Favourable Outcome in Two Pregnancies in a Patient with 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

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Abstract In patients with 3-hydroxy-3-methylglutaryl (HMG)-CoA lyase deficiency (OMIM 246450), five pregnancies have been described worldwide, which were either terminated or resulted in severe metabolic sequelae during pregnancy or delivery. Here, we report on a patient with HMG-CoA lyase deficiency, who underwent two uncomplicated pregnancies. The 19-year-old patient was admitted because of recurrent vomiting and nausea. Diagnostics revealed pregnancy at week 8 of gestation. Metabolic analyses revealed normal lactate and blood glucose levels and normal acid-base status. Urine organic acid analysis showed an elevated excretion of 3-CH₃-glutaric acid, 2,3-CH₃-glutaconic acid, and 3-CH₃-3-OH-glutaric acid. Oral treatment with carnitine and glucose was administered intravenously during the period of nausea and vomiting. After clinical recovery, a diet with 0.89 g/kg of protein/d

and 38 kcal/kg body weight/d was given. Meals were taken every 3 h. Additionally, 70 g of starch was given at midnight to maintain normoglycemia at night time. Peripartum, a complete parenteral nutrition, was delivered through a central venous catheter. The patient delivered a healthy male infant by Caesarean section at week 38 of gestation (Apgar 9/10/10) and remained metabolically stable throughout the peripartum period. Postpartum nutrition was gradually changed from parenteral to oral diet. Two years later, the patient became pregnant again and presented with hyperemesis gravidarum. With metabolic monitoring and treatment as before no decompensation occurred. At week 38 of gestation, she delivered a healthy female infant by elective Caesarian section (Apgar 9/10/10). This case report describes the metabolic and obstetric management of two pregnancies in a patient with HMG-CoA lyase deficiency with favorable outcome without metabolic complications.

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Introduction

3-Hydroxy-3-methylglutaryl(HMG)-CoA lyase deficiency (OMIM 246450) is an autosomal recessive error of metabolism characterized by an impaired leucine catabolism and ketogenesis (Fig. 1). So far, 43 mutations in 124 patients have been reported in the HMGCL gene (Menao et al. 2009). Common clinical features of the disease at first presentation are hypoketotic hypoglycemia, acidosis, vomiting, and a reduced level of consciousness. Moreover, epilepsy and severe coma can develop. On MRI, white matter changes in the corticospinal tract, and the pons have been described (Yılmaz et al. 2006). White matter changes

Fig. 1 Ketone body formation and leucine degradation are impaired in 3-hydroxy-3-methylglutaryl(HMG)-CoA lyase deficiency. Ketone bodies are synthesized in liver mitochondria. The enzyme β -ketothiolase catalyzes the formation of two molecules acetyl-CoA to acetoacetyl-CoA. Mitochondrial HMG-CoA synthase catalyzes the condensation of acetyl-CoA to the carbonyl group of acetoacetyl-CoA to form HMG-CoA. HMG-CoA lyase then cleaves HMG-CoA to form acetyl-CoA and acetoacetate. Acetoacetate is reduced to β -hydroxybutyrate by β -hydroxybutyrate dehydrogenase, which occurs also in extrahepatic tissues. Acetone is produced by nonenzymatic decarboxylation of acetoacetate. In extrahepatic tissues, HMG-CoA lyase is necessary for the degradation of leucine to ketones. Deficiency of HMG-CoA lyase leads to impairment of ketogenesis and leucine degradation

have been reported to be reversible on serial brain MRI in patients on leucine-restricted diet (Zafeiriou et al. 2007). With prompt diagnosis, prognosis of HMG-CoA lyase deficiency is good (Gibson et al. 1988). Today, an increasing number of patients reach adulthood.

