Fructose-1,6-Bisphosphatase Deficiency: A Case of a Successful Pregnancy by Closely Monitoring Metabolic Control

Genki Sugita • Hideaki Tsuyoshi • Koji Nishijima •
Yoshio Yoshida

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Abstract In patients with fructose-1,6-bisphosphatase (FBPase) deficiency, maternal and fetal neurodevelopmental abnormalities can be induced by severe hypoglycemia and lactic acidosis, which is triggered by pregnancy. The patient was a 24-year-old and primipara. Via pre-pregnancy education and management including self-monitoring of blood glucose and prompt medical intervention with glucose infusions, she never experienced hypoglycemia with impaired consciousness. She delivered a 2,406 g male infant at 38 weeks of gestation by cesarean section. No neurological abnormalities in either the mother or the child appeared during the following 2 years. This is the first report with detailed descriptions of the management of a pregnant woman with FDPase deficiency. This report suggests that for a patient with FBPase deficiency, the maternal and fetal complications can be reduced by pre-pregnancy education and self-monitoring of blood glucose to prevent hypoglycemia.

Introduction

Fructose-1,6-bisphosphatase (FBPase) deficiency is a rare metabolic disorder that is caused by a reduction in activity of FBPase, the rate-limiting enzyme of gluconeogenesis. Because of a deficiency of this enzyme, the inability to convert lactic acid or glycerol into glucose leads to

hypoglycemia and lactic acidosis; it was first recognized in 1970 by Baker and Winegrad (1970). The disease is caused by mutations in the FBPase gene and is transmitted as an autosomal recessive (the frequency is 1–9/100,000) (Douillard et al. 2012). Patients with FBPase deficiency have limited amounts of glycogen stores. The disease is diagnosed by an enzymatic assay of FBPase activity from hepatic specimens and peripheral cultured monocytes (Kikawa et al. 2002); mutational analysis is useful for the differential diagnosis. By instituting appropriate treatment for hypoglycemia and dietary education, the long-term neurological prognosis is generally good.

The literature contains only two reports of the management of a pregnancy with FBPase deficiency (Table 1); one of the patients suffered recurrent lactic acidosis and hypoglycemia during pregnancy, and subsequently developed sensorineural hearing loss and early-onset cognitive impairment (Krishnamurthy et al. 2007). Hyperemesis, glucose metabolism during pregnancy, and fasting before and after vaginal delivery or cesarean section often lead to hypoglycemia. Furthermore, there is a possibility of not only a maternal cognitive disorder but also deterioration in the development and neurological function of the infant. In this report, we describe a woman with FBPase deficiency in whom hypoglycemic episodes were prevented by pre-partum education and strict glycemic control with self-monitoring of blood glucose throughout the pregnancy; as a result, neither maternal nor fetal cognitive disorders manifested.

Case Report

Since infancy, the patient experienced two episodes of hypoglycemia and metabolic acidosis with vomiting and

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G. Sugita • H. Tsuyoshi (✉) • K. Nishijima • Y. Yoshida
Faculty of Medical Sciences, Department of Obstetrics and
Gynecology, University of Fukui, 23-3 Matsuoka-Shimoaizuki,
Eiheiji-cho, Yoshida-Gun, 910-1193, Fukui, Japan
e-mail: go242h@yahoo.co.jp

Table 1 Literature review of pregnancies complicated with FBPase deficiency

Authors	Management of pre-pregnancy	Management during pregnancy	Maternal prognosis	Newborn prognosis
Krishnamurthy et al. 2007	None (recurrent episodes of lactic acidemia and hypoglycemia)	Strict compliance with dietary management, including nocturnal uncooked cornstarch	Sensorineural hearing loss and early-onset cognitive impairment	No complications
Asberg et al. 2010	Ingesting some food just before retiring	None (uneventful pregnancy)	No complications	No complications
Current	Instruction regarding the risk of hypoglycemia during pregnancy	Self-monitoring of blood glucose and prompt medical intervention with glucose infusions	No complications	No complications

impaired consciousness. She was diagnosed with FBPase deficiency at age 1 via the lack of FBPase activity in peripheral cultured monocytes (0 nmol/min per mg protein; reference: 4.1–15.3). This assay was conducted by pediatricians at the University of Fukui who specialized in inherited metabolic diseases. Mutation analysis was not performed. Subsequently, the patient received medical treatment including administration of intravenous glucose and sodium bicarbonate two to three times a year because of episodes of fasting hypoglycemia. She had normal growth and attended a regular school without problems.

