Management of an LCHADD Patient During Pregnancy and High Intensity Exercise

D.C.D. van Eerd • I.A. Brussé • V.F.R. Adriaens •
R.T. Mankowski • S.F.E. Praet • M. Michels •
M. Langeveld

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Abstract In this report we describe a female Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD) patient who suffered from severe exercise intolerance. At age 34, the patient became pregnant for the first time. After an uneventful first 32 weeks of pregnancy she developed sinus tachycardia (resting heart rate 120–134 bpm) and lactate and creatinine kinase levels increased (3.3 mmol/L and 264 U/L, respectively). Increasing MCT supplementation (dose and frequency of administration) lowered heart rate and improved biochemical parameters. At 34 weeks the heart rate rose again and it was decided to deliver the child by caesarean section. Postpartum both mother and child did well.

Prior to pregnancy, she performed exercise tests with different doses of medium chain triglycerides (MCTs) to establish a safe and effective exercise program (baseline test, second test with 10 g MCTs and third test with 20 g of MCTs). In the MCT supplemented tests the maximal power

output was 23% (second test) and 26% (third test) higher, while cardiac output at maximal power output was the same in all three tests (~15.8 L/min).

In conclusion, this is the first report of pregnancy in an LCHADD patient, with favourable outcome for both mother and child. Moreover, in the same patient, MCT supplementation improved cardiac performance and metabolic parameters during high intensity exercise. Using impedance cardiography, we got a clear indication that this benefit was due to improved muscle energy generation at high intensity exercise, since at the same cardiac output a higher power output could be generated.

Introduction

Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD, OMIM 600890) is a rare inborn error of long chain fatty acid metabolism, resulting in mitochondrial dysfunction with subsequent energy shortage as well as toxic effects of fatty acid metabolites (den Boer et al. 2002). Clinically, this results in hypoketotic hypoglycaemia, metabolic acidosis, cardiomyopathy and liver disease presenting in infancy (den Boer et al. 2002). In those patients who survive early childhood, the main characteristics are fatigue and exercise intolerance, retinopathy and less common peripheral neuropathy (Spiekerkoetter 2010). Prognosis in early treated patients is generally favourable (Sim et al. 2002), but still not all patients survive into adulthood and long term complications are common.

Acute metabolic decompensation, leading to elevated CK concentrations or rhabdomyolysis, acidosis and eventually hypoglycaemia, can be triggered by fasting, infection

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D.C.D. van Eerd • M. Langeveld (✉)
Center for Lysosomal and Metabolic Disease,
Erasmus University Medical Center, 's Gravendijkwal 230,
3015 CE Rotterdam, The Netherlands
e-mail: m.langeveld.1@erasmusmc.nl

I.A. Brussé
Department of Obstetrics and Gynaecology, Erasmus University
Medical Center, Rotterdam, The Netherlands

V.F.R. Adriaens
Department of Anaesthesiology, Erasmus University Medical Center,
Rotterdam, The Netherlands

R.T. Mankowski • S.F.E. Praet
Department of Rehabilitation Medicine, Erasmus University Medical
Center, Rotterdam, The Netherlands

M. Michels
Department of Cardiology, Erasmus University Medical Center,
Rotterdam, The Netherlands

or other causes of increased energy demand. Treatment consists of immediate supply of extra energy in the form of carbohydrates and medium chain triglycerides (MCTs) and strict limitation in intake of long chain fatty acids (Spiekerkoetter et al. 2009). Carnitine supplementation can be considered, though it may theoretically increase levels of hydroxyacylcarnitines, one of the toxic fatty acid metabolism intermediates that accumulate in LCHADD (Spiekerkoetter et al. 2010). Given the restriction in long chain fatty acid intake additional essential fatty acids (especially docosahexaenoic acid) should be given (Spiekerkoetter et al. 2010).

