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The Management of Pregnancy and Delivery in 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

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Abstract

3-hydroxy-3-methylglutaric (HMG)-CoA lyase is required for ketogenesis and leucine degradation. Patients with HMG-CoA lyase deficiency typically present with hypoketotic hypoglycemia and metabolic acidosis, which can be fatal if untreated. The patient is a 28-year-old female with HMG-CoA lyase deficiency who presented at 4 weeks gestation for prenatal care. Protein intake as well as carnitine supplementation were gradually increased to support maternal and fetal demands up to 65 g per day for protein and 80 mg/kg/day for carnitine. Fetal growth was appropriate. At 36 5/7 weeks, she presented with spontaneous rupture of membranes. Twice maintenance 10% glucose-containing intravenous fluids were initiated. During labor, vomiting and metabolic acidosis developed. Delivery was by cesarean. Preeclampsia developed postpartum. The patient recovered well and was discharged home on postpartum day 5. Stress of pregnancy and labor and delivery can lead to metabolic decompensation in HMG-CoA lyase deficiency. Patients should be monitored closely by a biochemical geneticist, dietitian, and high-risk obstetrician at a tertiary care center during their pregnancy. Fasting should be avoided. Intravenous 10% glucose-containing fluids should be provided to prevent catabolism and metabolic decompensation during labor and delivery.

Keywords

3-hydroxy-3-methylglutaric CoA lyase deficiency; HMG-CoA lyase deficiency; pregnancy

INTRODUCTION

3-hydroxy-3-methylglutaric (HMG)-CoA lyase deficiency is an organic acid disorder resulting from a defect in ketogenesis and leucine catabolism [Fukao et al., 2014]. Typically, severely affected patients present in the first year of life with hypoglycemic crisis without

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ketosis. In addition to nonketotic hypoglycemia, patients can develop severe metabolic acidosis, liver dysfunction, hyperammonemia, and elevated free fatty acids [Fukao et al., 2014] which may be fatal. Management includes avoidance of prolonged fasting, adherence to a low fat and mildly protein restricted diet, and carnitine supplementation. Urinary organic acids are diagnostic [Fukao et al., 2014]. 3-hydroxy-3-methylglutarate, 3-methylglutaconate, 3-methylglutarate, 3-hydroxyisovalerate, and 3-methylcrotonylglycine are present.

The susceptibility to hypoglycemic crises does not resolve in childhood and can continue into adulthood, especially during times of fasting and intercurrent illness. Pregnancy is considered to be particularly stressful due to constant changes in fetal growth and subsequent metabolic demand. Published information on counseling and management of women with HMG-CoA lyase deficiency contemplating pregnancy is scarce. Langendonk et al. published the only case series with two women with HMG-CoA lyase deficiency in pregnancy. Severe metabolic decompensation complicated three of the four pregnancies and resulted in both maternal and fetal demise at 9 weeks gestation for one woman. This woman had one prior full-term delivery. The second woman had residual foot drop and fetal demise from an episode of metabolic decompensation and subsequently chose to terminate her second pregnancy [Langendonk et al., 2012].

In the limited experience with managing patients with HMG-CoA lyase deficiency during pregnancy, first trimester nausea and vomiting appears to be particularly problematic [Langendonk et al., 2012]. There is even less experience in caring for patients during the second and third trimesters of pregnancy, as well as during labor, delivery and postpartum.

CLINICAL REPORT

The patient is a 28-year-old female with HMG-CoA lyase deficiency, who presented at 4 weeks gestation for prenatal care. She was diagnosed with HMG-CoA lyase deficiency at 3 months of age when she presented with severe metabolic acidosis and hypoglycemia. She had several episodes of metabolic decompensation prior to age 12, but has been relatively stable thereafter. The patient is cognitively normal, works as a registered nurse, and lives with her husband.

Maintenance of strict metabolic control through adequate nutrition and monitoring of maternal and fetal weight gain was employed. Nutrition goals during pregnancy included promotion of optimal caloric, protein, and fat intake to achieve adequate fetal growth, while minimizing the risk for maternal metabolic decompensation. Plasma amino acid levels were measured monthly and protein intake adjusted as required. Protein intake was gradually increased to meet maternal and fetal demands. In the third trimester, protein intake goals were 65 g per day or about 1 g/kg; which was well tolerated. Plasma amino acids were maintained in the normal range.

Plasma total and free carnitine levels were evaluated monthly as increased carnitine consumption was anticipated due to fetal tissue uptake. At 24 weeks gestation, the carnitine

levels had decreased below normal. The levocarnitine dose of 45 mg/kg/day was increased to 75 mg/kg/day. This increased dose was adequate for the remainder of her pregnancy.