To our knowledge, five pregnancies in three patients with HMG-CoA lyase deficiency have been described (Langendonk et al. 2012; Pipitone et al. 2016). One patient underwent the first pregnancy with recurrent metabolic decompensation, but delivered a healthy child. During the second pregnancy, the patient developed severe lactic acidosis and hypoglycemia and died in the following course due to sepsis and pulmonary edema. The second patient with underlying polycystic ovarian syndrome (PCOS) developed lactic acidosis with hyperammonemia during her first pregnancy. Subsequently, spontaneous abortion occurred. Three years later, she presented again at week 6 of gestation and, although well, decided to terminate pregnancy (Langendonk et al. 2012). The third patient had an uneventful pregnancy and delivered a healthy child, but developed several complications during labor and delivery including metabolic acidosis (Pipitone et al. 2016).

Pregnancy in these patients presents a challenge to the mother and the caring physician due to pregnancy-associated altered energy and nutrient expenditure. Here, we describe the uncomplicated clinical course and successful metabolic management in a patient with HMG-CoA lyase deficiency during two pregnancies.

Case Report

The diagnosis of HMG-CoA lyase deficiency in our patient was made at the age of 15 months by analysis of organic acids in the urine. Already 1 h after birth, the female newborn of consanguineous Turkish parents had to be treated because of hypoglycemia (1.5 mmol/l). Repeated decompensations with hypoglycemic episodes down to blood glucose level of 0.2 mmol/l at age of 15 months and unconsciousness in the course of infections (mainly gastroenteritis and respiratory infections) resulted in emergency treatments with intravenous glucose treatment and finally led to the diagnosis. During childhood and adolescence, treatment consisted of oral carnitine with a regular high-carbohydrate, low-protein, and low-fat diet (3-hourly meals). Infections with hypoglycemia resulted in inpatient treatment every 2–3 years. At the age of 19 years, the patient was treated at her local hospital for 4 days because of nausea and vomiting. Having reached adulthood, she was referred to our department.

On admission, we found the patient to be pregnant at week 8 of gestation. Nausea and vomiting was attributed to hyperemesis gravidarum. Organic acids in urine were elevated (3-methyl-glutaric acid, 3-methyl-glutaconic acid, and 3-methyl-3-hydroxy-glutaric acid). Glucose 10% i.v. was commenced, and vomiting was successfully controlled with intravenous dimenhydrinate. After improvement of clinical symptoms, diet with 3-hourly meals (containing 50 g carbohydrates per meal) was reinitiated, and intravenous glucose was discontinued. In addition to 3-hourly meals, maltodextrin was given orally in instances of blood glucose levels <4.4 mmol/l (initially up to 215 g maltodextrin/24 h divided in 8 doses, in the following course 30 g maltodextrin/24 h with one dose at night and one in the morning). Starch (70 g) was given at midnight due to repeated low glucose levels at night (down to 3.3 mmol/l; range, 3.3–5.9 mmol/l). Detailed nutritional instruction and dietary protocol (40 g protein, 1,711 kcal/d, 0.89 g/kg) were given, and the patient was discharged from hospital.

Gynecologic ultrasound revealed an intact pregnancy without any fetal dysplasia. Metabolic monitoring showed lactate and blood glucose levels within the reference range and no episodes of hypoglycemia during the whole pregnancy. C5-OH + HMB acylcarnitines (1.26 μ mol/l, reference range <1 μ mol/l) and C6DC acylcarnitines (0.18 μ mol/l, reference range <0.15 μ mol/l) were slightly elevated and remained stable during repeated measurements. At week 28 of gestation, deficiencies of zinc and vitamin D required oral supplementation. At week 33 of gestation, the patient complained of recurrent nausea and flatulence. Lactose intolerance was suspected and after reduced lactose intake symptoms improved. Further regular medication consisted of 100 mg iron/d, multivitamin

supplement, and carnitine 3×1 g per day. Daily protein intake was increased to 60.5 g per day (0.96 g/kg) with a total of 2,031 kcal/d at week 35 of gestation. The patient's weight gain during the whole pregnancy was 16 kg. Three days prior to the elective Caesarean section at week 36 + 5 days, the patient was admitted to hospital for metabolic monitoring. Due to vomiting 2 days prior to delivery, a total parenteral nutrition via a central venous line was started immediately (2,131 kcal/d, 50 g of amino acids/d, 400 g of glucose/d, and 48 g of 20% MCT lipid infusion/d). Acid-base status, lactate, electrolytes, and ammonia measured every hour prior to delivery were within normal limits. Delivery was performed by elective Caesarean section under spinal anesthesia at week 37 + 1 day of gestation. The healthy male newborn had a length of 49 cm, head circumference of 34 cm, and birth weight of 3,055 g, and Apgar scores were 9/10/10. Regular screening examination at postnatal day 3–10 and metabolic screening were uneventful.