Exercise increases energy demand and therefore supplementation of additional energy before exercise initiation can be necessary in LCHADD patients to prevent complications. MCTs unique kinetics, with faster intestinal as well as mitochondrial uptake compared to long chain fatty acids, make them a very effective energy source. In the small intestines MCTs can diffuse passively into the portal system (as opposed to LCT that require active uptake into the lymphatic system), without modification (Bach and Babayan 1982). MCT uptake into the mitochondrion does not require the formation of acylcarnitines and MCTs can thus be used as a source of energy in LCHADD patients. A study in nine LCHADD patients showed a positive effect of MCT supplementation (0.5 g/kg lean body mass) on exercise tolerance (Gillingham et al. 2006). A second study in 11 patients showed a lower steady state heart rate at the same workload after using pre-exercise MCT supplementation (0.5 g/kg lean body mass) compared to isocaloric carbohydrate supplementation in long chain fatty acid oxidation disorders (Behrend et al. 2012). In addition, a positive effect of an odd chain triglyceride, triheptanoate, on exercise performance in a single LCHADD patient has been reported (Karall et al. 2014). Since no cardiac output measurements were performed, these studies cannot distinguish between a positive effect of MCTs at the level of the heart versus the skeletal muscle.

To our knowledge, there are no published reports of pregnancy in an LCHADD patient, though pregnancies in other fatty acid oxidations, e.g. CPT2 deficiency, MCADD and VLCADD have been described in several case reports (Ramsey and Biggio 2005; Santos et al. 2007; Yamamoto et al. 2015).

Case Description

We here describe a 34-year-old female LCHADD patient who was diagnosed in early childhood when she presented with hypotonia, hypoglycaemia and failure to thrive. This was first attributed to a systemic carnitine deficiency. At age 10 the correct diagnosis of LCHAD deficiency was

established based on the presence of a typical acylcarnitine pattern in plasma, reduced enzyme activity and genetic testing (homozygous for the c.1528G > C mutation). With dietary management, she did quite well during childhood, experiencing only mildly reduced exercise tolerance compared to peers. From age 21 onwards her exercise capacity has declined considerably, her last measured maximal uninterrupted walking distance was 200 m. She did try to exercise frequently, but often suffered from post-exercise myalgia. Further symptoms consisted of poor eyesight due to retinitis pigmentosa (OD 2/60: able to count fingers at 2 m distance, OS: can see hand movements only) and peripheral neuropathy. On echocardiography her cardiac function was normal, but resting heart rate was elevated at outpatient clinic visits (± 100 bpm). Because of intermittent episodes of palpitations she was treated with low dose beta-blockade (50 mg slow acting metoprolol once daily).

The patient adhered to a long chain triglyceride restricted, high carbohydrate diet, supplemented with MCTs. Her weight was 65.5 kg, total energy intake 2,151 kcal per 24 h of which 9% came from long chain fatty acids, 21% from medium chain fatty acids, 58% from carbohydrates and 15% from protein. Protein intake was ample at 1.5–2 g/kg bodyweight. She used the following supplements: MCTs three times 10 g daily (MCT Procal, VitaFlo, UK), essential fatty acids once daily (KeyOmega, one dose containing 200 mg of arachidonic acid and 100 mg of docosahexaenoic acid, VitaFlo, Liverpool, UK), maltodextrin six times daily 5 g (Fantomalt, Nutricia, the Netherlands), 30 g of uncooked cornstarch at nighttime and levocarnitine 1 g three times daily.

Pregnancy and Birth

At age 34 the patient became pregnant for the first time. Early on in pregnancy the beta-blockade treatment was discontinued because of its potential negative effects on placental function. At 10 weeks pregnancy duration maternal echocardiography showed a structurally normal heart with normal left and right ventricular function. 24 hour ECG Holter monitoring at 17 weeks showed sinus rhythm with a mean heart rate of 94 bpm without arrhythmia.

During pregnancy the caloric intake was gradually increased by increasing both carbohydrate (simple and complex) and MCT intake. During the first 31 weeks of pregnancy there were no specific complaints or symptoms and biochemical parameters remained stable. Fetal development, biometry and structural ultrasonography were unremarkable.

At 32 weeks pregnancy duration the patient developed complaints of intermittent, mostly nightly, palpitations and