Fetal growth as measured by ultrasonography was appropriate throughout the pregnancy. Maternal echocardiogram remained normal during pregnancy.

At 36 weeks 5 days, the patient presented with spontaneous rupture of membranes. 10% glucose-containing intravenous fluids at twice maintenance were started immediately. Intravenous levocarnitine at 200 mg/kg/day in four divided doses was also supplemented during labor and delivery. After delivery, to minimize catabolism, 10% dextrose based intravenous fluids were maintained until adequate oral intake was achieved.

During the course of labor, the patient developed several complications. At the time of pushing, she had two episodes of vomiting and subsequently developed a metabolic acidosis despite the increased rate of 10% dextrose containing intravenous fluids. Serum electrolytes were monitored frequently during the laboring process. Bicarbonate dropped to 14 in the setting of otherwise normal electrolytes and a pH of 7.34 on venous blood gas.

Due to maternal exhaustion and decline of operative vaginal delivery, cesarean delivery was performed. Intravenous sodium bicarbonate (approximately 0.4 mg/kg) was administered prior to cesarean delivery. The delivery was complicated by an estimated blood loss of 1 L and anemia requiring transfusion of packed red blood cells. The baby was a vigorous male weighing 2,790 g.

Electrolytes were monitored every 4–6 hr postpartum for 48 hr. At 12 hr after delivery she developed tachycardia and hypertension in the setting of anemia due to intrapartum blood loss and volume-overload secondary to aggressive fluid support. Hypertension improved with administration of nifedipine. Intravenous fluids were continued and gradually weaned until the third day postpartum when the patient was able to tolerate oral intake well. Protein intake was monitored and goals were maintained at 65 g per day to accommodate increased need for lactation. Subsequently, the patient recovered and was discharged home 5 days after delivery.

Newborn screening of her son, collected on the second day of life, was reported as abnormal, as expected because of the abnormal metabolites transmitted from his mother. The following analytes in the acylcarnitine profile of newborn screening sample were elevated, C3DC 0.27 μM (normal <0.19), C5DC 0.36 μM (normal <0.28), C5OH 0.89 μM (normal <0.83), C5OH/C0 0.02 (normal <0.02), and C6DC 0.40 μM (normal <0.27). Urine organic acid analysis collected on the second day of life showed high normal levels of 3-methylglutaric and 3-hydroxy-3-methylglutaric acids, and mildly elevated levels of 3-methylglutaconic acid, definitely not in the high range as in HMG-CoA lyase deficiency but at levels consistent with transmission from an affected mother. The urine organic acid profile repeated on 17th day of life was completely normal. Clinically, her son is doing well; his growth and development are normal.

DISCUSSION

This is the third report in the literature of pregnancy in a patient with HMG-CoA lyase deficiency [Langendonk et al., 2012] and only the second reported patient to successfully deliver a viable infant. Although the patient's pregnancy was uneventful, during labor and delivery she had several complications including metabolic acidosis as well as obstetrical complications of premature rupture of membranes, intrapartum bleeding requiring transfusion, and tachycardia and hypertension.

As reported in pregnancy with other inborn errors of metabolism, pregnant women with HMG-CoA lyase deficiency can tolerate higher amounts of dietary protein as the pregnancy progresses [Raval et al., 2015]. Levocarnitine does not have any detrimental effects to pregnancy and supplementation should be continued as needed [Raval et al., 2015]. Fetal growth restriction can be a complication of a maternal protein restricted diet, therefore, maternal protein intake should be closely monitored and increased as needed. Fetal growth should be monitored serially with ultrasonography. We were able to maintain normal fetal growth in our patient by monitoring branched chain amino acids and increasing maternal protein intake as tolerated.

As compared to the patients reported by Langendonk, our patient did not experience metabolic decompensation in the first trimester but did at the time of labor and delivery. The stress of labor and delivery is, therefore, another vulnerable time for patients with HMG-CoA lyase deficiency that can lead to metabolic decompensation.

Based on our experience and limited case reports, pregnant patients with HMG-CoA lyase deficiency should be monitored at a tertiary care center during their pregnancy, delivery and postpartum period by a biochemical geneticist, dietitian, and high-risk obstetrician. The maternal diet and carnitine levels should be monitored closely and routinely adjusted for the increased protein and carnitine uses for fetal growth and development. Carnitine supplementation should be optimized during pregnancy to maintain normal levels. Fasting should be avoided. Intravenous 10% glucose-containing fluids should be provided to prevent catabolism during labor and delivery and postpartum period. Prolonged observation in the postpartum period is essential as postpartum adaptations can induce metabolic decompensation.

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