Peripheral Neuropathy, Episodic Rhabdomyolysis, and Hypoparathyroidism in a Patient with Mitochondrial Trifunctional Protein Deficiency

Peter van Vliet • Annelies E. Berden •
Mojca K. M. van Schie • Jaap A. Bakker •
Christian Heringhaus • Irenaeus F. M. de Coö •
Mirjam Langeveld • Marielle A. Schroyen •
M. Sesmu Arbous

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Abstract A combination of unexplained peripheral neuropathy, hypoparathyroidism, and the inability to cope with metabolic stress could point to a rare inborn error of

metabolism, such as mitochondrial trifunctional protein (MTP) deficiency.

Here, we describe a 20-year-old woman who was known since childhood with axonal motor sensory polyneuropathy of unknown origin. She presented with progressive dyspnoea, and increased muscle weakness, preceded by 6 days of fever, vomiting, and diarrhoea. Laboratory testing showed rhabdomyolysis, and hypocalcaemia with low parathyroid levels. The patient was intubated because of respiratory insufficiency and a viral and bacterial pneumonia was diagnosed. She was discharged after 16 days of admission. Metabolic screening, performed at the time of rhabdomyolysis, showed increased concentrations of long-chain 3-hydroxyacyl carnitine species, together with elevated urinary excretion of 3-hydroxy dicarboxylic acids. Decreased activity of long-chain 3-hydroxyacyl-CoA dehydrogenase and long-chain 3-ketoacyl-CoA thiolase in peripheral lymphocytes and fibroblasts confirmed a MTP deficiency. Sequence analysis of the *HADHB* gene showed two heterozygous variants: c.209+1G>C (splicing defect) and c.980T>C (p.Leu327Leu). When the acylcarnitine profile was repeated after the episode of rhabdomyolysis had resolved it showed no abnormalities.

Our case illustrates a cluster of peripheral neuropathy, episodic rhabdomyolysis, and hypoparathyroidism in a patient with MTP deficiency caused by mutations in the *HADHB* gene. It stresses the importance of performing metabolic screening when patients are most symptomatic, as normal results can be found at times when no metabolic stress is present. Screening is relatively easy and timely diagnosis has important implications for treatment.

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Peter van Vliet and Annelies E. Berden contributed equally to this work.

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P. van Vliet (✉) • M. S. Arbous
Department of Intensive Care Medicine, Leiden University Medical Center, Leiden, The Netherlands
e-mail: p.van_vliet@yahoo.com

A. E. Berden • M. A. Schroyen
Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

M. K. M. van Schie
Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

J. A. Bakker
Department of Clinical Chemistry, Leiden University Medical Center, Leiden, The Netherlands

C. Heringhaus
Emergency Department, Leiden University Medical Center, Leiden, The Netherlands

I. F. M. de Coö
Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands

M. Langeveld
Department of Endocrinology and Metabolism, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Introduction

Mitochondrial trifunctional protein (MTP) is a multi-enzyme complex which catalyses the last three steps of the β -oxidation of long-chain fatty acids in mitochondria. MTP is a hetero-octamer consisting of four α -subunits and four β -subunits that harbour enzyme activity of long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), long-chain enoyl-CoA hydratase (LCEH), and long-chain 3-ketoacyl-CoA thiolase (LCKAT). MTP deficiency and isolated LCHAD deficiency are clinically indistinguishable. MTP deficiency is caused by mutations in the genes *HADHA* and *HADHB*, encoding the α - and the β -subunits, respectively, resulting in decreased enzyme activity of all three enzymes, whereas the majority of patients of European origin with isolated LCHAD deficiency are homozygous for a common mutation in the *HADHA* gene (Spiekerkoetter et al. 2003a; Brackett et al. 1995).