a reduction in exercise tolerance. Resting heart rate was 120 bpm (sinus rhythm). There were no signs of cardiac decompensation. Reinstitution of low dose beta-blockade for 1 week did not have any effect on the complaints or the heart rate and at 33 weeks she was admitted to the cardiac care unit with a resting heart rate of ~120/min. Both plasma lactate and CK levels (both previously in the normal range) were mildly elevated (3.3 mmol/L and 264 U/L, respectively). We increased the dose and the number of administrations of MCT supplementation from 40 to 60 g/day (in six doses). The next day her heart rate was lower (~100 bpm), palpitations diminished and CK levels normalised. This improvement lasted 12 days, after which heart rate rose again and the patient felt worse. After a multidisciplinary discussion and consulting the patient and her partner it was decided to deliver the child by caesarian section at 34 + 1 weeks. Her weight at that time was 74.9 kg, total energy intake 3,230 kcal per 24 h of which 8% came from long chain fatty acids, 23% from medium chain fatty acids, 55% from carbohydrates and 14% from protein. During pregnancy, levels of long chain hydroxyacylcarnitines dropped initially, but at 34 weeks the levels were similar to the preconceptional levels. For example, the C16OH-carnitine level was 0.20 $\mu\text{mol/L}$ preconceptionally, 0.09 $\mu\text{mol/L}$ at 17 weeks of pregnancy and 0.17 $\mu\text{mol/L}$ at 34 weeks of pregnancy. Free carnitine levels remained normal throughout pregnancy.

To prevent metabolic decompensation the patient continued taking her oral MCT supplements right up to surgery and 10% glucose infusion (2 L per 24 h) was started on the ward. Premedication consisted of oral metoclopramide and oral ranitidine (aspiration-prophylaxis). Standard non-invasive heart rhythm, blood pressure and oxygen saturation monitors were applied.

Because of the need for frequent blood samples and continuous blood pressure monitoring, an arterial line was placed in the right radial artery. Normal saline preload was administered intravenously. To prevent interference with the patient's serum lactate levels, ringers lactate infusion was avoided. A combined spinal epidural was placed in sitting position. After spinal injection, a phenylephrine infusion was started to prevent hypotension. The patient was placed supine in the left lateral tilt position. An adequate sensory block was reached 10 min after spinal injection.

Surgery commenced and a baby girl was born 5 min after incision. Routine prophylactic antibiotics were injected intravenously after clamping of the cord. An oxytocin bolus was avoided to prevent sudden extreme contraction of the uterus musculature, which might cause metabolic derangement. An oxytocin infusion of 10 IU in 500 mL of glucose 5% solution was infused over 2 h. Estimated intra-operative blood loss was 300 mL.

The patient remained haemodynamically stable throughout the whole procedure. Postoperative analgesia was delivered by means of intravenous paracetamol and a patient controlled epidural infusion. The patient was admitted to the intensive care unit for postoperative monitoring. The following day, she was returned to the obstetric high care unit in good condition.

Postpartum the patient did clinically very well. Biochemically there was slight further increase in plasma lactate (maximal level 4.9 mmol/L) and a drop in bicarbonate (lowest level 16.1 mmol/L) which corrected spontaneously over the next few days. Oral energy intake (carbohydrates and MCTs) was high (3,230 kcal per 24 h) the first days after delivery and IV glucose administration could be discontinued after 1 day. The patient left the hospital 4 days postpartum in good clinical condition. 14 weeks postpartum she was in good clinical condition, had no palpitations or other complaints and her resting heart rate was ~82 bpm using 25 mg of metoprolol.

Exercise Testing

Approximately 6 months prior to her pregnancy, the patient was referred to the rehabilitation outpatient clinic because she wanted to improve her endurance capacity. She completed three incremental cycle ergometry exercise tests over the course of 1 month to examine the effects of MCT supplementation on exercise tolerance and cardiac function, in order to establish a safe training program with adequate dietary advice. The patient performed a symptom limited exercise stress test. This standard ramp test started with a 2 min rest period followed by 4 min of unloaded cycling as warming-up. Next, the workload increased with a slope of 1 W/5 s. The subject was instructed to cycle until exhaustion with a pedal frequency of 60–80 revolutions per minute (rpm). The loaded phase was terminated when pedalling frequency dropped below 60 rpm after which a 5 min unloaded recovery phase ended the exercise test. During warming-up, workload and recovery phase of the exercise protocol, VO_2 and VCO_2 were measured (Oxycon Pro, Carefusion, Houten, the Netherlands). Using these respiratory indices the respiratory exchange ratio (RER) was calculated (VCO_2/VO_2). The RER was then used to determine the ventilatory threshold ($\text{RER} = 1$), at which point lactate starts to accumulate in the bloodstream. Expiratory VCO_2 rises exponentially after this point, as a byproduct of lactate buffering in the bloodstream, to prevent the occurrence of severe acidosis.