At age 24, she wanted to achieve a pregnancy; therefore, she was instructed regarding the risk of hypoglycemia during pregnancy. At 6 weeks of gestation, she presented at our medical center with a complaint of hyperemesis. She was in good health, and the physical examination was within normal limits. During a fasting state, the serum glucose level was 112 mg/dl (reference: 75–105) and the lactate level was 15 mg/dl (reference: 4–16). The venous blood gases were as follows: pH, 7.38 (reference: 7.32–7.40); pCO₂, 44.9 mmHg (reference: 42–51); HCO₃, 25.8 mmol (reference: 21–27); pO₂, 29.6 mmHg (reference 35–45); and base excess, 0.8 mmol (reference: –2 to 2). She received intravenous fluids of 1,000–2,000 ml including glucose 100–200 g/day during hospitalization because she experienced difficulty with oral intake. We instructed her regarding self-monitoring of blood glucose at home to prevent hypoglycemia and avoidance of overeating; blood glucose was measured three times daily before meals and if she felt unwell. In addition, we advised her regarding oral ingestion or intravenous administration of glucose when her blood glucose level was below 86 mg/dl or she could not tolerate oral intake.

After her discharge, when her blood glucose level dropped, she immediately orally ingested glucose, including candy, chocolate, and juice. When she could not tolerate oral intake, she immediately presented at our hospital. Although she was hospitalized three times, the prompt infusion of glucose 100–200 g/day avoided hypoglycemia or metabolic acidosis, and she did not experience

hypoglycemia with impaired consciousness. Weight gain during pregnancy was 6 kg. A 75 g oral glucose tolerance test (OGTT) at 28 weeks of gestation revealed a normal pattern: fasting serum glucose level, 83 mg/dl; 1-h level, 148 mg/dl; and 2-h level, 106 mg/dl. The pregnancy course was uneventful.

An elective cesarean section was performed at 38 weeks, 3 days of pregnancy because of a breech presentation. Via measurement of glucose and blood gases as well as 200–220 g/day glucose administration when fasting before and after surgery, we maintained strict glycemic control. As a result, she never experienced hypoglycemia or metabolic acidosis. A 2,406 g male infant (–1.4 standard deviation) was delivered with an Apgar score of 8 and 10 at 1 and 5 min. The umbilical arterial blood gases were as follows: pH, 7.37 (reference: 7.32–7.40); glucose level, 112 mg/dl (reference: 75–105). The postoperative course was uneventful, and she had no neurological abnormalities during the following 2 years. Her child's developmental milestones were normal and were equivalent to age 2 years.

Discussion

Patients with FDPase deficiency exhibit severe fasting hypoglycemia and lactic acidosis. The primary treatment is to prevent hypoglycemia by the administration of exogenous glucose, either by frequent meals or by glucose infusion. If the treatment for hypoglycemia is properly administered, the prognosis is good. However, hypoglycemia with severe neurological complications has been reported following the administration of fructose or glycerin (Hasegawa et al. 2003) or during pregnancy. The literature contains only two case reports regarding the management of pregnancy with FBPase deficiency. When the patient was admitted due to recurrent severe hypoglycemic attacks and lactic acidosis, she was found to be pregnant and in her second trimester. Despite compliance with monitoring and treatment of hypoglycemia, she developed sensorineural hearing loss and early-onset cognitive

impairment (Krishnamurthy et al. 2007). Another patient was hospitalized many times during her first 3 years of life, but she never felt that she was significantly affected by her illness after early childhood; in addition, she was the mother of two healthy children after two uneventful pregnancies (Asberg et al. 2010). Therefore, if a patient has suffered from recurrent hypoglycemic attacks during her adult life, it is suggested that pre-partum patient education and strict management during pregnancy are important for maternal neurological outcome (Table 1).

Glucose requirements are altered during pregnancy. Pregnant women must provide fuel not only for their own energy needs but also for the growth and metabolic requirements of the fetus. In the early pregnancy of a healthy woman, the increase in peripheral insulin sensitivity possibly causes diminished glucose availability in the circulation that can be compensated for by increased endogenous glucose production in times of need (Catalano et al. 1998). However, a patient with FBPase deficiency who cannot produce an endogenous glucose supply is prone to severe hypoglycemia and lactic acidosis when the exogenous glucose supply is interrupted due to emesis.

It is well known that an association exists between maternal hypoglycemia during pregnancy and fetal growth restriction as well as overall perinatal mortality. A higher incidence of small-for-gestational-age infants was found in the group with the low (<86 mg/dl) mean blood glucose level (Langer et al. 1994). Hypoglycemia might hinder fat-storage or growth-promoting factors in the fetal environment, which could result in low-birth-weight infants (Vadakekut et al. 2011). Moreover, Pugh et al. reported that patients with maternal hypoglycemia may be more likely to develop preeclampsia (Pugh et al. 2009). Increasing oral glucose requirements to prevent hypoglycemia can result in gestational diabetes.