MTP deficiency is a rare disorder; during a 6-year period only 11 patients were identified out of 1.2 million newborns screened in the routine neonatal screening program in Germany (Sander et al. 2005). Since the start of screening in the Netherlands in 2007, 8 patients with MTP deficiency have been identified, which corresponds to an annual incidence of 1 patient per 200,000 newborns (personal communication). MTP deficiency has a heterogeneous clinical presentation, with disease severity depending on both residual enzyme activity and the exposure to stress (Morris and Spiekerkoetter 2016). Patients with severe deficiency present with severe neonatal disease, characterized by cardiomyopathy, arrhythmias, (hepatic) encephalopathy, and early death. Another phenotype, resembling that of patients with isolated LCHAD deficiency, is characterized by recurrent episodes of hypoketotic hypoglycaemia that are generally induced by illness and prolonged fasting. A milder phenotype, with late-onset (juvenile/adolescent) type of disease, presents with myopathy, episodic rhabdomyolysis, peripheral neuropathy, and retinopathy (Morris and Spiekerkoetter 2016; Boutron et al. 2011; Spiekerkoetter et al. 2003b). Although there is no strict genotype–phenotype correlation, mutations in *HADHB* gene are primarily associated with the severe neonatal disease form, whereas mutations in the *HADHA* gene associate with all disease phenotypes (Boutron et al. 2011). Because MTP deficiency is a rare disease with a highly variable clinical presentation, establishing the diagnosis can be challenging.

Here we report a 20-year-old patient with MTP deficiency who was diagnosed after an episode of severe rhabdomyolysis and respiratory weakness requiring mechanical ventilation, following a pneumonia. Interestingly, a concomitant diagnosis of hypoparathyroidism was made.

Case Presentation

A 20-year-old woman presented to the emergency department with progressive dyspnoea and difficulty swallowing since 2 days. These symptoms were preceded by 6 days of fever, abdominal pain, vomiting, and diarrhoea. She also reported increased muscle weakness with difficulty moving her arms and she had not been able to walk for days. In the previous weeks she suffered from a common cold and a persistent cough.

Her medical history included slowly progressive distal weakness and sensory deficits (gnostic more than vital) of the lower extremities, pes cavus, areflexia, and electromyographic signs of an axonal motor sensory polyneuropathy (Supplementary Table 1). This was attributed to hereditary motor and sensory neuropathy (HMSN), although this diagnosis was not confirmed on a molecular level. Later obtained medical history also revealed shuddering attacks with reduced consciousness, which started from 40 days after birth. A concomitant hypocalcaemia, caused by hypoparathyroidism, was interpreted as the possible explanation for these attacks. The patient used active vitamin D for a short-term, which was discontinued for unknown reasons. In recent years she experienced muscle pain and cramps with exercise and occasionally had red urine. Her parents were non-consanguineous and from North-African descent. Both parents and her younger brother and sister were healthy and none had signs of peripheral neuropathy.

In the emergency room the patient was tachycardic (105 beats per minute), breathing was shallow at a rate of 25 breaths per minute, accompanied by the use of accessory muscles of respiration and difficulty speaking, but with sufficient oxygenation without oxygen support. There was upper quadrant abdominal tenderness. Neurological examination revealed weakness of neck extensors and -flexors with head drop, and symmetrical weakness of proximal and distal muscles of upper and lower extremities. Muscle strength was ‘Medical research council’ (MRC)-scale 3/3 of proximal arm muscles, 4/4 of distal arm muscles, 3/3 of proximal leg muscles, 4/4 of foot extensors, and 1/1 of foot flexors. Sensory testing revealed hypoaesthesia of the lower extremities, and absent vibration sense in all extremities. Deep tendon reflexes were absent, corresponding with previous examinations.

Laboratory testing showed severe rhabdomyolysis with creatine kinase (CK) of 193,936 U/L (normal range: 0–145 U/L). Aspartate aminotransferase (ASAT) was 2,781 U/L (0–31 U/L), alanine aminotransferase (ALAT) was 791 U/L (0–34 U/L), and lactate dehydrogenase (LDH) was 3,583 U/L (0–247 U/L), with otherwise normal liver enzyme tests. Corrected calcium was 1.48 mmol/L (2.15–2.55 mmol/L), and anorganic phosphate 2.41 mmol/L

(0.90–1.50 mmol/L), with otherwise normal electrolyte levels and renal function. Parathyroid hormone (PTH) level was 0.6 pmol/L (0.7–8.0 pmol/L), and 25-OH-vitamin D level was 17 nmol/L (50–250 nmol/L). Complete blood count and coagulation tests were normal. Chest X-ray and abdominal ultrasonography showed no relevant abnormalities.