Stroke volume and cardiac output were assessed during the test using impedance cardiography (SM-ICG, PhysioFlow PF05 Lab1, PhysioFlow, France). Blood was drawn at rest, just before reaching the ventilatory threshold and at

maximal power output. The first test was performed without MCT supplementation, the second test with 16 g of MCT Procal supplement (containing 10 g of MCTs, total 112 kcal) and the third test with 32 g (containing 20 g of MCTs, total of 224 kcal). The MCT supplement was taken 25 min prior to the test. The diet was otherwise unchanged and body weight remained stable between the tests.

The observed peak oxygen consumption in the baseline test was only 40% of predicted (using the Fairbairn equation which takes into account age, gender and weight) (Fairbairn 1994). Compared to the baseline test, in the second test (using 10 g of MCTs) maximal power output was increased by 25% (70 vs 88 W) and maximal oxygen consumption by 26% (956 mL/min vs 1,209 mL/min). At maximal workload, in the second test the stroke volume was lower and maximal heart rate higher, resulting in the same cardiac output at maximal power output. Thus, the 25% higher power output in the second test was reached at the same cardiac output (Table 1).

When comparing the second to the first exercise test, power output at the ventilatory threshold was more than doubled (64 vs 28 W) and the oxygen consumption per Watt produced was much lower (16 vs 28 W). No further

improvement of the increase in MCT dose from 10 to 20 g on power output or cardiac parameters was observed.

In the MCT supplemented second and third test, both at rest and during exercise, plasma lactate concentrations were lower compared to the baseline test. The same was true for plasma creatinine kinase levels (Table 2). There were no clear differences between the tests in plasma glucose, ammonia and free fatty acid (FFA) concentrations (Table 2). Plasma beta-hydroxybutyrate was higher in the second test, but this increase was not observed in the third test (Table 2).

Discussion

MCTs are an ideal source of energy to be used prior or during exercise since, in contrast to long chain fatty acids, they do not delay gastric emptying and are rapidly taken up and transported to peripheral tissues (Beckers et al. 1992; Jeukendrup and Saris 1996). Combining MCTs with carbohydrates accelerates MCT oxidation without negatively affecting endogenous carbohydrate oxidation. The positive effect of MCT supplementation on exercise performance in long chain fatty acids disorders has been described before, but it remained unclear whether this effect was due to improved metabolic efficiency at the level of the heart, the skeletal muscle or both (Gillingham et al. 2006; Behrend et al. 2012).

During exercise, carbohydrates and fatty acids are the main source of energy for skeletal muscle and the heart. In terms of substrate preference, the heart favours fatty acids over glucose, both at rest and during exercise. Fatty acids

Table 1 Physiological and cardiac measurements during exercise tests

Test	1	2	3
Grams of MCTs	0	10	20
Maximal power output (W)	70	88	86
Time to exhaustion (mm:ss)	12:21	13:37	13:30
Power output at RER = 1 (W)	28	64	40
Heart rate rest (bpm) ^a	96 ± 3	93 ± 4	112 ± 3
Heart rate max (bpm)	150	160	174
VO ₂ max (mL/min)	956	1,209	1,245
VO ₂ /W at RER = 1 (mL/min)	27	16	19
RER rest	0.99	0.93	1.02
RER max	1.18	1.26	1.24
Stroke volume rest (mL) ^a	97 ± 4	88 ± 6	80 ± 2
Stroke volume at max power (mL) ^b	111 ± 4	100 ± 1	92 ± 1
Cardiac output rest (L/min) ^a	9.4 ± 0.5	8.2 ± 3.1	9.0 ± 0.4
Cardiac output at max power (L/min) ^b	15.6 ± 0.5	15.9 ± 0.3	15.9 ± 0.2

Heart rate max maximal heart rate measured during test, VO₂ max the highest VO₂ measured during the test, RER max RER measured at the highest power output during the test

^a Average of 21 measurements

^b Average of 3 measurements

Table 2 Biochemical measurements during exercise tests

Test	1	2	3
Glucose rest (mmol/L)	5.5	4.5	4.3
Glucose max (mmol/L)	5.0	5.2	5.1
CK rest (IU/L)	183	135	110
CK max (IU/L)	197	139	115
Lactate rest (mmol/L)	1.7	0.9	0.8
Lactate max (mmol/L)	3.5	2.4	1.9
NH ₃ rest (μmol/L)	41	<10	16
NH ₃ max (μmol/L)	30	22	39
FFA rest (mmol/L)	0.21	0.27	0.32
FFA max (mmol/L)	0.31	0.26	0.24
BHB rest (mmol/L)	0.10	0.29	0.14
BHB max (mmol/L)	0.10	0.22	0.12