Metabolic deterioration or fasting during delivery can be a serious risk for the child because lactic acidosis in the mother can cause serious problems in the neonate. Long-term anesthesia, a blood transfusion, and/or hypoglycemia can produce significant metabolic acidosis (Hashimoto et al. 1978). Because neonatal hypoglycemia has been demonstrated to be associated with long-term neurological dysfunction, including brain dysfunction, recurrent episodes of severe maternal hypoglycemia during pregnancy might affect the developing fetal brain.

In this case, via pre-pregnancy education, dietary counseling, and glucose infusion, we attained successful glycemic control during early pregnancy, which is the period when hypoglycemia is likely to occur. In the second and third trimesters, we instructed the patient regarding self-monitoring of blood glucose at home to prevent hypoglycemia and avoidance of overeating. By self-monitoring blood glucose and rapid medical intervention

when oral intake was inadequate, she never experienced hypoglycemia with impaired consciousness. We screened for the risk of gestational diabetes mellitus due to over-eating by conducting a 75 g OGTT. At the cesarean section, we prevented hypoglycemia and lactic acidosis by a continuous glucose infusion during fasting both before and after the cesarean section. Moreover, we closely monitored blood glucose and arterial blood gases until adequate oral intake had been established. No neurological abnormalities in either the mother or the child manifested during the following 2 years.

In August 2013, we searched the electronic database of Medline for publications containing the terms “fructose-1,6-bisphosphatase deficiency” and “pregnancy” and “fructose-1,6-bisphosphatase deficiency” and “long-term prognosis.” We identified eight reports in the English literature, but found no case reports with detailed descriptions of the management of a pregnant woman with FDPase deficiency. This report suggests that for a patient with FBPase deficiency, the maternal and fetal complications can be reduced by pre-pregnancy education and self-monitoring of blood glucose to prevent hypoglycemia.

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Synopsis

For a patient with fructose-1,6-bisphosphatase deficiency, the maternal and fetal complications can be reduced by pre-pregnancy education and self-monitoring of blood glucose to prevent hypoglycemia.

Conflict of Interest

Genki Sugita, Hideaki Tsuyoshi, Koji Nishijima, and Yoshio Yoshida 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.

Animal Rights

This report does not contain any studies with animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

I acknowledge that all authors have contributed significantly to the planning, conduct, and reporting of the manuscript, and that all authors are in agreement with the content of the manuscript. The guarantor for this report is the corresponding author, Hideaki Tsuyoshi, M.D.

References

- Asberg C, Hjalmarson O, Alm J, Martinsson T, Waldenström J, Hellerud C (2010) Fructose 1,6-bisphosphatase deficiency: enzyme and mutation analysis performed on calcitriol-stimulated monocytes with a note on long-term prognosis. *J Inherit Metab Dis* 33(Suppl 3):S113–S121
- Baker L, Winegrad AI (1970) Fasting hypoglycemia and metabolic acidosis associated with deficiency of hepatic fructose-1,6-diphosphatase activity. *Lancet* 2:13–16
- Catalano PM, Ishizuka T, Friedman JE (1998) Glucose metabolism in pregnancy. In: Cowett R (ed) *Principles of perinatal-neonatal metabolism*. Springer, New York, pp 356–389
- Douillard C, Mention K, Dobbelaere D, Wemeau JL, Saudubray JM, Vantyghem MC (2012) Hypoglycaemia related to inherited metabolic diseases in adults. *Orphanet J Rare Dis* 7:26
- Hasegawa Y, Kikawa Y, Miyamaoto J et al (2003) Intravenous glycerol therapy should not be used in patients with unrecognized fructose-1,6-bisphosphatase deficiency. *Pediatr Int* 45:5–9
- Hashimoto Y, Watanabe H, Satou M (1978) Anesthetic management of a patient with hereditary fructose-1,6-diphosphatase deficiency. *Anesth Analg* 57:503–506
- Kikawa Y, Shin YS, Inuzuka M, Zammarchi E, Mayumi M (2002) Diagnosis of fructose-1,6-bisphosphatase deficiency using cultured lymphocyte fraction: a secure and noninvasive alternative to liver biopsy. *J Inherit Metab Dis* 25:41–46
- Krishnamurthy V, Eschrich K, Boney A et al (2007) Three successful pregnancies through dietary management of fructose-1,6-bisphosphatase deficiency. *J Inherit Metab Dis* 30:819
- Langer O, Rodriguez DA, Xenakis EM, McFarland MB, Berkus MD, Arrendondo F (1994) Intensified versus conventional management of gestational diabetes. *Am J Obstet Gynecol* 170:1036–1046
- Pugh SK, Doherty DA, Magann EF, Chauhan SP, Hill JB, Morrison JC (2009) Does hypoglycemia following a glucose challenge test identify a high risk pregnancy? *Reprod Health* 6:10
- Vadakekut ES, McCoy SJ, Payton ME (2011) Association of maternal hypoglycemia with low birth weight and low placental weight: a retrospective investigation. *J Am Osteopath Assoc* 111:148–152