%, n)[b]	CPTII (N=13) (%, n)[c]
UPTs reported to require special accommodations for social events "most" or "all" of the time	31%, 16	25%, 4	47%, 7	25%, 5	45%[c], 9	19%, 3	15%, 2
UPTs reported to spend "most" or "all" relaxation time recovering from LC-FAOD	22%, 11	13%, 2	13%, 2	35%, 7	20%, 4	31%, 5	8%, 1

[a,b,c]Indicates statistical significance between indicated groups of each analysis at $\alpha = 0.10$.

LIMITATIONS

- Data was collected through an online survey and participants were recruited from a small sample of known patients with LC-FAOD and caregivers, so respondents may not be representative of the entire LC-FAOD community
- Due to extreme rarity, patients with CPT I and CACT enzyme deficiencies had no representation in this study. The worldwide prevalence of each is estimated to be <1/1,000,000 [7]

DISCUSSION/CONCLUSIONS

IMPACTFUL SIGNS/SYMPTOMS

- **Patients with LC-FAOD and their caregivers indicate that they experience substantial physical burden due to signs and symptoms associated with LC-FAOD**
  - Caregivers of young patients (0–6 years old) report developmental delays (i.e., speech delays and motor delays) are significantly more impactful than in other age groups
  - Caregivers of young patients (0–6 years old) also report symptoms that may necessitate a hospital visit (i.e., hypoglycemia and heart conditions) are significantly more impactful than those in other age groups

IMPACT ON SOCIAL EVENTS AND REST/RELAXATION

- **LC-FAOD imparts burdens that may not be evident from signs and symptoms**
- Substantial portion of patients and caregivers of patients report requiring special accommodations for social events and needing to spend rest or relaxation time recuperating from effects of LC-FAOD
  - UPTs 7–17 years old (i.e., older children and adolescents) required special accommodations for social events more frequently than other age groups (non-significant), possibly due to increased expectations of autonomy compared to 0–6 year-olds and greater transitional challenges

CONCLUSIONS

- **LC-FAOD can present a substantial burden on the lives of patients with LC-FAOD through effects on energy production and physical activity, notably the high impact of muscle weakness, physical fatigue, and rhabdomyolysis**
- LC-FAOD signs and symptoms may have various levels of impact at different stages of a patient's life
- This burden can vary heavily from patient to patient, with some groups of patients or their caregivers reporting more impact of certain symptoms or requiring special accommodation for social events more frequently

DISCLOSURES

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- Funding for the research was provided by Ultragenyx Pharmaceutical Inc.
- Miller Judge, John Galla, Jeffrey Kung, and Diego Rodriguez are employees of Magnolia Innovation, which received payment from Ultragenyx Pharmaceutical for research and analysis
- Eliza Kruger, Kristin Voorhees, and Nina Thomas are employees of Ultragenyx Pharmaceutical, Inc.

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