Genetic, biochemical and clinical spectrum of patients with mitochondrial trifunctional protein deficiency identified after introduction of newborn screening in the Netherlands

Marit Schwantje[1,2], Sabine Fuchs[1], Lonneke de Boer[3], Annet Bosch[2], Inge Cuppen[1], Eugenie Dekkers[4], Terry Derks[5], Sacha Ferdinandusse[2], Lodewijk IJlst[2], Riekelt Houtkooper[2], Rose Maase[4], Ludo van der Pol[1], Maaike de Vries[3], Rendelien Verschoof-Puite[4], Ronald Wanders[2], Monique Williams[6], Frits Wijburg[2], Gepke Visser[1,2]

1) Wilhelmina Children's Hospital, University Medical Center Utrecht. 2) Amsterdam Gastroenterology, Endocrinology, and Metabolism institute, Amsterdam University Medical Center. 3) Amalia Children's Hospital, Radboud University Medical Center, Nijmegen. 4) National Institute for Public Health and the Environment (RIVM), Bilthoven. 5) Beatrix Children's Hospital, University Medical Center Groningen. 6) Department of Pediatrics, Erasmus MC, University Medical Center Rotterdam

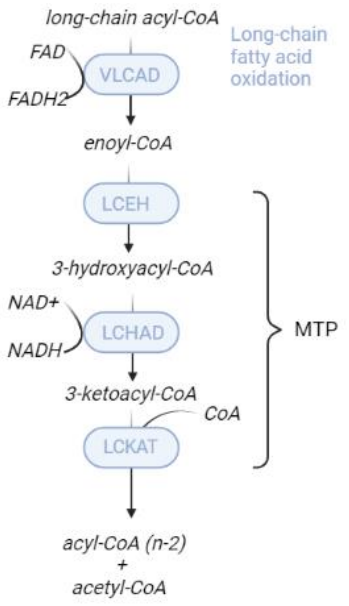
Aim

To gain insight in the outcomes of mitochondrial trifunctional protein (MTP)-deficient patients diagnosed after introduction of newborn screening (NBS) for LCHADD in the Netherlands.

Background

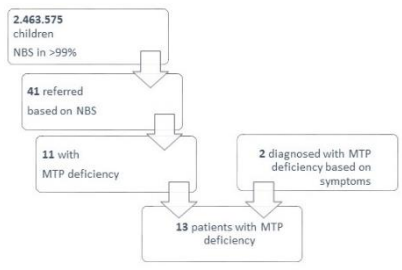
Acylcarnitine-based NBS for LCHADD not only identifies LCHADD, but all different deficiencies of the mitochondrial trifunctional protein (MTP), a multi-enzyme complex involved in long-chain fatty acid β-oxidation.
Besides LCHAD, MTP harbors two additional enzyme activities: long-chain enoyl-CoA hydratase (LCEH), and long-chain ketoacyl-CoA thiolase (LCKAT).

Deficiency of one or more MTP activities causes generalized MTP deficiency (MTPD), LCHADD, LCEH deficiency (not yet reported), or LCKAT deficiency (LCKATD).



Methods

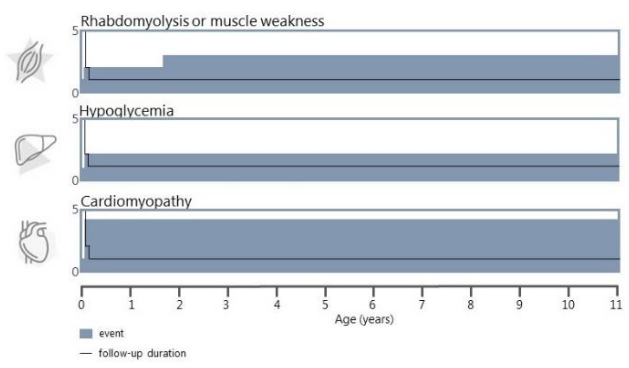
Retrospective evaluation of patients with MTP deficiency (comprising LCHADD, MTPD and LCKATD), diagnosed since the introduction of LCHADD in the Dutch NBS program (2007) until May 2021.



Clinical characteristics

Generalized MTPD

4 MTPD patients (NBS diagnosis) died due to cardiomyopathy within the first month of life (median age of death: 8 days, range: 3-31 days).