The patient was admitted to the intensive care unit, where intravenous hydration was started for severe rhabdomyolysis and calcium was supplemented. Because of the severe rhabdomyolysis, plasma, and urine samples were collected for metabolic screening. On the second day of admission the patient was intubated because of respiratory insufficiency. Shortly hereafter she developed fever and was treated with broad-spectrum antibiotics for community acquired pneumonia. Oseltamivir was added after molecular diagnostics revealed Influenza B RNA. Sputum cultures showed *Staphylococcus aureus* and *Moraxella catarrhalis* and antibiotics were narrowed-down accordingly. After 9 days the patient was extubated and 2 days later she was transferred to the neurology ward. Muscle strength normalized to pre-admission levels, and she was discharged after 16 days of admission. Laboratory testing 4 weeks later revealed complete normalization of aminotransferases and a still slightly elevated CK of 580 U/L.

Fourteen weeks after the first presentation the patient suffered another episode of rhabdomyolysis that followed two weeks of diarrhoea and several days without oral intake, most likely caused by a viral gastroenteritis. Laboratory testing revealed a CK of 28,660 U/L, ASAT of 416 U/L, ALAT of 125 U/L, LDH of 801 U/L, corrected calcium of 1.74 mmol/L, and PTH level of 0.6 pmol/L. Intravenous hydration was started for rhabdomyolysis, and the hypoparathyroidism was treated with intravenous and oral calcium supplementation, as well as alfacalcidol. She quickly recovered and was discharged after 7 days.

During the second admission the metabolic screening results became available and showed increased concentrations of long-chain 3-hydroxyacyl carnitine species, together with elevated urinary excretion of 3-hydroxy dicarboxylic acids. Following this, activity of enzymes involved in the β -oxidation of long-chain fatty acids was measured in peripheral lymphocytes and fibroblasts

(Table 1). Both LCHAD and LKAT activity were strongly reduced, pointing towards a MTP deficiency. Sequence analysis of the *HADHB* gene showed two heterozygous variants: c.209+1G>C (splicing defect) and c.980T>C (p. Leu327Leu). The *HADHA* gene did not contain potential pathogenic variants.

A pulmonologist was consulted because of the respiratory insufficiency during the first admission and complaints of shortness of breath during exercise. Pulmonary function showed slightly decreased vital capacity of 2.98 L (82% of predicted), normal maximum inspiratory pressure of 7.82 kPa (105% of predicted), and decreased maximum expiratory pressure of 4.62 kPa (49% of predicted), which was interpreted as decreased abdominal wall muscle strength accompanying MTP deficiency. Histamine provocation showed signs of bronchial hyper-reactivity, for which salbutamol and formoterol/beclomethasone were started.

Treatment for MTP deficiency was started with a long-chain fatty acids restricted, high carbohydrate and protein diet, supplemented with medium chain fatty acids, essential fatty acids, maltodextrin, and uncooked corn starch before bedtime. This improved her exercise endurance initially, but adherence to the diet proved difficult.

Discussion

Our case illustrates the difficult and long trajectory from first symptoms to the correct diagnosis of rare inborn errors of metabolism that can occur specifically in milder phenotypes of these diseases. MTP deficiency is a mitochondrial fatty acid β -oxidation disorder with a variable clinical phenotype. Timely diagnosis has important implications for management, mainly to prevent episodes of metabolic decompensation.

Although our patient had non-classified motor and sensory neuropathy discovered in childhood, and had been seen in our outpatient clinic months before, diagnosis of MTP deficiency was not made until she presented to our hospital with an episode of severe weakness and rhabdomyolysis, accompanying an Influenza B infection. Recording of the previous clinical history revealed that the patient

Table 1 Enzymatic activity measured in lymphocytes and fibroblasts

Cell type	LCHAD activity (nmol/(mg min protein))	Reference value	LKAT activity (nmol/(mg min protein))	Reference value
Fibroblasts	12	34–114	6	58–110
Lymphocytes	6	22–74	2	23–43

LCHAD long-chain 3-hydroxyacyl-CoA dehydrogenase, *LKAT* long-chain 3-ketoacyl-CoA thiolase

suffered from episodic weakness throughout her life triggered by gastroenteritis, fasting, and menstruation.