Following a Caesarean section, nutrition was gradually changed from parenteral to enteral (50.1 g protein, total of 1,929 kcal/d, starting with 50% in the first 24 h). Regular metabolic review in hospital and after discharge revealed stable parameters. Afterward, the dose of carnitine (3×1 g/d) and starch (70 g at midnight) remained unchanged, and 2-hourly meals were taken from 6:00 a.m. until 10 p.m.

Two years later, the patient presented at the outpatient clinic with vaginal spotting and nausea. The patient was pregnant at week 6 of gestation. Dietary assistance was immediately provided, and the patient prepared a 3-day dietary record. Six weeks later, the patient continued to have nausea and also complained of intermittent vomiting attributed to early pregnancy. The patient refused hospital admission and was subsequently seen in the metabolic outpatient clinic at 2–3-week intervals. Intake of 70 g of starch was recommended at midnight because of low blood glucose levels in the morning (3.3 mmol/l). The mother of the patient was appointed as a legal custodian. Intelligence quotient was 68, as measured by the nonverbal intelligence test SON-R 2.5–7. At 34 gestational weeks, an additional intake of 20 g protein as a caloric drink was started (total protein 70 g/d). Amino acids, free carnitine, lactate, acid-base status, and blood glucose were within normal limits. Obstetric ultrasound 2 weeks prior to delivery showed good placental function and normal fetal growth.

Elective Caesarean section was planned at week 38 of gestation. Inpatient treatment was started 2 days prior to the planned procedure with metabolic monitoring (blood glucose levels every 3 h, peripartum 8-hourly monitoring of electrolytes, acid-base status, ammonia, and blood count). Peripartum nutrition was started on day of Caesarean section and consisted of 2,113 kcal per day with an intravenous 50% glucose infusion ($=1,200$ kcal/d), a

20% MCT lipid infusion ($=687$ kcal/d), and vitamin supplementation (1 amp. Soluvit®, 1 amp. Vitalipid®). Furthermore, a 10% infusion of amino acids was given ($=226$ kcal/d, 54 g/d). A single dose of 2 g cefazolin was given perioperatively. An uneventful Caesarean section was performed at week 37 and 6 days under epidural anesthesia delivering a healthy female newborn (length 47 cm, head circumference 33 cm, weight 2,795 g, Apgar scores 9/10/10). Clinical examination of the child at postnatal day 3–10 and metabolic screening were within normal limits.

At the follow-up presentations, the patient was free of any clinical symptoms. The abovementioned metabolic parameters remained stable.

Molecular genetics following the second pregnancy, which was performed by MVZ Dr. Eberhard & Partner Dortmund, Laboratoriumsmedizin, Dortmund, revealed a homozygous mutation at position 876 of the HMG-CoA lyase gene with transversion of G $\rightarrow$ C (c.876 + G > C). This transversion at position +1 of the intron is downstream from the exon containing the catalytic site in the encoded protein and has been reported in a Turkish patient with HMG-CoA lyase deficiency (Buesa et al. 1996).

Discussion

An increasing number of young women affected by inborn errors of metabolism reach child-bearing age. Pregnancy-related changes in energy expenditure and altered nutritional requirements represent a challenge for monitoring and treatment of metabolic diseases in pregnant patients. Here, we present a case report of a favorable outcome of two pregnancies and offspring in a patient with HMG-CoA lyase deficiency.

