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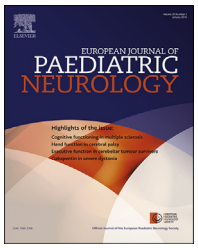

Original Article

# Peripheral neuropathy in patients with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency – A follow-up EMG study of 12 patients☆

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ABSTRACT

*Background:* The neonatal screening and early start of the dietary therapy have improved the outcome of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD). The acute symptoms of LCHADD are hypoketotic hypoglycemia, failure to thrive, hepatopathy and rhabdomyolysis. Long term complications are retinopathy and neuropathy. Speculated etiology of these long term complications are the accumulation and toxicity of hydroxylacylcarnitines and long-chain fatty acid metabolites or deficiency of essential fatty acids.
*Aims:* To study the possible development of polyneuropathy in LCHADD patients with current dietary regimen.
*Methods:* Development of polyneuropathy in 12 LCHADD patients with the homozygous common mutation c.G1528C was evaluated with electroneurography (ENG) studies. The ENG was done 1–12 times to each patient, between the ages of 3 and 40 years. Clinical data of the patients were collected from the patient records.
*Results:* The first sign of polyneuropathy was detected between the ages of 6–12 years, the first abnormality being reduction of the sensory amplitudes of the sural nerves. With time, progression was detected by abnormalities in sensory responses extending to upper limbs, as well as abnormalities in motor responses in lower limbs. Altogether, eight of the patients had polyneuropathy, despite good compliancy of the diet.
*Conclusions:* This study is the first to report the evolution of polyneuropathy with clinical neurophysiological methods in a relative large LCHADD patient group. Despite early start,

*Abbreviations:* DHA, docosahexaenoic acid; EFA, essential fatty acids; FAO, mitochondrial fatty acid β-oxidation; EMG, electromyography; ENG, electroneurography; LCHADD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; PNP, polyneuropathy; TFP, mitochondrial trifunctional protein.

☆ All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Helsinki University Central Hospital, Ethics Committee for gynecology and obstetrics, pediatrics and psychiatry) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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and good compliance of the therapy, 6/10 of the younger patients developed neuropathy. However, in most patients the polyneuropathy was less severe than previously described.


## 1. Introduction

Mitochondrial β-oxidation of fatty acids is essential for energy production during fasting.[1] The most common mitochondrial fatty acid β-oxidation (FAO) defect in Finland is long-chain 3-hydroxyacyl dehydrogenase (LCHAD) deficiency.[2] FAOs are inherited autosomally recessively and some are screened neonatally in several countries worldwide.[3] LCHADD usually manifests during the first two years of life as periods of hypoketotic hypoglycaemia, hepatomegaly, cardiomyopathy and hypotonia. The first manifestation can be sudden death.[4] Episodes of rhabdomyolysis provoked by prolonged exercise or acute infections may occur. Characteristic long term complications of LCHADD, not typical of other β-oxidation defects, are progressive peripheral neuropathy and retinopathy. Amongst the mitochondrial fatty acid oxidation defects peripheral neuropathy seems to be specific to LCHADD and mitochondrial trifunctional protein (TFP) deficiency.[5–15] Speculated pathogenetic mechanism of LCHADD complications are the accumulation and toxicity of hydroxylacylcarnitines and long-chain fatty acid metabolites or deficiency of essential fatty acids, especially (DHA) docosahexaenoic acid.[16] Dietary therapy for LCHADD includes avoidance of fasting and limiting the intake of long-chain fatty acids (LCFA) by giving medium-chain triglyceride (MCT) and carbohydrate supplementations.[17,18]

In a smaller series of patients peripheral neuropathy in LCHADD was reported to be often quite severe, predominantly axonal with possible secondary demyelination and more prominent in lower limbs.[7,8,10] Although the outcome of LCHADD has improved, due to the neonatal screening programs in many countries, it's still unknown, whether the current treatment strategies prevent the progression of the long-term complications of LCHADD, such as pigmentary retinopathy and peripheral neuropathy. The aim of this study is to describe and shed light in the course of neuropathy in 12 patients with LCHADD with the homozygous common mutation G1528C.

## 2. Material and methods

A total of 47 patients with LCHADD were diagnosed in Finland from 1976 through 2014. To date only 15 of the patients are alive. All the surviving patients were treated and followed up in Helsinki University Hospital and had the homozygous common mutation c.G1528C. The mutation of each patient was confirmed by mutation analysis from DNA extracted from blood or cultured fibroblasts. One of the patients was diagnosed prenatally because of family history of LCHADD. None of the patients was diagnosed by neonatal screening.

The patients visited child neurologist, dietitian and physiotherapist every 6 months to 2 years depending on the age. The dietitian collected detailed records of the diet and planned dietary recommendations at every visit. The compliance of the diet was assessed measuring the acylcarnitine and free fatty acid profiles.

The electroneurography (ENG) follow-up was started at the earliest from 3 years of age to follow up the course of peripheral neuropathy during the current dietary therapy of LCHADD. For compliance reasons needle electromyography (EMG) was not routinely performed: only patient 1 underwent EMG at the age of 21 years. ENG examinations were done to 12 patients (age range 3–40 yr at time of ENG).

The ENGs were performed in the Department of Clinical Neurophysiology at the Children's Hospital in Helsinki during 1982–2014. Each patient underwent 1–12 ENG measurements (Fig. 1). Most studies were performed by either of two neurophysiologists and there were some variation in the measuring technique and peripheral nerves analyzed.

The median, ulnar and radial nerves were the sensory nerves studied in the upper extremities and the sural nerve in the lower extremities. The median and deep peroneal nerves were the most commonly studied motor nerves. The measurements included were motor conduction velocity (MCV), distal latency, motor amplitude, and sensory conduction velocity (SCV) and sensory amplitude. Polyneuropathy was diagnosed from ENG if there were absent or diminished responses in at least two nerves (especially nervus suralis: the lower limit was 8.4 μV) or slowed conduction velocity. Clinically polyneuropathy was diagnosed according to the following criteria: combination of clinical symptoms, signs and ENG findings, modified from England et al. 2005.[19] Visual evoked potentials (VEPs) were recorded in all of the patients and they were mainly normal but will be reported separately by ophthalmologists.

Clinical data of the patients were collected from the patient records, including the age, height, physical performance, dietary therapy, neurological condition, the course and balance of the disease.

The low-fat and high in carbohydrates diet consisted of 5% of energy (5E%) long-chain triglycerides (LCTs), and 15–20E% medium chain triglycerides (MCTs), covering the daily needs for essential fatty acids (EFA) and fat soluble vitamins. The patients had hydrolyzed corn starch as carbohydrate supplementation.

## 3. Results

The clinical findings of the patients are presented at Table 1. The first clinical signs of polyneuropathy were absent tendon