Nowadays, neonatal screening for MTP deficiency is performed by determination of the acylcarnitine profile in dried blood spots by tandem mass spectrometry. However, acylcarnitine profile can be completely normal when the test is performed in the absence of metabolic stress (Yagi et al. 2011), as was the case in our patient when her profile was tested 2 months after the second episode of rhabdomyolysis. As such, an earlier normal acylcarnitine profile, obtained as part of neonatal screening or otherwise, does not rule out the diagnosis of a long-chain fatty acid oxidation disorder in a patient that presents with symptoms fitting the diagnosis.

The clinical presentation, dominated by progressive peripheral neuropathy accompanied by episodic rhabdomyolysis, suggests that our patient suffered from the milder late-onset phenotype, which is most often caused by mutations in the *HADHA* gene. Sequence analysis, however, showed mutations in the *HADHB* gene, whereas previous case series showed that *HADHB* mutations are associated with phenotypes of either the severe neonatal form or the infantile hepatic form (Boutron et al. 2011). One of the variants (c.209+1G>C) demonstrated in our patient has previously been identified in a patient with a neonatal phenotype, who was homozygous for this mutation (Boutron et al. 2011). The second mutation (c.980T>C) has not been described earlier. It is possible that compound heterozygosity with the two described variants in our patient explains the MTP deficiency with a milder than expected phenotype. Compound heterozygosity has been described both in patients with *HADHA* gene mutations (Boutron et al. 2011), and in patients with *HADHB* gene mutations (Yagi et al. 2011).

A remarkable finding in our patient was a severe hypocalcaemia, caused by primary hypoparathyroidism. Although not a common feature of MTP deficiency, (congenital) hypoparathyroidism has been reported in five patients before (Dionisi-Vici et al. 2003; Tyni et al. 1997; Labarthe et al. 2006; Naiki et al. 2014). In four patients, including two siblings, MTP deficiency was caused by mutations in the *HADHB* gene (Dionisi-Vici et al. 2003; Labarthe et al. 2006; Naiki et al. 2014), whereas one patient had isolated LCHAD deficiency (Tyni et al. 1997). All four patients with MTP deficiency showed a clinical picture similar to our patient, dominated by distal peripheral neuropathy with lower limb weakness, and episodic rhabdomyolysis triggered by (viral) infections and fasting. Although hypocalcaemia is frequently observed during rhabdomyolysis due to renal failure, in our patient kidney function remained normal and PTH was low during both admissions. Moreover, the patient's medical history reported hypoparathyroidism earlier on in

life. The pathophysiological link between (congenital) hypoparathyroidism and MTP deficiency is unclear. It has been suggested that mutations in enzymes involved in the β -oxidation of fatty acids cause congenital malformation leading to absence of parathyroid glands (Tyni et al. 1997). However, since all other organs develop normally this is not a very likely explanation. In some reported patients and in our patient, there was partial recovery of parathyroid function following treatment, suggesting parathyroid hypoplasia or impaired secretion of PTH (Labarthe et al. 2006). Others suggested that the accumulation of long-chain fatty acids in parathyroid glands could cause direct cellular toxicity (Saudubray et al. 1999). This may explain why PTH is lower at the time of metabolic decompensation.

Our case underlines the importance of determination of an acylcarnitine profile in adult patients with unexplained peripheral neuropathy, when this is accompanied by episodic exacerbations of weakness, exercise intolerance, or documented rhabdomyolysis. Recording of the previous clinical history should focus on known triggers, such as fasting or infections. Metabolic screening should preferably be performed during these exacerbations, since screening may be unremarkable in patients with MTP deficiency in absence of high metabolic demand. Lastly, primary (congenital) hypoparathyroidism may be a feature of MTP deficiency and could be the initial presentation of the disease in infancy.

Synopsis

Mitochondrial trifunctional protein deficiency can present as a cluster of peripheral neuropathy, hypoparathyroidism, and episodic exacerbations during metabolic stress, with the important notice that metabolic screening may be normal when performed when no metabolic stress is present.

Compliance with Ethics Guidelines

Author Contributions

All authors were involved in drafting the manuscript and revising it critically for important intellectual content and have agreed upon submission of the manuscript.

Competing Interest/Funding

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Ethics Approval/Consent

This case report did not need evaluation by a medical ethical committee. Informed consent to publish the case report was obtained from the patient.

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