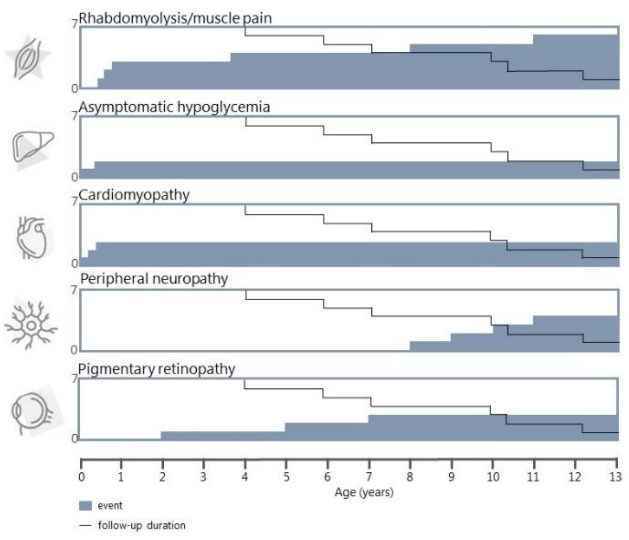


1 MTPD patient (clinical diagnosis) is 11 years old and experienced febrile illness and exercise-induced muscle pain and weakness (no elevated CK measured) from 2 years onwards. Enzyme diagnostics showed a thermo-sensitive MTP deficiency (Table 1).

Isolated LCHADD

All 7 LCHADD patients (1 missed by NBS, clinical diagnosis) were alive. Despite early diagnosis by NBS and treatment initiation, they still developed LCHADD-specific signs and symptoms.

All were treated with a maximum fasting time according to age and an LCT-restricted and MCT-enriched diet.



Isolated LCKATD

The LCKATD patient developed severe rhabdomyolysis, hypoglycemia and cardiomyopathy within the first week of life. Despite treatment with glucose infusion, MCT and β-hydroxybutyrate, she died at the age of 13 months due to cardiac failure. For more detailed information on the clinical course, see poster '2852'.

Additional information

Published in JIMD, July 2022, DOI: 10.1002/jimd.12502
Contact: m.schwantje@umcutrecht.nl

This work was financially supported by Metakids and PNO-zorg.

Link to article

Genetic characteristics

All MTPD patients were homozygous or compound heterozygous for *HADHB* variants. All LCHADD patients carried *HADHA* variants, with at least one allele carrying the common c.1528G>C (p.Glu510Gln) variant. The LCKATD patient was compound heterozygous for the following *HADHB* variants: c.182G>A (p.Arg61His) and c.1289T>C (p.Phe430Ser).

Biochemical characteristics

Patient number	Enzyme activities in lymphocytes		Enzyme activities in skin fibroblasts		IcFAO-flux in skin fibroblasts
	LCHAD	LCKAT	LCHAD	LCKAT	
MTPD					
#1	20%	5%	20%	5%	-
#2	29%	3%	-	-	-
#3	-	-	14%	18%	-
#4	50%*	8%	-	-	-
#5	-	-	40%	33%	99%
			At 40°C: 10%	At 40°C: 7%	At 40°C: 34%
LCHADD					
#6	23%	161%	10%	138%	24%
#7	41%	89%	7%	103%	28%
#8	26%	88%	10%	92%	83%
#9	19%	133%	-	-	-
#10	19%	82%	10%	43%	27%
#11	25%	89%	-	-	-
#12	41%	89%	14%	56%	22%
LCKATD					
#13	146%	9%	74%	4%	17%

Table 1: Biochemical characterisation of lymphocytes and fibroblasts of all patients studied. LCHAD and LCKAT activities and long-chain fatty acid β-oxidation (IcFAO)-flux in the patient samples are expressed as % of the mean of the reference values or of the mean IcFAO-flux in two or three control cell lines.

Discussion

Highly variable patient outcomes

- The clinical presentation and outcomes were highly variable, ranging from severe neonatal cardiomyopathy to febrile illness-induced muscle symptoms.

Prognosis prediction remains difficult

- The current knowledge on a relation between enzymatic or genotypic characteristics and clinical outcomes is still too limited for accurate prognostication after diagnosis by NBS.

Benefits of NBS

- The most apparent benefit was prevention of symptomatic hypoglycemia.
- None of the LCHADD patients developed symptomatic hypoglycemia or neurological consequences, whereas in an international pre-NBS cohort study, hypoglycemia was reported as one of the symptoms in 78% of the LCHADD patients (Den Boer et al., 2002).
- Despite early diagnosis and treatment initiation, patients still developed signs and symptoms, including peripheral neuropathy and pigmentary retinopathy.
- To enhance the benefits of NBS, more effective treatment strategies are needed.

Risk of missing patients

- Two patients were missed by NBS.
- Especially the MTPD patient might have had a more favorable outcome with less metabolic decompensations and a shorter diagnostic trajectory, had she been identified by NBS.

Recommendation

Accurate classification of and discrimination between the different MTP deficiencies with both enzymatic and genetic analysis are required to improve insight in the yield of NBS, prognosis prediction and patient outcomes.