CK creatine kinase, NH₃ ammonia, FFA free fatty acids, BHB betahydroxybutyric acid, Rest before starting exercise, max at maximal exercise capacity

become a more important energy source during high intensity and prolonged exercise as muscle and liver glycogen stores are gradually depleted (Massicotte et al. 1992; van Loon et al. 2001). Given the preference of the heart for fatty acids as fuel and the fact that acute dilated cardiomyopathy can develop in LCHADD patients at times of acute metabolic stress (Dyke et al. 2009) we expected the improvement in exercise performance after MCT supplementation in our patient to be due to improved cardiac performance. However, after MCT supplementation maximal cardiac output was the same, but maximal power output increased considerably. This points in the direction of more efficient ATP generation at the level of the skeletal muscle. The more than doubled power output at ventilatory threshold after MCT supplementation indicates improved aerobic oxidation. Since we used a high intensity exercise protocol aimed at reaching exhaustion, we cannot exclude a positive effect of MCT supplementation on cardiac function at lower intensity exercise. In addition to the positive effect of the MCTs, the small amount of protein present in the MCT supplement (2 g in the second test and 4 g in the third test) may have had an anaplerotic effect in energy.

In this report, we describe for the first time a pregnancy in an LCHADD patient. Pregnancies in the mothers carrying a fetal with LCHADD or mitochondrial trifunctional protein deficiency (MTP deficiency) can be complicated by acute fatty liver of pregnancy or HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome (Ibdah et al. 1999; Yang et al. 2002). This is thought to be due to the spill of toxic fatty acid oxidation intermediates from the fetal and/ or placenta into the maternal circulation (Strauss et al. 1999). In the pregnancy here described, LCHADD or MTP deficiency in the foetus was highly unlikely since molecular diagnostics showed that the patient's partner did not carry a mutation in the relevant genes. What the risk of these pregnancy complications is in a mother who is homozygous for an LCHADD mutation, carrying a heterozygous foetus, is unknown. We closely monitored our patient throughout pregnancy and no signs of fatty liver of pregnancy or HELPP were found.

The pregnancy was uneventful up to 32 weeks when the increase in heart rate and the slight changes in biochemical parameters indicated the onset of metabolic decompensation. Most likely, the increase in heart rate was a result of a higher oxygen demand resulting from peripheral energy shortage and not a sign of cardiomyopathy, since repeated echocardiography showed no signs of either dilatation of the heart or of decreased cardiac muscle function. Increasing the dose and the number of administrations of MCTs initially lowered heart rate and improved the patient's well-being. However, at 34 weeks the heart rate increased again and the patient was feeling less well. It was then decided to not risk full metabolic decompensation, but to deliver the

child. We debated whether a caesarean section or assisted vaginal deliverance would give the best outcome for both mother and child, since in, for example, patients with cardiomyopathy assisted vaginal birth gives better maternal outcome compared to caesarean section (Ruys et al. 2013; Ruys et al. 2014) because of substantial haemodynamic instability during surgery. Since we wanted to prevent further metabolic derangement resulting from muscle activity during a vaginal delivery we chose to perform a caesarean section.

In conclusion, this is the first report of pregnancy in an LCHADD patient, with favourable outcome for both mother and child. Moreover, in the same patient, MCT supplementation improved cardiac performance and metabolic parameters during high intensity exercise. Our results indicate that at high intensity exercise this benefit is a result of improved aerobic muscle energy generation. This finding needs to be confirmed in a larger patient cohort.

Take Home Message

This report describes the first documented pregnancy in an LCHADD patient, with favourable outcome for both mother and child.

Compliance with Ethics Guidelines

Conflict of Interest

D.C.D. van Eerd, M. Langeveld, I.A. Brussé, V.F.R. Adriaens, R.T. Mankowski, S.F.E. Praet and M. Michels declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Medical Ethics Committee Erasmus MC) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from the patient described in this case report.

Contributions of Individual Authors

Data collection: DCDvE, RTM, SFEP and MM; analysis and interpretation of the data: DCDvE, IAB, RTM, SFEP, MM and ML; drafting the article: DCDvE, IAB, VFRA, RTM and ML; critically revising the article: SFEP

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