Possible complications in pregnant patients with HMG-CoA lyase deficiency are metabolic decompensation with metabolic acidosis and hypoglycemia, potentially leading to death of the patient and the fetus. Indeed, four pregnancies in two patients reported previously followed a complicated course with recurrent metabolic decompensations, abortions, and death of one mother (Langendonk et al. 2012), while one patient developed metabolic decompensation during labor and delivery (Pipitone et al. 2016). One reason for decompensation may be the reportedly low compliance of one patient, which was also due to learning difficulties. One woman did not attend the outpatient clinic for metabolic review for several years. She also did not attend medical follow-up after undergoing her first successful pregnancy with several episodes of metabolic acidosis. During her second pregnancy, missing emergency ID and past medical records led to underestimation of the clinical situation, and subsequent coagulopathy resulted in spontaneous abortion. Further clinical course was complicated by

hyperammonemia, sepsis, and pulmonary and cerebral edema eventually leading to cardiac arrest. The second patient with HMG-CoA lyase deficiency and polycystic ovarian syndrome (PCOS) also experienced metabolic acidosis with hyperammonemia and respiratory distress during her first pregnancy. Subsequently, she had spontaneous abortion. The same patient, although well at the 6th gestational week, decided to have termination of her second pregnancy (Langendonk et al. 2012). The third reported patient (Pipitone et al. 2016) had an uneventful pregnancy, but developed complications during labor and delivery including metabolic acidosis as well as premature rupture of membranes, intrapartum bleeding requiring transfusion, tachycardia, and hypertension.

The patient reported here had a favorable outcome of two pregnancies without any metabolic decompensation. The favorable course in our patient may on the one hand be due to the clinical assumption that she had a less severe form of the underlying disease. Genetic analysis demonstrated a donor splice site mutation, c.876 + G > C. To date, there are no data on the clinical phenotype of this mutation. As stated by Menao et al. (2009), it is generally difficult to establish a genotype-phenotype correlation in patients with HMG-CoA lyase deficiency. Further, there is no specific clinical or laboratory parameter that can predict the severity of the disease, especially in pregnancy. A tight clinical observation and metabolic monitoring therefore is key to the successful metabolic management in these patients, especially in pregnancy.

Furthermore, our patient showed a good compliance, as she attended for follow-up appointments during and between the two pregnancies. Her mother provided excellent support supervising her disease monitoring and treatment, e.g., continuous blood glucose monitoring, strict diet, etc. To ensure most optimal care within the family, her mother was appointed as the legal custodian. Good compliance was achieved by repeated tuition regarding medical and dietary instructions given during repeated visits in the outpatient clinic. In contrast, lack of compliance, which was also due to learning difficulties, promoted metabolic decompensations and eventually led to fatal decompensation in the case described above (Langendonk et al. 2012).

Third, total parenteral peripartum nutrition and delivery by elective Caesarean section in our case kept the time of delivery short. This is thought to be a crucial factor for an uneventful delivery in HMG-CoA lyase deficiency. As known from various other inborn metabolic diseases, delivery presents a high risk period for complications due to a catabolic state.

Preconceptional counseling of patients with inborn metabolic diseases should be the central part of the transition from pediatric to adult outpatient clinic. It is suggested that female patients with inborn metabolic diseases, although metabolically stable, should be seen in metabolic outpatient clinic every year and repeatedly trained in pregnancy-related risks, the special metabolic needs in pregnancy, and the crucial importance of reliable contraception. Pregnancy should be planned with the caring obstetrician and the metabolic clinic.

In summary, successful metabolic and obstetric management of a patient with HMG-CoA lyase deficiency undergoing two pregnancies is reported. This report illustrates that a favorable maternal and neonatal outcome in patients with HMG-CoA lyase deficiency without complications is possible. The course of the presented patient elicits recommendations for metabolic management of patients with HMG-CoA lyase deficiency at risk for hypoglycemia and metabolic acidosis under the circumstances of altered metabolic needs during pregnancy.

Take-Home-Message

Uneventful pregnancy and a favorable neonatal outcome are possible in patients with HMG-CoA lyase deficiency under continuous metabolic review and treatment.

Conflict of Interest

David Santosa, Markus G. Donner, Stephan vom Dahl, Markus Fleisch, Thomas Hoehn, Ertan Mayatepek, Katrin Heldt, Tim Niehues, and Dieter Häussinger 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 (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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